Olfactory vulnerability in older adults undergoing endoscopic skull base surgery: insights from olfactory strip elevation

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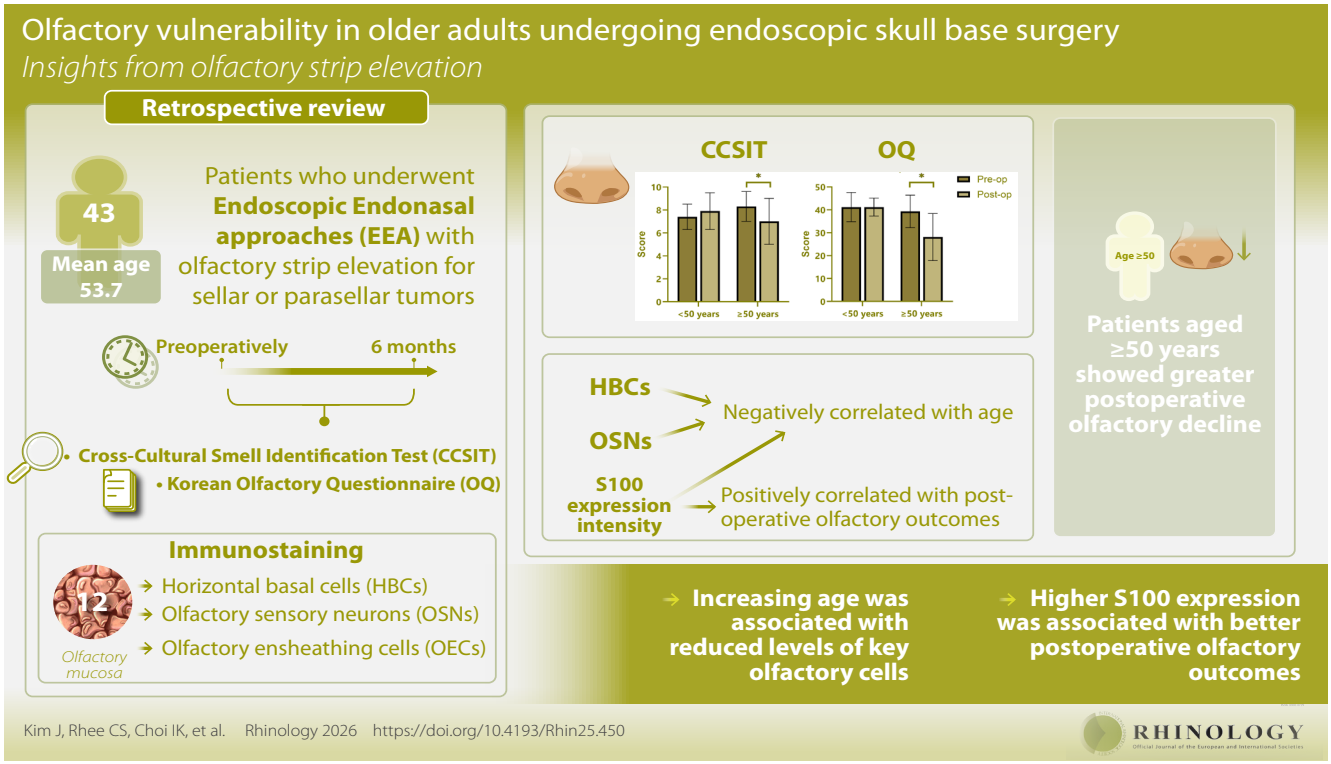
Rhinology 64: 3, 0 - 0, 2026
https://doi.org/10.4193/Rhin25.450



Abstract

Introduction: Postoperative olfactory outcomes after endoscopic endonasal approaches (EEA) vary, and the influence of age remains uncertain. This study evaluated whether age affects postoperative olfaction in patients undergoing EEA with a uniformly performed nasal phase including olfactory strip elevation. Age-related histologic features of the olfactory mucosa were also examined. **Methods**: We retrospectively reviewed patients who underwent EEA with olfactory strip elevation for sellar or parasellar tumors. Olfactory function was assessed preoperatively and at 6 months postoperatively using the Cross-Cultural Smell Identification Test (CCSIT) and the Korean Olfactory Questionnaire (OQ). In a subgroup, olfactory mucosa was immunostained for markers of horizontal basal cells (HBCs), olfactory sensory neurons (OSNs), and olfactory ensheathing cells (OECs) to evaluate age-related histologic patterns and associations with postoperative olfaction. **Results**: Forty-three patients (mean age 53.7 years) were analyzed. CCSIT decreased from 8.0 to 7.3 and OQ from 39.9 to 33.1. Age ≥50 years was associated with lower postoperative CCSIT and OQ. Olfactory mucosa available for analysis showed negative correlations between age and OSN counts, HBC counts, and S100 expression intensity. S100 expression correlated positively with postoperative olfactory outcomes. **Conclusions**: Patients aged ≥50 years showed greater postoperative olfactory decline after EEA with olfactory strip elevation. Increasing age was associated with reduced levels of key olfactory cells. Higher S100 expression was associated with better postoperative olfactory outcomes.

Key words: age factors, endoscopic surgical procedures, immunohistochemistry, olfactory mucosa, skull base/surgery

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Introduction

The endoscopic endonasal approach (EEA) is widely used for lesions of sellar/parasellar regions because it provides improved visualization and allows a higher rate of gross total resection, resulting in better overall functional outcomes, including olfaction, compared with the traditional transnasal microscopic approach [1,2]. However, even with EEA, postoperative olfactory outcomes remain a significant challenge and should be addressed from a rhinologic perspective.

It is known that when preservation of the olfactory strip is achieved, olfactory function can be preserved [3-5]. However, even when the olfactory strip is anatomically preserved, postoperative olfactory outcomes may still be influenced by factors such as the extent of surgery and the use of a nasoseptal flap [1,6,7]. Meanwhile, to our knowledge, the potential impact of olfactory strip elevation on postoperative olfactory outcomes has not been systematically examined. Although this maneuver may improve surgical exposure, it inevitably entails subtle manipulation of the olfactory mucosa, which could contribute to postoperative functional impairment even in the absence of overt structural damage.

The human olfactory mucosa consists of the olfactory epithelium, which is composed of horizontal basal cells (HBCs), globose basal cells (GBCs), and olfactory sensory neurons (OSNs), and the underlying lamina propria, which contains olfactory ensheathing cells (OECs) [8]. The human olfactory mucosa supports lifelong turnover and injury-induced regeneration of the olfactory epithelium, aided by basal stem cells and OECs [9,10]. Therefore, characterization of the olfactory mucosa from those who underwent EEA, could provide insights into the underlying mechanisms that affect olfactory recovery after surgery.

