Olfactory dysfunction management following unilateral cranial resection for olfactory neuroblastoma

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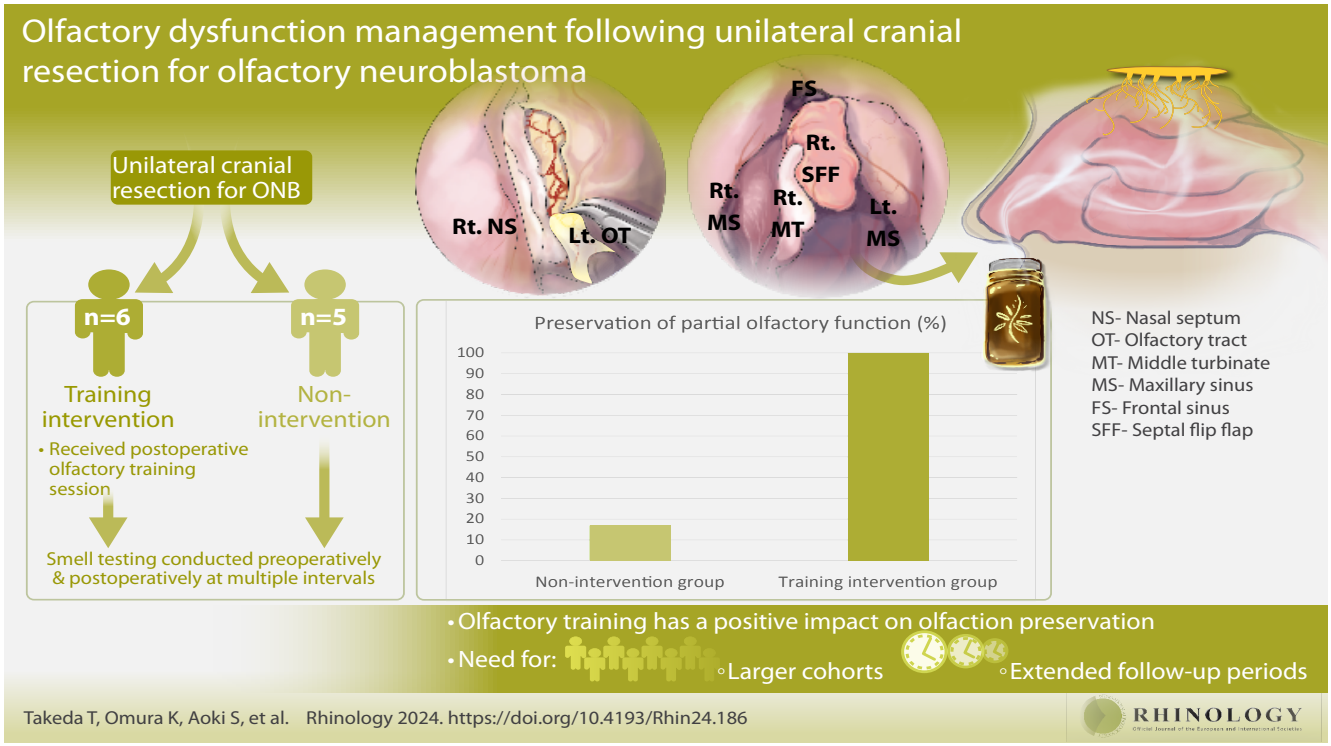

Abstract

Background: Despite advances in techniques for olfactory neuroblastoma (ONB), such as unilateral cranial resection, preserving the patient's sense of smell remains a challenge. This study aimed to examine the effectiveness of post-operative olfactory training in patients who underwent unilateral resection of ONB. **Methods**: This retrospective cohort study assessed the effect of post-operative olfactory training on olfactory preservation in patients with ONB undergoing unilateral cranial resection. Patients were divided into training intervention (n = 5) and non-intervention (n = 6) groups. Olfactory tests were conducted pre-operatively and at multiple post-operative intervals. **Results**: Partial olfactory function was preserved in all cases in the training intervention group, whereas only 17% of cases in the non-intervention group maintained partial olfactory function. Significant improvements in olfactory test scores were observed in the training intervention group compared with the non-intervention group. **Conclusions**: Our findings suggest that post-operative olfactory training could aid in olfactory preservation for patients with ONB after unilateral cranial resection. However, these results should be interpreted with caution, and further research with larger cohorts and extended follow-up periods is needed to confirm these observations.