The olfactory epithelium is one of the few regions where adult neurogenesis occurs, but with aging, the extent of neurogenesis diminishes. Reduced differentiation capacity of HBCs, along with a decreased number of OSNs and proliferating basal cells, was observed in the aged olfactory epithelium [11,12]. These age-related biological changes led us to hypothesize that age may influence postoperative olfactory outcomes after EEA and that the olfactory epithelium may show age-dependent histological characteristics.

In this study, we evaluated clinical factors influencing postoperative olfactory outcomes after EEA with a uniform nasal phase including olfactory strip elevation, and found that age was significantly associated with olfactory outcome. In a subgroup of patients with available olfactory mucosa, we further examined age-related histological features and explored how these findings related to postoperative olfactory recovery.

Materials and methods

Participants

A retrospective review was conducted on patients who underwent EEA for skull base tumors in the sellar and parasellar area from January 2021 to March 2023 at Seoul National University Bundang Hospital.

Our surgical approach is similar to the technique described by Hong et al., commonly referred to as the "one-and-a-half" approach, along with a type III sphenoidotomy as previously described [2,13,14]. To increase space and improve visualization, several modifications were implemented. First, the right-sided rescue flap was enlarged by extending the incision anteriorly to the level of the head of the inferior turbinate. The flap was then reflected inferiorly to avoid interference with endoscopic insertion. Next, the lateral corridor was widened through a right partial superior turbinectomy, removing the segment inferior to the level of the sphenoid ostium (the lower half) and posterior ethmoidectomy. And finally, additional exposure was achieved by elevating the right olfactory strip, tucking it into the olfactory cleft, and flattening the anterior sphenoid wall up to the planum (Figure 1; Supplementary Video).

The elevated olfactory strip was repositioned at the end of surgery. When necessary, for example in cases of high-flow cerebrospinal fluid (CSF) leaks, a significantly descended diaphragmatic sella, or carotid artery exposure, the original right-sided septal mucosal incision was extended to harvest a nasoseptal flap. Surgical approaches were further categorized as either transsellar or transtuberculum/transplanum.

To ensure consistency in the nasal phase of surgery, patients were excluded if they did not undergo unilateral posterior ethmoidectomy, partial superior turbinectomy, and olfactory strip elevation, or if they underwent additional procedures such as middle turbinectomy.

Patients with coexisting inflammatory sinonasal diseases, such as chronic rhinosinusitis or sinonasal tumors involving the skull base, were also excluded, as were those with a history of revision surgery due to CSF leakage, intracranial hemorrhage, or tumor recurrence.

Pre-operative demographics, tumor characteristics, and pre- and post-operative olfactory outcomes were measured. Preoperative sellar magnetic resonance imaging (MRI) was conducted for all subjects using a 3 Tesla MRI system with 1 mm thin slices. Tumor size was assessed on contrast-enhanced T1-weighted coronal images by measuring the largest diameter. Age was dichotomized at 50 years to facilitate subgroup analysis, based on prior studies suggesting differential olfactory recovery before and after this age threshold [15,16].

Olfactory function test

Olfactory function was quantified using the Cross-Cultural Smell Identification Test (CCSIT, Sensonics International, Haddon Heights, NJ, USA), alongside a Korean version of Olfactory Questionnaire (OQ) during the same time period. OQ is comprised of 11 questions, including one about odor occurrences in

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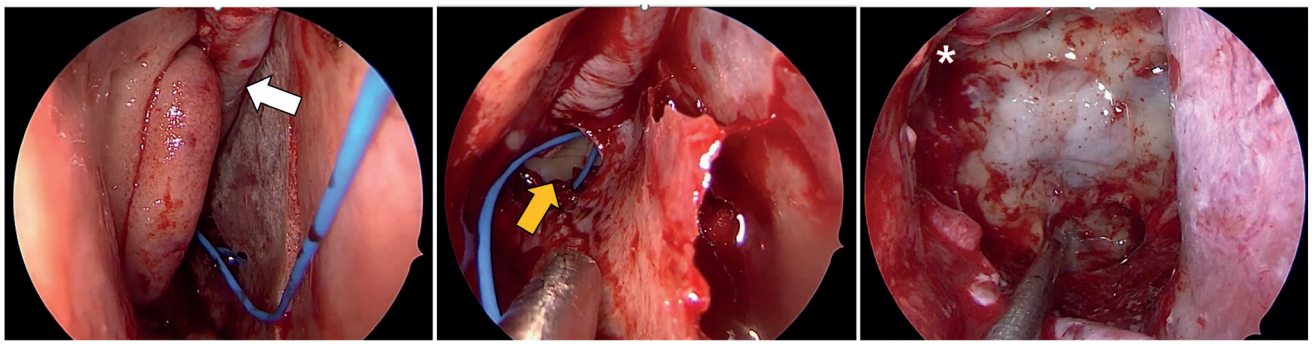

Figure 1. Intraoperative images illustrating key steps of the nasal phase during endoscopic endonasal approach. (A) Elevation of the right olfactory strip and tucking into the olfactory cleft to widen the surgical corridor (white arrow). (B) Endoscopic view at the level of the sphenoid ostium (yellow arrow). Olfactory strip elevation enhances exposure and facilitates drilling of the bony compartment. (C) Final exposure after completion of drilling. The lateral corridor is widened via right posterior ethmoidectomy (*).

daily life, seven on specific odors familiar to Koreans, and three on trigeminal nerve-related odors. Each question consisted of a maximum of 4 points, with a total maximum score of 44 points [17]. This questionnaire has been recognized for its utility in assessing olfactory function in patients undergoing EEA [18]. Olfactory function test results at six months after surgery were compared with baseline measurements.

Immunohistological analysis

Among patients who provided informed consent, a portion of the superior turbinate routinely removed during the nasal phase of surgery was collected for histological analysis. Tissues were embedded in paraffin and sectioned in a vertical orientation to include both the bony concha and the overlying mucosa. After initial screening with hematoxylin and eosin staining to confirm an intact pseudostratified epithelial layer, sections meeting this criterion were subsequently examined using immunofluorescence to identify olfactory epithelial and supporting cell markers.