Key words: olfaction disorders, olfactory neuroblastoma, olfactory training, skull base, esthesioneuroblastoma

Introduction

Olfactory neuroblastoma (ONB), also clinically recognised as esthesioneuroblastoma, is a rare and aggressive malignancy originating from the olfactory epithelium. ONB constitutes only 3%–6% of all cancers of the nasal cavity and paranasal sinuses [1]. Surgical resection is the primary treatment approach, with consideration of adjuvant therapy in patients with an advanced Kadish classification and a high Hyams grade [2].

Traditionally, the treatment for this tumour has been open craniofacial resection, but currently, endoscopic treatments have become the standard. These provide long-term survival rates and oncological outcomes comparable to those of craniofacial resection, with much less impact on quality of life (QOL) [3, 4]. Furthermore, evolving techniques such as unilateral cranial resection are emerging as key therapeutic options for patients with limited disease and without involvement of the cribriform plate, aiming to preserve the sense of smell [5]. Despite advancements in surgical techniques, post-operative olfactory preservation rates for the unilateral resection of ONB range from 43% to 91%, with no complete preservation. This makes post-operative olfactory impairment a persistent challenge that affects patients' well-being and QOL [5-8].

Olfactory dysfunction contributes substantially to decreased QOL following surgery [9], underscoring the urgency for tailored management strategies for this distinct patient population. Olfactory training, a rehabilitative technique involving repetitive exposure to various odours, has demonstrated potential for addressing post-traumatic anosmia and other olfactory disorders [10-18]. However, its efficacy in patients with ONB who have undergone surgical resection remains an area of exploration, revealing gaps in our current understanding.

Therefore, the primary objective of this study was to evaluate the effectiveness of post-operative olfactory training as a management strategy for olfactory dysfunction in patients who underwent unilateral resection of ONB.

Materials and methods

Ethical considerations

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from The Jikei University School of Medicine Ethics Committee (approval number: 33-410) prior to data collection and analysis.

Study design, population, and data source

We conducted a retrospective cohort study to evaluate the effect of post-operative olfactory training on the preservation of olfactory function in patients diagnosed with ONB. This study included patients who underwent surgical treatment at The Jikei University School of Medicine between July 2018 and December 2022. Written informed consent was obtained from all patients. Exclusion criteria were applied to ensure homogeneity within the cohort. Patients who met any of the following criteria were excluded:

1. Patients who underwent bilateral resection, combined craniotomy, or re-operation procedures;
2. Patients who lacked both pre- and post-operative olfactory test results;
3. Patients who underwent surgeries performed by different surgeons using different techniques; and
4. Patients subjected to adjuvant radiation therapy (RT).

Recent data suggest that adjuvant RT and elective nodal irradiation (ENI) are indicated for patients with Kadish C, Kadish D, or high-grade Hyams (III or IV) disease, or positive dura [2, 19-24]. However, in the early treatment of ONB, where adjuvant RT and ENI are not as commonly employed, the decision to use adjuvant RT and ENI at our institution was made through the decision-making process of a multidisciplinary tumour board. The rationale and potential effects were thoroughly explained, and adjuvant RT and ENI were only administered after obtaining informed consent from the patients.

The exclusion criteria were implemented to minimise potential confounding factors and ensure a focus on unilateral cranial resection cases for ONB. Excluding cases with bilateral procedures, combined craniotomies, or re-operations helped isolate cases in which the primary procedure was unilateral cranial resection. Additionally, standardised surgical techniques and surgeons reduced the variability in the procedures performed. Patients who underwent post-operative radiation therapy were excluded to maintain the clarity and integrity of the study objectives.

Our primary data source was the medical records of 49 patients with ONB who underwent surgical intervention at our institution during the study period. These records provided comprehensive information on patient demographics, clinical characteristics, details of the surgical procedures, post-operative outcomes, and follow-up data.

Operative technique for endoscopic unilateral cranial resection

(Figure 1 and Supplemental Video)

The surgical procedure for unilateral endoscopic cranial resection involved several precise steps for tumour removal. The surgery was performed by two otolaryngologists (TT, KO) and two neurosurgeons (YI, RM). The primary technique consisted of the following approach:

1. Frontal sinusotomy: The procedure began with the opening of the frontal sinus using the Draf 3 technique [25, 26]. This involved careful and controlled access to the frontal sinus, allowing adequate visualisation and access.
2. Paraseptal sphenoidotomy: The sphenoid sinus was accessed through the transnasal septum. If the disease extended to the nasal septum, the approach was switched

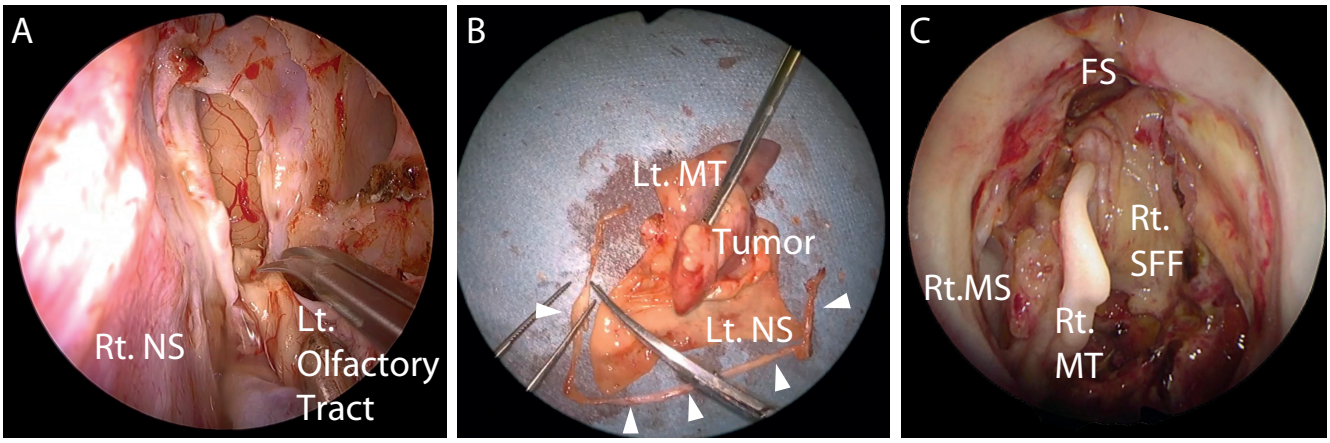

Figure 1. Operative technique for endoscopic unilateral cranial resection. The surgical technique for endoscopic unilateral cranial resection is described for a case of olfactory neuroblastoma (ONB) (Kadish A) on the left side. A) The tumour is excised using a central incision made along the olfactory tract. Rt. NS: nasal septal mucosa on the right side. B) The resected tumour is promptly sent for pathological evaluation to assess its margins. White triangle: mucosa for the evaluation of truncation. Lt. NS: nasal septal mucosa on the left side; Lt. MT: middle turbinate on the left side; C) Skull base reconstruction is performed using a septal flip flap. Photographs are taken 1 week after surgery. Rt. SFF: septal flip flap on the right side; Rt. MT: middle turbinate on the right side; FS: frontal sinus; Rt. MS: maxillary sinus on the right side.

to bilateral resection rather than unilateral resection of the frontal skull base.