After deparaffinization and rehydration, sections were immersed in an antigen retrieval buffer of 0.01 M citric acid (pH 6.0) and microwaved for 20 minutes. The sections were then incubated for 30 minutes with a blocking solution containing 10% normal goat serum (S-1000. Vector Laboratories, Burlingame, CA, USA). Primary antibodies used included anti-OMP, anti-PGP 9.5, anti-K5, anti-p63 (rabbit polyclonal, 1:200 dilution; Abcam, Cambridge, MA, USA), anti-S100 (mouse monoclonal, 1:200 dilution; Invitrogen, Eugene, OR, USA), anti-TUJ1 (rabbit polyclonal; 1:100 dilution; Sigma-Aldrich, St. Louis, MI, USA), and anti-ECAD (goat polyclonal; 1:100 dilution; R&D Systems, Minneapolis, MN, USA). Then samples were incubated with secondary antibodies (1:1000; Invitrogen, Eugene, OR, USA). Cells were counted at the center of the olfactory epithelium (OE) at 200x magnification. The number of cells was assessed by counterstaining with DAPI (Figure S1). Co-staining of PGP 9.5 and OMP was used to identify mature OSNs that are both PGP 9.5-positive and OMP-positive. K5 and p63 were used as markers for HBCs [19].

In addition to olfactory epithelial cells, we examined the expression pattern of the S100 protein. S100 is a marker of olfactory ensheathing cells (OECs), which are located in the lamina propria beneath the olfactory epithelium [11,19]. For the quantification of S100, confocal microscopy was used to acquire tile images at 200× magnification. Quantitative analysis was performed using ZEN 2.3 software (Carl Zeiss Microscopy GmbH, Jena, Germany) on 8-bit images, with pixel intensity values ranging from 0 (no signal) to 255 (maximum signal). To assess signal intensity, five regions of interest (ROIs) were manually selected per image, and the software calculated the mean pixel intensity within each ROI, providing a relative measure of S100 expression.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. For variables with small sample size or non-normal distribution, data are presented as median and interquartile range (IQR). Changes in olfactory function before and after surgery were evaluated using paired t-tests or Wilcoxon signed-rank tests, as appropriate based on data distribution. To identify factors associated with postoperative olfactory outcomes, analysis of covariance (ANCOVA) was performed, adjusting for baseline olfactory scores. In addition, a multivariable logistic regression analysis was conducted using predefined cutoff values for normosmia versus hyposmia (CCSIT ≤ 8 and OQ ≤ 41), to evaluate the direction and magnitude of odds ratios for postoperative olfactory status [17,20]. A meaningful decline in postoperative CCSIT was defined as a decrease of ≥2 points.

The continuous effect of age on postoperative outcomes was further assessed using partial Spearman correlation analyses controlling for baseline performance. Associations between age

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Table 1. General patient characteristics.

Characteristics	Value
Sex, No. (%)	
Male	24 (55.8)
Female	19 (44.2)
Age, mean (SD), years	53.7 (14.4) (range, 14-85)
Baseline pre-op CCSIT (SD)	8.0 (1.3)
Baseline pre-op OQ (SD)	39.9 (6.9)
Tumor pathology, No. (%)	
Pituitary adenoma	29 (67.4)
Craniopharyngioma	7 (16.3)
Rathke's cleft cyst	2 (4.7)
Meningioma	2 (4.7)
Others	3 (7.0)
Tumor size, mean (SD), mm	27.3 (9.2)
Surgical approach, No. (%)	
Transsellar	30 (69.8)
Transtuberculum/Transplanum	13 (30.2)
Septal flap elevation, No. (%)	
Yes	17 (39.5)
No	26 (60.5)

CCSIT, Cross-Cultural Smell Identification Test; OQ, Olfactory Questionnaire; SD, Standard Deviation.

and histological markers of the olfactory epithelium were analyzed using Spearman's rank correlation coefficient (ρ). Correlation trends were visualized with scatter plots incorporating linear regression lines and 95% confidence intervals.

Statistical analyses were performed using SPSS (version 29.0; IBM Corp), R (version 4.4.3; R Foundation for Statistical Computing), and Python (version 3.11.8; Python Software Foundation). Statistical significance was defined as $P < 0.05$ for all tests.

Ethics statement

This study was approved by the Institutional Review Board of the research institution concerned (B-2409-926-101). All subjects who underwent tissue analysis provided written informed consent for participation in the study. All methods were performed in accordance with the relevant guidelines and regulations.

Results

Patient characteristics

A total of 43 patients were included in the analysis. The mean age was 53.7 ± 14.4 years, and the cohort consisted of 24 males and 19 females. The baseline CCSIT and OQ score was 8.0 ± 1.3 and 39.9 ± 6.9, respectively. The underlying pathologies included pituitary adenoma (n = 29), craniopharyngioma (n = 7), Rathke's cleft cyst (n = 2), meningioma (n = 2), and others (n = 3). The mean tumor size was 27.3 ± 9.2 mm. 30 patients (69.8%) underwent a transsellar approach, while the remaining 13 patients (30.2%) underwent a transtuberculum/transplanum approach. A nasoseptal flap was harvested in 17 patients (39.5%) (Table 1).

Postoperative olfactory outcomes and their association with age

A significant overall decline was observed in both CCSIT and OQ scores between the preoperative and postoperative periods (CCSIT: 8.0 ± 1.3 to 7.3 ± 1.9; $P = 0.04$; OQ: 39.9 ± 6.9 to 33.1 ± 10.7; $P < 0.001$). As described in the Methods section, we further stratified patients into two age groups: <50 years (n = 13) and ≥50 years (n = 30). Age-stratified analysis showed no significant changes in the <50-year group in either CCSIT (7.4 ± 1.1 to 7.9 ± 1.8; $P = 0.09$) or OQ scores (41.2 ± 6.4 to 41.2 ± 3.9; $P = 0.89$). In contrast, the ≥ 50-year group exhibited a significant decline in both CCSIT (8.3 ± 1.3 to 7.0 ± 2.0; $P = 0.004$) and OQ scores (39.3 ± 7.1 to 28.1 ± 10.3; $P < 0.001$) (Table 2).

Multiple linear regression analyses were performed to identify predictors of postoperative olfactory function, using CCSIT and OQ scores as outcome variables (Table S1). Explanatory variables included age group (≥50 vs <50 years), sex, tumor size, surgical approach, septal flap use, and the corresponding preoperative olfactory score. Older age (≥50 years) was significantly associated with poorer postoperative outcomes for both CCSIT ($F = 4.96$; $P = 0.03$) and OQ ($F = 14.86$; $P < 0.001$). The preoperative CCSIT score was also significantly associated with postoperative CCSIT ($F = 8.17$; $P = 0.007$), whereas the preoperative OQ score was not significantly associated with postoperative OQ ($F = 2.401$; $P = 0.13$). Other variables were not significantly associated with postoperative olfactory function. On multivariate logistic regression, patients aged ≥50 years were more likely to develop postoperative hyposmia (Table S2).