3. Centripetal ethmoidectomy: The ethmoid sinus was accessed following the opening of the frontal and sphenoid sinuses. This step completed the comprehensive surgical access required for the procedure.
4. Anterior skull base osteotomy and dural resection: Anterior, lateral, and posterior margins were secured, and anterior skull base osteotomy was performed to achieve thorough access and visualisation. After the dura mater was fully circumferentially exposed, a dural incision was made on the tumour side, and the olfactory tract was dissected as the central margin (Figure 1A).
5. Evaluation of the resection margins: The tumour, middle and superior nasal turbinates on the tumour side, and nasal septal mucosa were excised together. Following tumour excision, the entire circumference of the excised specimen was subjected to frozen section analysis for margin evaluation (Figure 1B, white triangles). A thorough evaluation of the resection margins was conducted to ascertain the extent of tumour removal and the adequacy of the procedure.
6. Skull base reconstruction: Following tumour removal and evaluation of the resection margin, skull base reconstruction was performed. The reconstruction approach involved a multilayered technique utilising a vascularised flap [27]. A septal flip flap pedicled with the contralateral ethmoidal arteries was employed as the flap for reconstruction [28] (Figure 1C).

Post-operative olfactory training

Olfactory training spanned 12 months, commencing 1 week post-operatively. Patients engaged twice daily with four odours as follows: phenyl ethyl alcohol for rose, eucalyptol for eucalyptus, citronellal for lemon, and eugenol for cloves. During training, each patient received four brown glass jars (total volume, 50 mL) containing one odour each (1 mL) held within cotton pads to prevent leakage. All jars were marked with their respective odour names. The patients were instructed to inhale each odour for approximately 10 s, both in the morning and evening. This approach was based on the olfactory training method proposed by Hummel et al. [10]. During each outpatient visit, we inquired about the patients' adherence to the olfactory training regimen.

Olfactory tests

Olfactory testing was performed using the T&T olfactometer test, Open Essence (OE) test, and visual analogue scale (VAS). These tests were performed both pre- and post-operatively at multiple time points: 1 week, 3 months, 6 months, 9 months, and 12 months post-operatively.

1. T&T olfactometer: The T&T olfactometer test (Takasago Industry, Tokyo, Japan) assesses olfaction using five reference odours: β-phenyl ethyl alcohol, cyclotene, isovaleric acid, γ-undecalactone, and skatole. Administered by an independent technician, the odours had eight concentration levels from -2 to 5. For cyclotene, owing to solubility concerns, seven levels were used up to a concentration of four. Nasal insertion and a double press of a button initiated testing from -2, determining the recognition threshold. Averaging

the cognitive thresholds provided a comprehensive assessment of olfactory sensitivity across odours. Olfactory dysfunction severity was defined by T&T odour recognition thresholds (≤1.0, normal; 1.1–2.5, mild hyposmia; 2.6–4.0, moderate hyposmia; 4.1–5.5, severe hyposmia; ≥5.6, anosmia) [29].

2. OE: We used the OE odour identification test cards (Wako Pure Chemical Industries, Osaka, Japan) for odour identification assessment. Designed specifically for the Japanese population, this test kit comprises 12 folded cards sealed with unique glue. On opening the card, the left side contains the microencapsulated test odorants that quickly evaporate upon exposure. Patients chose from six response options, including the correct answer, four alternatives, "detectable but not recognisable," and "no smell detected." The OE test cards offer a swift and comprehensive means of evaluating odour identification skills tailored to the Japanese population. This concise version effectively captures the key aspects of the OE odour identification testing methodology. A score of 8 (67%) or higher on the OE test is considered normal [30].
3. VAS: We conducted a subjective evaluation of the patients' olfactory perceptions using the VAS. The patients rated their sense of smell on a scale from 0 to 100. A score of 0 represented the absence of perception, whereas a score of 100 indicated the strongest olfactory sensation. Patients marked the score on the scale to denote the intensity of their sensations.

This study categorised olfactory dysfunction types as follows: "normosmia" indicated normal or higher olfactory function levels with both the T&T olfactometer and OE tests (T&T odour recognition thresholds ≤1.0 and OE test score of 8 (67%) or higher); "hyposmia" referred to the ability to distinguish only a few odours in either test (T&T odour recognition thresholds 1.1–5.5 or OE test score of 1–7 (8–58%)); and "anosmia" represented the inability to perceive any odours with both tests (T&T odour recognition thresholds ≥5.6 and OE test score of 0 (0%)).

Evaluation items

We extracted data on patient age, sex, medical history, post-operative Hyams grade, Kadish classification, resection margin assessment, outcomes, follow-up duration, and olfactory test outcomes.

Grouping

The patients were categorised into two distinct groups based on their exposure to post-operative olfactory training at the institution.

1. Training intervention group: This group comprised patients who underwent surgery between January 2022 and December 2022 and received post-operative olfactory training.
2. Non-intervention group: This group included patients who underwent surgery between July 2018 and December 2021 but did not receive post-operative olfactory training.

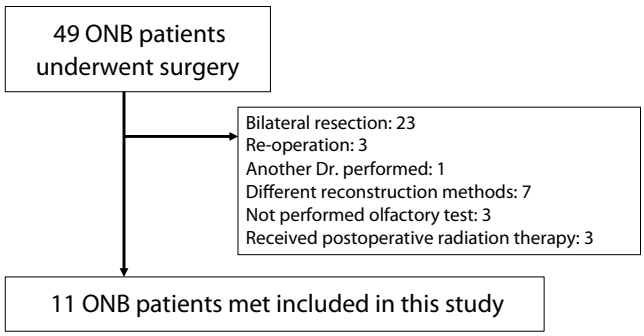

Figure 2. Flowchart of patient inclusion and exclusion. This figure illustrates the flow of patients throughout the study, including the number of patients initially considered, excluded, and included in the final analysis.

Outcome

The primary endpoint was the preservation of the sense of smell in any of the post-operative olfactory tests within a 1-year observation period after surgery. If the sense of smell was preserved, the level of olfaction at the best perceived point during that period was extracted. Additionally, the percentage of olfactory dysfunction types was compared between the training intervention and non-intervention groups.

Statistical analysis

Descriptive statistics, including means and standard errors, were used to summarise clinical data. Non-parametric equivalence values were used to compare the pre- and post-training olfaction test scores. The qualitative variables were described using frequency (%) and were compared using the chi-square test or Fisher's exact test. All data analyses were conducted using GraphPad Prism 8 software (GraphPad Software, Inc., La Jolla, CA, USA), and statistical significance was set at $p < 0.05$.

Results

Demographic characteristics and group comparison

Eleven patients were included in this study. Details of the excluded patients are presented in Figure 2. The demographic and clinical characteristics of the 11 patients are shown in Table 1. The average age of the patients was 52 years, with one patient classified as grade 1, nine patients as grade 2, and one patient as grade 3, according to Hyams grading. Ten patients were classified as Kadish A, and one patient was classified as Kadish B. One patient died during the study period owing to a cause unrelated to the disease. The mean follow-up duration for all patients was

Table 1. Patient characteristics (n = 11).

No.	Age	Sex	Smoking	Medical history	Hyams grading	Kadish stage	Resection margin	Status	Follow-up (month)
1	59	F	-	-	2	A	-	ANED	43
2	67	M	+	DM	2	A	-	ANED	40
3	39	M	-	-	3	A	-	ANED	36
4	41	M	-	-	1	B	-	ANED	45
5	55	F	-	-	2	A	-	ANED	24
6	71	M	-	HF	2	A	-	ANED	60
7	53	M	-	HT	2	A	-	DOC	6
8	50	M	-	-	2	A	-	ANED	18
9	55	M	-	-	2	A	-	ANED	18
10	40	F	-	-	2	A	-	ANED	18
11	37	F	-	-	2	A	-	ANED	12

DM: diabetes mellitus, HT: hypertension, HF: heart failure, ANED: alive with no evidence of disease, DOC: dead of other causes. - : None. + : history of use.