To evaluate the continuous effect of age on olfactory function, partial Spearman correlation analyses were performed between age and postoperative outcomes, adjusting for baseline scores. Age showed significant inverse correlations with postoperative OQ ($\rho = -0.42$; $P = 0.006$) and CCSIT scores ($\rho = -0.33$; $P = 0.04$), indicating poorer recovery with increasing age.

In summary, patients aged ≥50 years showed significantly lower postoperative olfactory scores compared with younger patients.

Age-related immunohistological characteristics and their association with postoperative olfactory outcomes

Among the 43 patients, 17 provided written consent for biopsy tissue analysis. Of these 17 biopsy specimens, 12 samples contained olfactory mucosa, defined as preserved epithelial integrity with positive OMP and PGP9.5 staining (Figure S1). Although these 12 patients who underwent histological analysis tended to be younger than those who did not, no significant dif-

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Table 2. Comparison of pre- and post-operative olfactory outcomes across age groups.

Age Group	CCSIT		P-value	OQ Score		P-value
	Pre-op	Post-op		Pre-op	Post-op	
All Patients (N=43)	8.0 ± 1.3	7.3 ± 1.9	0.04	39.9 ± 6.9	33.1 ± 10.7	<0.001
Age < 50 years (N=13)	7.4 ± 1.1	7.9 ± 1.6	0.09	41.2 ± 6.4	41.2 ± 3.9	0.89
Age ≥ 50 years (N=30)	8.3 ± 1.3	7.0 ± 2.0	0.004	39.3 ± 7.1	28.1 ± 10.3	<0.001

CCSIT, Cross-Cultural Smell Identification Test; OQ, Olfactory Questionnaire; SD, standard deviation.

ferences were observed in baseline or postoperative olfaction, tumor size, surgical approach, or use of a nasoseptal flap. The characteristics of these patients are presented in Table S2.

Paraffin sections of the identified olfactory mucosa were immunostained for several olfactory markers (Figure 2), and their expression levels were compared across different ages. Age showed a significant inverse correlation with the number of OMP(+)/PGP9.5(+) mature OSNs (Spearman $\rho = -0.76$; $P = 0.004$) and K5(+)/P63(+) HBCs ($\rho = -0.78$; $P = 0.002$) (Figure 3A, B). In addition to olfactory epithelial cells, we additionally assessed S100(+) OECs. The intensity of the S100 immunostaining signal was also negatively correlated with age ($\rho = -0.84$; $P < 0.001$) (Figure 3C).

The association between olfactory epithelial markers and changes in olfactory function was assessed using ΔCCSIT and ΔOQ, defined as the difference between postoperative and preoperative scores (Figure S2). Owing to the small sample size, ANCOVA and partial correlation analyses were not conducted. Among these markers, only S100 expression was positively associated with ΔCCSIT scores ($\rho = 0.63$; $P = 0.03$). No significant association was found between ΔCCSIT and any other marker, and none of the markers correlated with ΔOQ scores.

When a meaningful CCSIT decline was defined as a ≥2-point decrease, S100 signal intensity was significantly lower in patients with olfactory function not preserved (median, 5.79 [IQR, 5.22–7.15]) than in those with preserved function (median, 22.18 [IQR, 14.71–25.30]; $P = 0.02$) (Figure 3D).

Discussion

In the current study, we observed age-dependent differences in postoperative olfactory function among patients who underwent EEA with unilateral superior partial turbinectomy, posterior ethmoidectomy, and olfactory strip elevation. Immunohistological analysis of the olfactory mucosa revealed a strong negative association between age and the expression of olfactory markers. The expression of S100 was especially notable because it showed a strong positive correlation with postoperative olfactory function.

When EEA is performed, olfactory function tends to significantly deteriorate within 1 to 3 months postoperatively, with recovery occurring by around 6 months [21,22]. Therefore, olfactory function is considered to stabilize by this time, making the 6 month interval an appropriate point for postoperative assessment [23]. Obstruction of airflow to the olfactory cleft due to crusting or mucosal edema may cause immediate postoperative olfactory dysfunction, whereas olfactory decline resulting from injury to the sensorineural components requires a longer recovery period. Given that our olfactory function was assessed at 6 months postoperatively, the measured outcomes likely reflect dysfunction related to sensorineural injury. HBCs play a central role in the regeneration of the olfactory epithelium following injury [24, 25]. Age-related decline in the expression of HBC markers (K5 and P63) and OSN markers (OMP and PGP9.5) at the time of surgery may suggest reduced baseline regenerative potential and neuronal integrity in older individuals (aged ≥50 years), which may help explain their lower postoperative olfactory outcomes. The 50-year cutoff was initially chosen for interpretability and not derived from EEA-specific evidence. However, post-hoc analysis comparing multiple thresholds (45, 50, 55, and 60 years) showed that 50 years provided the most distinct separation in S100, OMP, and p63 expression (Table S4), supporting it as a biologically reasonable division.

However, no strong association was observed between surgical approach and postoperative olfactory function in our cohort. This may be because both extended and transsellar approaches shared a largely similar nasal phase, resulting in wide exposure of the olfactory region with substantial mucosal manipulation, including olfactory strip elevation. Because no comparison group without olfactory strip elevation was available, its effects on surgical outcomes or postoperative olfaction could not be directly assessed and warrant further investigation. Interestingly, among several olfactory markers, only S100 expression showed a significant positive correlation with olfactory function. S100 expression, a marker of OECs, was reduced in the lamina propria underlying the olfactory epithelium with aging. Double immunostaining demonstrated that S100(+) cells were adjacent to TUJ1(+) OSN axons (Figure S3), consistent with the known role of OECs in ensheathing OSN axons [11, 19]. Even though the olfactory strip is repositioned and the olfactory epithelial structure is well preserved after surgery, elevating the olfactory