29 months. All participants reported that they were following the olfactory training regimen diligently.

Pre-operative olfactory levels

The training intervention group and non-intervention group consisted of five and six patients, respectively. The mean age was 47 years in the training intervention group and 55 years in the non-intervention group; there was no statistically significant difference in age between the two groups ($p = 0.19$). Additionally, no significant differences were observed in the Hyams grading and Kadish stage between the two groups. The follow-up duration was 14 ± 2 months for the intervention group and 41 ± 5 months for the non-intervention group (Table 2).

All cases in the pre-operative olfactory assessments were classified as normosmia, and no significant differences were found between the two groups (Table 2). The T&T olfactometer scores were 1.5 ± 0.8 and 2.5 ± 1.0 in the training intervention and non-intervention groups, respectively ($p = 0.23$). OE scores were 81 ± 2% and 71 ± 29% in the training intervention and non-intervention groups, respectively ($p > 0.99$). VAS scores were 85 ± 12 and 79 ± 17 in the training intervention and non-intervention groups, respectively ($p = 0.83$).

Post-operative olfactory changes

One week post-operatively, hyposmia and anosmia were reported in 20% and 80% of patients in the intervention group, respectively, compared with 0% and 100% of patients in the non-intervention group, respectively; there was no significant difference between the two groups (Table 2). The mean T&T olfactometer scores were 5.6 ± 0.2 and 5.8 ± 0.0 in the training intervention and non-intervention groups, respectively ($p > 0.99$); OE scores were 8 ± 5% and 0 ± 0% in the training intervention and non-intervention groups, respectively ($p = 0.44$); VAS scores were 1 ± 1 and 1 ± 1 in the training intervention and non-intervention groups, respectively ($p > 0.99$).

One year after surgery, the hyposmia and anosmia rates were 100% and 0% in the intervention group, respectively, compared with 17% and 83% in the non-intervention group, respectively ($p = 0.02$, Table 2). This reveals that all patients in the intervention group had preserved partial olfactory function, contrasting with a 17% improvement in the non-intervention group. Significant differences were observed in post-operative olfactory test scores between the two groups. The mean T&T olfactometer scores were 4.8 ± 0.4 and 5.8 ± 0.0 in the training intervention and non-intervention groups, respectively ($p = 0.02$). The mean OE scores were 40 ± 7% and 3 ± 3% in the training intervention and non-intervention groups, respectively ($p = 0.004$). The mean VAS scores were 17 ± 2 and 2 ± 1 in the training intervention and non-intervention groups, respectively ($p = 0.004$).

Figure 3 shows the changes in olfactory levels in patients who underwent post-operative olfactory training during the first year after surgery. Post-operatively, patients' overall olfactory function was significantly reduced compared with pre-operative levels. Unfortunately, patient 7 developed a putaminal haemorrhage at 6 months post-operatively and did not survive; therefore, olfactory data collection for this patient was prematurely terminated at 3 months post-operatively. Four patients exhibited improved olfactory perception within the initial 3 months, whereas patient 10 demonstrated improvement at 9 months. Patients 8 and 9 demonstrated improved post-operative olfaction but contracted coronavirus disease 2019 (COVID-19) at 6 months post-operatively, thus resulting in a subsequent decline in olfactory levels.

Table 2. Comparison of pre- and post-operative olfactory levels between training intervention and non-intervention groups.