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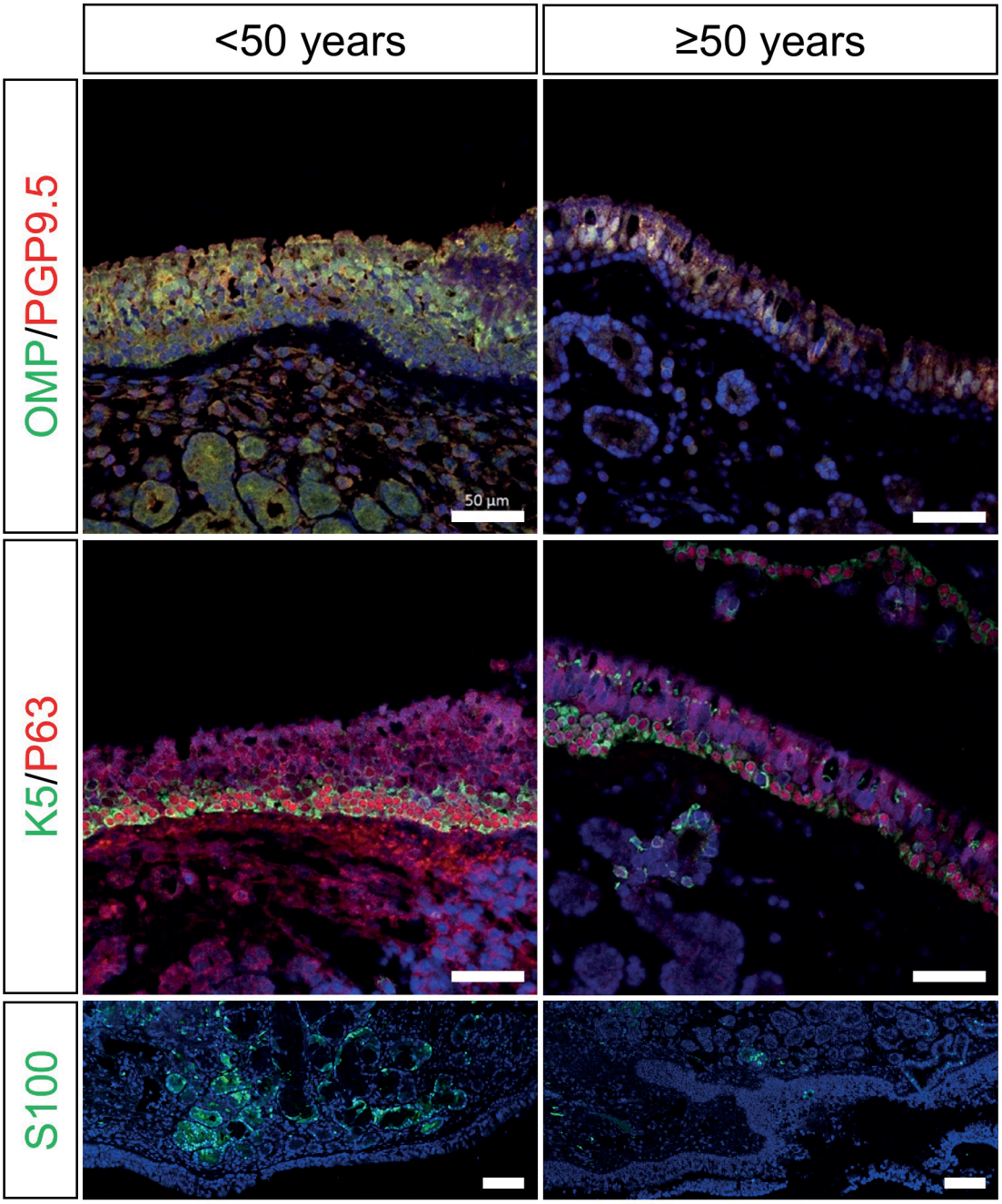

Figure 2. Representative confocal micrographs of the olfactory mucosa from each age group. The <50-year group includes immunostained images of olfactory epithelium from a 38-year-old male for OMP/PGP9.5 (OSN markers) and K5/P63 (HBC markers) (200x). Olfactory mucosa from a 33-year-old male was used for S100 immunolabeling (OEC marker) (100x). In the ≥50-year group, olfactory epithelium from a 66-year-old female was stained for OMP/PGP9.5 and K5/P63 (200x), and that from a 65-year-old female was used for S100 (100x). Scale bar for OMP/PGP9.5 & K5/P63: 50 µm. Scale bar for S100: 100 µm.

strip still subjects olfactory neuronal fibers to mechanical stress. Stretching is a common cause of nerve injury, and in contrast to other peripheral nerves, the olfactory nerve indeed lacks the typical connective tissue sheaths—endoneurium, perineurium, and epineurium [26]. These layers, which generally provide mechanical and physiological protection to peripheral nerves, are absent in the olfactory system. Instead, olfactory nerve fibers are ensheathed by OECs which contribute to axonal maintenance and repair [27]. These known OEC functions may help explain why patients with higher S100 expression have a greater propensity to preserve olfactory function after surgery.

Although S100 expression showed a significant association with

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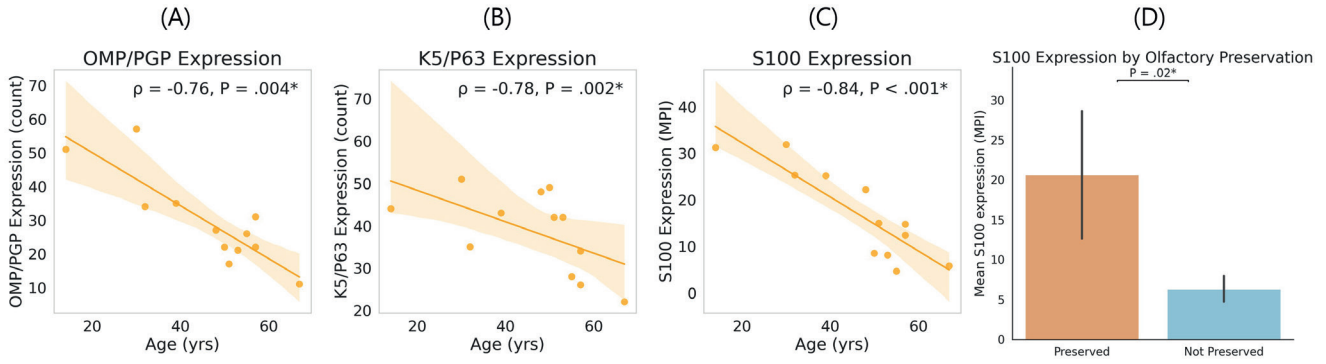

Figure 3. Age-related decline in olfactory epithelial markers and association of S100 expression with postoperative olfactory outcomes. All correlations were calculated using Spearman rank correlation. (A) Correlation between age and OMP(+)/PGP9.5(+) expression ($\rho = -0.76$, $P = 0.004$). (B) Correlation between age and K5(+)/P63(+) expression ($\rho = -0.78$, $P = 0.003$). (C) Correlation between age and S100 expression ($\rho = -0.84$, $P < 0.001$). (D) S-100 expression was compared between the olfactory function preserved and not preserved groups, defined by the presence or absence of a ≥2-point decline in CCSIT scores.

changes in postoperative CCSIT scores, no marker demonstrated a meaningful relationship with changes in OQ. This may reflect the fact that psychophysical testing and questionnaire-based assessment capture different dimensions of olfactory function. Whereas CCSIT reflects objective odor identification performance, OQ scores represent subjective perception and patient-reported experience, which may not always change in parallel. Furthermore, postoperative olfactory outcomes may be influenced not only by the baseline histological characteristics of the olfactory mucosa but also by factors such as altered airflow dynamics or inflammatory changes during the healing phase, which are not captured by histological analysis alone [28].