	Post-Operative Olfactory Training		
	Training Intervention Group	Non-Intervention Group	p-value
Case (n)	5	6	
Age	47 ± 4	55 ± 5	0.19
Sex (M:F)	3:2	4:2	>0.99
Kadish stage n (%)			>0.99
A	5 (100)	5 (83)	
B	0 (0)	1 (17)	
Hyams grade n (%)			>0.99
Low (I/II)	5 (100)	5 (83)	
High (III/IV)	0 (0)	1 (17)	
Follow-up period (M)	14 ± 2	41 ± 5	0.004 *
Pre-Operative Olfaction Levels			
Olfactory dysfunction types n (%)			
Normosmia	5 (100)	6 (100)	
Hyposmia	0 (0)	0 (0)	
Anosmia	0 (0)	0 (0)	
Olfactory tests			
T&T Olfactometer	1.5 ± 0.8	2.5 ± 1.0	0.23
OE (%)	81 ± 2	71 ± 29	>0.99
VAS (%)	85 ± 12	79 ± 17	0.83
Post-Operative Olfaction Levels (After 1 Week)			
Olfactory dysfunction types n (%)			0.46
Normosmia	0 (0)	0 (0)	
Hyposmia	1 (20)	0 (0)	
Anosmia	4 (80)	6 (100)	
Olfactory tests			
T&T Olfactometer	5.6 ± 0.2	5.8 ± 0	>0.99
OE (%)	8 ± 5	0 ± 0	0.44
VAS (%)	1 ± 1	1 ± 1	>0.99
Post-Operative Olfaction Levels (After 12 Months)			
Olfactory dysfunction types n (%)			0.02 *
Normosmia	0 (0)	0 (0)	
Hyposmia	5 (100)	1 (17)	
Anosmia	0 (0)	5 (83)	
Olfactory tests			
T&T Olfactometer	4.8 ± 0.4	5.8 ± 0	0.02 *
OE (%)	40 ± 7	3 ± 3	0.004 *
VAS (%)	17 ± 2	2 ± 1	0.004 *

Statistical significance is denoted by * ($p < 0.05$). Statistical comparison using the Mann–Whitney U test. The qualitative variables were compared using chi-square or Fisher's exact test. Data are presented as mean ± standard error. VAS: visual analogue scale, OE: Open Essence test.

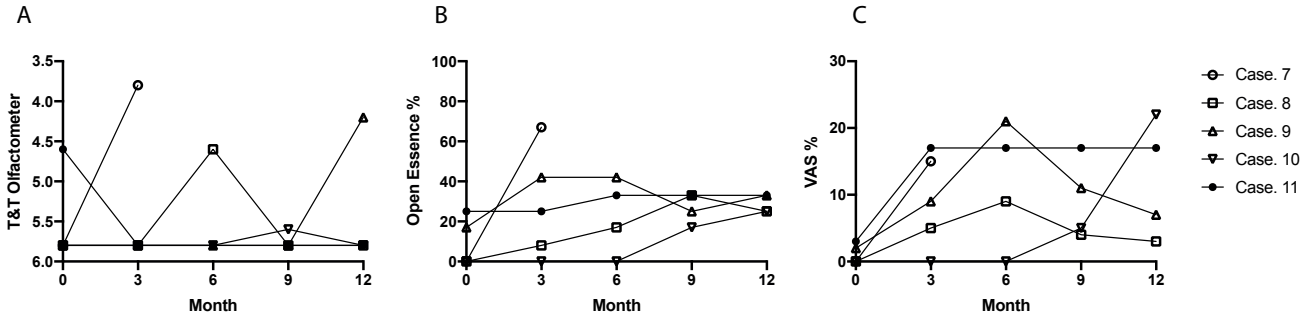

Figure 3. Change in olfactory levels over time after post-operative olfactory training. A) T&T olfactometer results for each case. B) Open Essence test results for each case. C) Visual analogue scale scores for each case.

Discussion

Here, we present the outcomes of our retrospective cohort study focusing on the effectiveness of post-operative olfactory training in patients who underwent unilateral cranial resection for ONB. Notably, a substantial disparity in post-operative olfactory outcomes was observed between the training intervention and non-intervention groups. The training intervention group displayed partial olfactory preservation in all cases, whereas the non-intervention group exhibited a preservation rate of only 17%. Furthermore, more significant enhancements in olfactory test scores were evident in the training intervention group than in the non-intervention group.