In our study, we analyzed biopsy specimens obtained from the lower half of the superior turbinate. Olfactory epithelium was identified in 12 of the 17 samples, yielding a rate similar to that reported previously [29]. This yield reflects our criterion that olfactory mucosa was confirmed only when histological integrity was preserved. The lower detection rate may be explained by tissue loss during slide preparation or by the possibility that olfactory mucosa does not consistently extend down to the lower half of the superior turbinate.

Although this tissue may not fully represent the entire olfactory mucosa, it remains the only practical and ethically acceptable source in living patients, as sampling the olfactory cleft or septal mucosa carries a risk of iatrogenic olfactory damage. Tissue resected during procedures that necessarily involve olfactory mucosa removal, such as endoscopic craniofacial resection for sinonasal malignancies, may provide valuable opportunities for further validation of our findings.

Limitations

The current study has several limitations. First, the sample size was small and included only a single ethnic group, which limits the generalizability of the findings. Although older age was associated with poorer postoperative olfactory outcomes, the small cohort may have reduced the ability to detect additional predictors. The number of immunohistological analyses was also limited (n = 12). In addition, the use of a 50-year cutoff to categorize age was exploratory, and this threshold requires validation in larger, independent cohorts.

Second, only patients who underwent olfactory strip elevation were included to maintain a consistent nasal phase. Middle turbinectomy cases were excluded for the same reason, even though this procedure is not known to impair olfaction [1]. Because olfactory strip elevation is not routinely performed in EEA, our findings may not be applicable to centers using different nasal-phase techniques.

Third, olfactory assessment was performed at 6 months after surgery. It has been reported that olfactory improvement may continue up to 12 months after surgery [30]. Therefore, longer-term follow-up beyond 6 months may further strengthen and validate our findings.

Finally, potential confounding factors such as smoking and the planum–sella angle [31], which may reduce olfactory epithelial trauma when wider, were not assessed.

Conclusion

This study shows that age is associated with postoperative olfactory outcomes after EEA with olfactory strip elevation. Patients aged 50 years or older were more likely to experience postoperative olfactory decline. Immunohistological analyses demonstrated age-related reductions in HBC, OSN, and OEC marker expression, and positive correlations of S100 expression with postoperative olfactory function. These findings indicate an age-related trend in olfactory recovery, although validation in a larger cohort is needed.

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Acknowledgements

We would like to acknowledge the
use of ChatGPT, an AI language model developed by OpenAI, for assistance with English language editing of this manuscript.

Author contributions

JK, CSR: Data analysis and manuscript drafting. IKC, JAP, JO, SAK: Data analysis and manuscript review. KH, JWK, TBW: Resources, Methodology, and manuscript review. HWS, SWC: Conceptualization, data analysis, provision of data, manuscript drafting, served as the corresponding authors and supervised the study.

Conflict of interest

None declared.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2022R1C1C1011966); the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00439991); the Seoul National University Bundang Hospital (SNUBH) Research Fund (grant numbers: 14-2021-0009, 16-2020-0009, 16-2019-0006, and 13-2022-0010 to Choi B.Y. and Shin H.W.); and by Ascending SNU Future Leader Fellowship through Seoul National University (Kim J.).

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Rhinology 64: 3, 0 - 0, 2026
https://doi.org/10.4193/Rhin25.395

Received for publication:
July 17, 2025
Accepted: December 22, 2025

Associate Editor:
Basile Landis

This manuscript contains online supplementary material

Corrected Proof

SUPPLEMENTARY MATERIAL

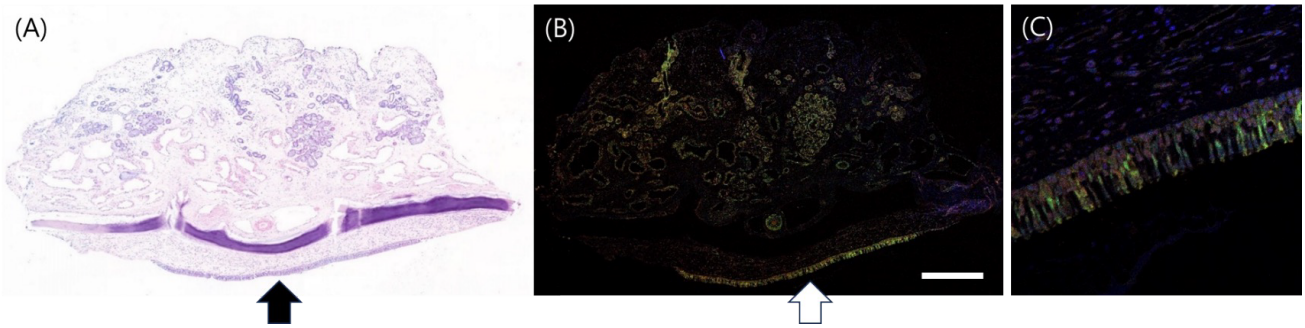

Figure S1. Identification and quantification of olfactory epithelium in the superior turbinate. (A) Hematoxylin and eosin (H&E) staining of a coronal section through the superior turbinate reveals pseudostratified epithelium, which is indicative of olfactory epithelium (indicated by the black arrow). (B) Immunostaining: Confirmation of the olfactory epithelium (indicated by the white arrow) is achieved through immunostaining with markers with OMP and PGP 9.5. (C) Magnification and Counting: Cell counting is performed at 200x magnification, focusing on the mid-portion of the olfactory epithelium.

Table S1. Factors associated with postoperative olfactory outcomes identified by multiple regression analysis.

Factors	Post operative CCSIT		Post operative OQ	
	F static	P-value	F static	P-value
Sex	0.28	0.60	3.35	0.08
Surgical approach (transtuberculum/transplanum)	0.634	0.43	1.65	0.21
Age (≥50 yrs)	4.96	0.03	14.86	**< 0.001**
Septal flap usage	0.47	0.50	0.19	0.66
Tumor size	0.20	0.65	1.80	0.19
Baseline olfaction*	8.17	0.007	2.40	0.13

* Baseline olfactory function was controlled for using preoperative CCSIT for the postoperative CCSIT outcome, and preoperative OQ score for the postoperative OQ outcome.

Table S2. Adjusted odds ratios for factors associated with postoperative olfactory outcomes.

Characteristics	CCSIT ≤8 hyposmia		OQ ≤41 hyposmia	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age ≥50 y	11.96 (1.46–187.43)	**0.04**	21.49 (2.95–383.33)	**0.01**
Sex (Female)	0.93 (0.15–5.72)	0.93	4.36 (0.47–78.72)	0.24
Extended approach	3.77 (0.33–93.05)	0.31	12.75 (0.31–3231.74)	0.24
Septal flap usage	4.66 (0.60–61.09)	0.17	0.43 (0.01–12.95)	0.64
Tumor size	0.98 (0.89–1.09)	0.70	1.18 (1.02–1.44)	0.05
Baseline olfaction*	0.37 (0.13–0.81)	**0.03**	0.79 (0.53–0.97)	0.07

* Baseline olfactory function was controlled for using preoperative CCSIT for the postoperative CCSIT outcome, and preoperative OQ score for the postoperative OQ outcome.

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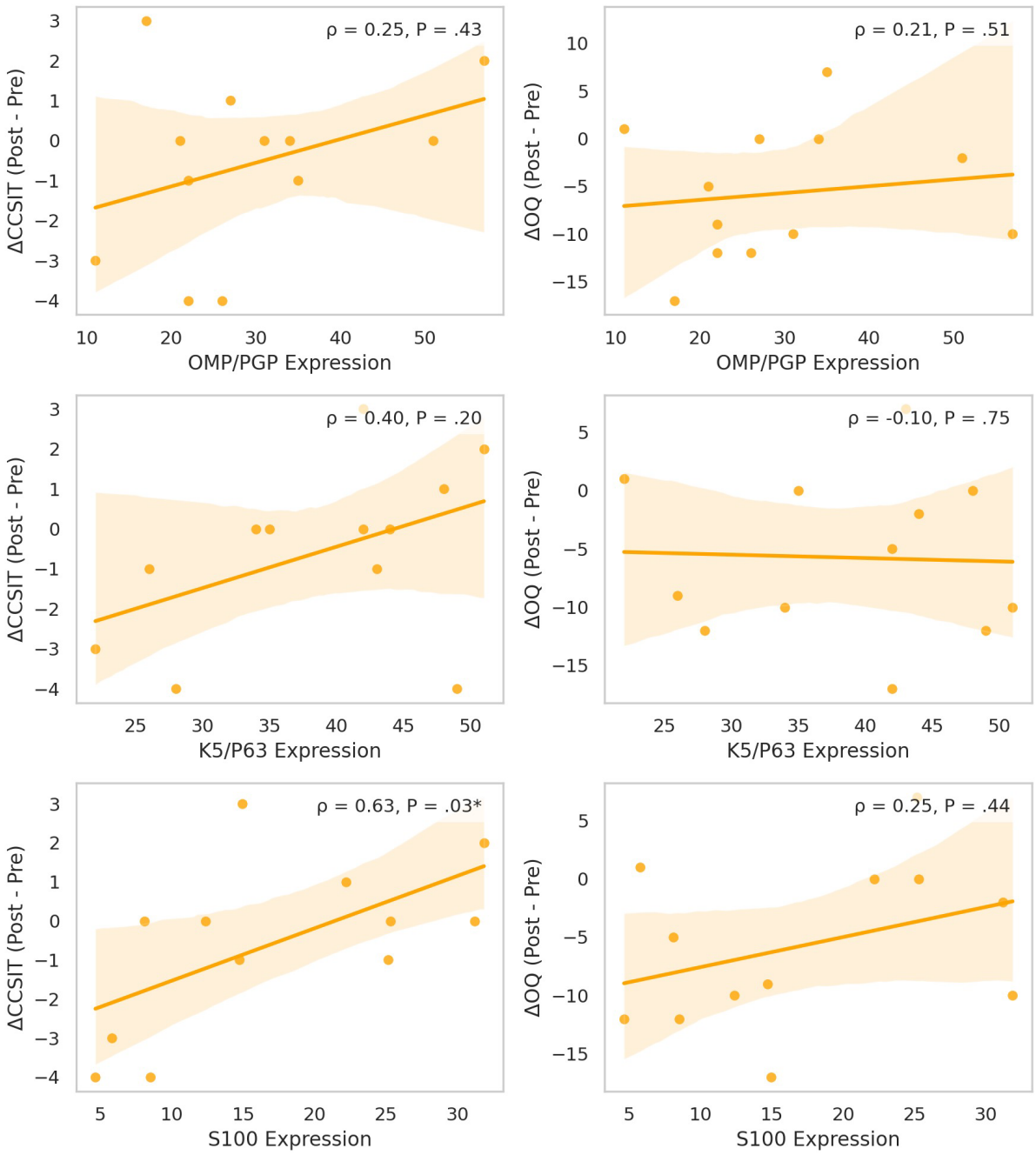

Figure S2. Correlation between olfactory epithelial markers and postoperative olfactory outcome changes. Scatter plots showing Spearman correlations between histological markers of the olfactory epithelium and postoperative changes in olfactory outcomes. Immunohistochemical markers represent olfactory ensheathing cells (S100), olfactory sensory neurons (OMP/PGP), and basal progenitor cells (K5/P63). ΔCCSIT (post – pre) indicates the change in olfactory identification ability measured by the Cross-Cultural Smell Identification Test. ΔOQ (post – pre) indicates the change in patient-reported olfactory function measured by the Olfactory Questionnaire. ρ indicates the Spearman correlation coefficient. Each plot includes a fitted linear regression line with the 95% confidence interval shaded in light orange. Correlation coefficients and P values are annotated in the upper-right corner of each panel.