The primary strength of this study is its pioneering contribution to the management of ONB-related olfactory dysfunction, as it is the first to explore the potential benefits of post-operative olfactory training in this unique patient population. Our findings suggest that olfactory training may serve as an effective management strategy, offering a promising preservation rate and improved post-operative olfactory test outcomes. This is particularly noteworthy given the limited options for addressing post-operative olfactory dysfunction in patients with ONB.

Our results are consistent with those of broader studies that have demonstrated the effectiveness of olfactory training in patients with olfactory impairment [10-18]. Olfactory training interventions have been associated with structural improvements in olfactory-related brain regions, including the olfactory bulb and various cortical areas [31, 32]. This suggests that if surgical procedures preserve olfactory pathways, such as the olfactory bulb and olfactory epithelium, olfactory training can effectively stimulate these regions. Olfaction is important in our daily lives, influencing our ability to detect hazards, appreciate food, and affect our emotional and sexual functions [33]. Given the critical role of olfaction, preserving it during endonasal skull base surgery, such as ONB, is of paramount importance [9].

Our study also revealed that olfactory training interventions may preserve the sense of smell while simultaneously reducing the overall level of olfactory perception. This outcome is consistent with the findings of Tajudeen et al., who reported varying post-operative olfactory outcomes in patients with ONB. Results ranged from a nearly normal sense of smell in 14% of patients to a reduced or lost sense of smell in 86% of patients [5]. Possible contributors to these outcomes include surgical invasiveness, decreased odour molecule input owing to structural changes, and potential blood flow alterations related to anaesthesia with epinephrine and electrocoagulation incisions. Fortunately, there were no indications of post-operative flap necrosis or pressure ulcer adhesions, and blood flow to the olfactory epithelium was not compromised. Although these results may indicate that the involvement of the olfactory nerve in surgical procedures is a plausible cause of post-operative olfactory loss, they may also suggest that olfactory training promotes plasticity of the olfactory mucosa and brain, improving olfactory function.

The ideal duration of olfactory training, the most effective number of odorants, and the specific patient population that would benefit most remain areas of uncertainty [11]. Existing literature has suggested that 12 weeks of olfactory training can be effective [13, 14], whereas longer-term training spanning 56 weeks may yield superior results, especially in patients with olfactory loss [16]. In our study, we observed varying response times among patients undergoing olfactory training. These results highlight the potential efficacy of continuous olfactory training for enhancing the sense of smell in post-operative patients. Further research is crucial for defining the optimal parameters for olfactory training in this unique patient population, potentially enhancing its clinical applicability and effectiveness.

Despite these intriguing findings, our study had some limitations. One limitation of this study is the differing follow-up periods between the intervention and non-intervention groups. The non-intervention group had a significantly longer follow-up period (41 ± 5 months) than the intervention group (14 ± 2 months). Given that the non-intervention procedures were performed earlier in the surgical learning curve, variations in surgical proficiency over time may have affected the results. Additionally, this study did not collect olfaction data beyond one year; therefore, long-term trends in olfaction levels in the intervention group remain a topic for future research. Lastly,

the effect of external factors, such as COVID-19 and radiation therapy, on olfactory outcomes was not studied and requires further investigation.

Conclusion

Our study suggests the potential benefits of post-operative olfactory training in improving olfactory dysfunction after surgery for patients who underwent unilateral resection of ONB. Given the limited number of patients and the preliminary nature of our findings, the results should be interpreted with caution. Olfactory training may play a valuable role in the comprehensive care of patients with ONB. However, further extensive research with larger patient cohorts and longer follow-up periods is necessary to validate these initial observations.

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Authorship contribution

Conceptualisation of this study, data analysis, and writing the original draft: TT. Editing of the manuscript: SA, RM, YI, EM, HN, TE, KT, AJK, BDT, BAS. Final review and editing of the manuscript: KO, NO.

Conflict of interest

The authors have no conflicts of interest to declare.

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