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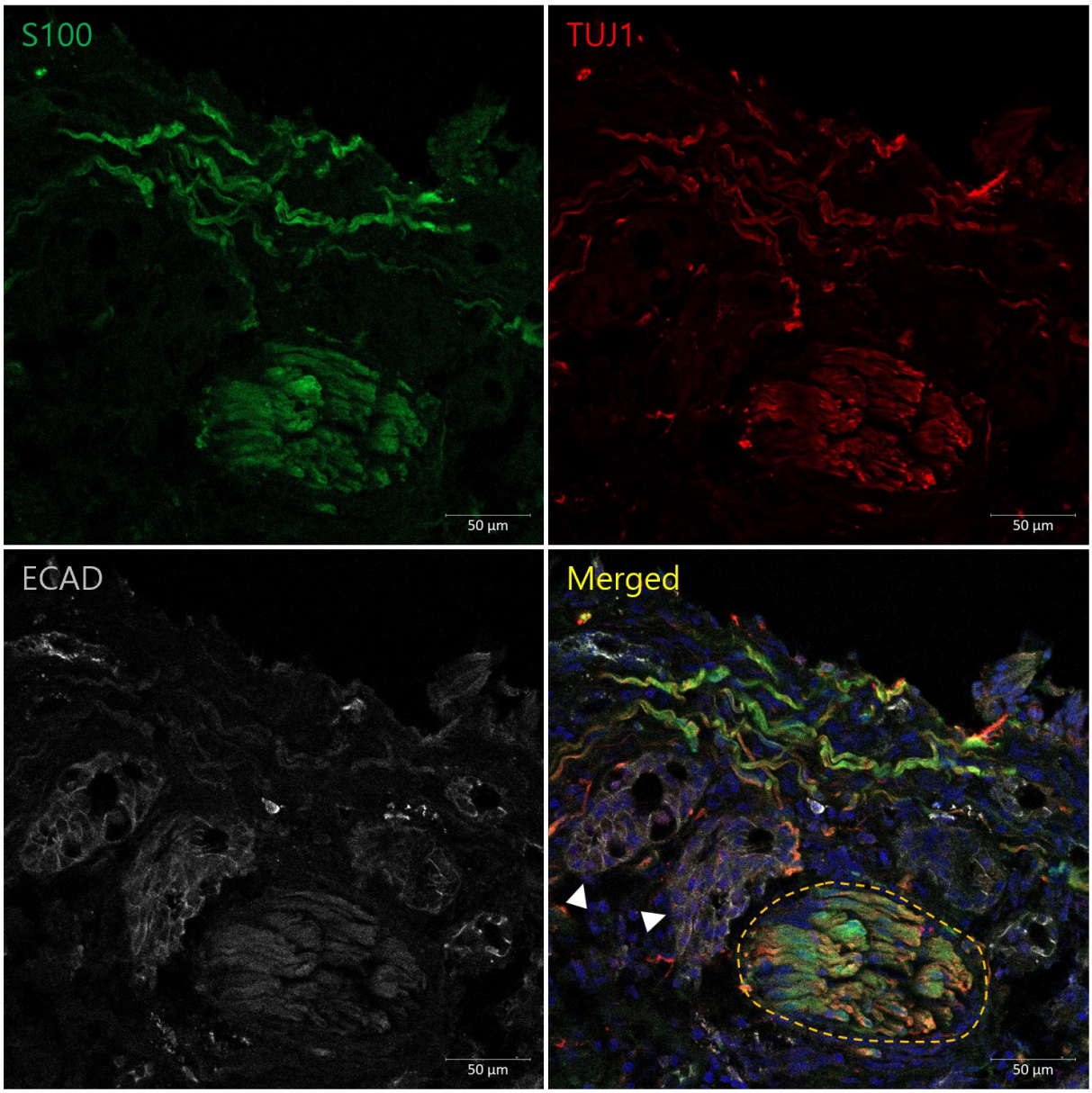

Figure S3. Immunofluorescence on the lamina propria of the olfactory epithelium (37-year-old; male). OEC marker S100 and OSN axon marker TUJ1 showed a close association. The region enclosed in the yellow dotted circle is a nerve fascicle. White arrowheads indicate glandular epithelium.

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Table S3. Characteristics of the patient subgroup according to histological analysis.

Characteristics	Patients without histological analysis from the superior turbinate (n=31)	Patients with histological analysis from the superior turbinate (n=12)	p-value
Age, mean (SD), yr	56.7 (13.3) (range, 24~85)	46.1 (14.7) (range 14-67)	**0.048**
Sex, No. (%)			>0.99
Male	17 (54.8)	7 (58.3)	
Female	14 (45.2)	5 (41.7)	
Pre-op OQ, mean (SD)	39.5 (7.5)	40.8 (5.0)	0.88
Post-op OQ, mean (SD)	31.0 (11.6)	35.0 (7.6)	0.46
Pre-op CCSIT, mean (SD)	7.93 (1.41)	8.08 (1.33)	0.80
Post-op CCSIT, mean (SD)	7.22 (2.01)	7.50 (1.78)	0.71
Tumor size, mean (SD), mm	26.5 (8.5)	29.3 (11.1)	0.64
Surgical approach, No. (%)			0.42
Transsellar	24 (77.4)	7 (58.3)	
Transtuberculum/Transplanum	7 (22.6)	5 (41.7)	
Septal flap elevation, No. (%)			>0.99
No	20 (64.5)	7 (58.3)	
Yes	11 (35.5)	5 (41.7)	

Patients were grouped according to whether superior turbinate tissue was obtained for histological analysis. Although age differed between the two groups, no significant differences were observed in olfactory outcomes (preoperative and postoperative OQ and CCSIT scores), tumor size, surgical approach, or use of a septal flap. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the χ^2 test. Values are presented as mean (SD) or No. (%). Abbreviations: OQ = Olfactory Questionnaire; CCSIT = Cross-Cultural Smell Identification Test.

Table S4. Olfactory marker expression according to age cutoff groups.

Age Cutoff	No. of patients		Marker	Median (IQR)		p-value
	< cutoff	≥ cutoff		< cutoff	≥ cutoff	
45 yr	4	8	S100	28.3 (6.1)	10.5 (7.3)	**0.004**
			OMP/PGP9.5	43.0 (17.8)	22.0 (6.3)	**0.008**
			K5/P63	43.5 (4.8)	38.0 (16.0)	0.20
50 yr	5	7	S100	25.3 (6.0)	8.51 (6.6)	**0.003**
			OMP/PGP9.5	35.0 (17.0)	22.00 (5.00)	**0.009**
			K5/P63	44.0 (5.0)	34.00 (15.00)	0.07
55 yr	8	4	S100	23.7 (13.5)	9.09 (7.5)	0.05
			OMP/PGP9.5	30.5 (17.3)	24.00 (8.0)	0.31
			K5/P63	43.5 (6.3)	27.00 (4.5)	**0.008**
60	11	1	S100	14.9 (14.8)	5.8 (0.0)	0.33
			OMP/PGP	27.0 (12.5)	11.0 (0.0)	0.15
			K5/P63	42.0 (11.5)	22.0 (0.0)	0.15

Comparison of olfactory marker expression according to age-based stratification thresholds (45, 50, 55, and 60 years). Values are presented as median (interquartile range). Group differences were assessed using the Mann–Whitney U test. The number of cases in each age stratum is indicated for every cutoff to demonstrate balance and sample size adequacy. A 50-year threshold demonstrated the most consistent segregation across S100 and OMP/PGP expression while maintaining sufficient sample size for a stable nonparametric comparison. Interpretation of the 60-year threshold is limited by the very small number of cases in the older group.