Received: 10 October 2024 | Revised: 23 November 2024 | Accepted: 26 November 2024

DOI: 10.1002/alr.23502

IFAR: International Forum of Allergy & Rhinology

REVIEW ARTICLE

Ectopic olfactory neuroblastoma is associated with increased frequency of syndrome of inappropriate antidiuretic hormone secretion and reduced disease control: Case series with systematic review and pooled analysis

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Abstract

Introduction: Olfactory neuroblastoma (ONB) is a rare malignant tumor originating from the olfactory neuroepithelium, typically within the sinonasal cavity. Cases of ONB originating outside of the olfactory cleft area are extremely rare and are referred to as "ectopic" (eONB), in contrast to "orthotopic" tumors (oONB). ONB has been associated with paraneoplastic syndromes (PNSs), including the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This

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study investigate the association between eONB and SIADH and compared the prognosis of eONB to oONB.

Methods: A systematic literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted, focusing on studies reporting eONB and oONB associated with SIADH. Data from four newly identified eONB cases were reported and a pooled analysis was performed. Statistical analyses were conducted to evaluate the prevalence of SIADH in eONB and oONB and to compare clinical outcomes in the two groups.

Results: eONB had a significantly higher prevalence of SIADH (18.3%) compared to oONB (2.0%; $p < 0.0001$). Patients with eONB were younger, with a slight predominance of females. Recurrence-free survival and time-to-recurrence of eONB were worse than oONB, independently of other prognosticators.

Conclusions: eONB is associated with a significantly higher incidence of SIADH than oONB, suggesting distinct biological characteristics. Moreover, patients with eONB had worse prognostic outcomes. Further research is needed to understand the underlying mechanisms and improve management strategies for eONB.

KEYWORDS

esthesioneuroblastoma, olfactory neuroblastoma, paraneoplastic syndrome, Schwartz–Bartter syndrome, sinonasal cancer, sinonasal tumor, skull base cancer, skull base tumor, syndrome of inappropriate antidiuretic hormone secretion, vasopressin

1 | INTRODUCTION

Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, is a rare malignant tumor that arises from the olfactory neuroepithelium within the sinonasal cavity. It was initially identified by Berger et al.[1] and accounts for approximately 3% of intranasal tumors and 5% of malignant nasal and paranasal sinus tumors.[2–4] Once believed to peak in the second and sixth decades of life, ONB is currently known to display a unimodal distribution in terms of age at diagnosis, frequently occurring in the fifth to sixth decades of life.[5] Moreover, no gender predisposition has been associated with this tumor.[6] ONB is often misidentified due to its nonspecific clinical presentation, which commonly includes nasal obstruction and epistaxis.[7] Less frequent symptoms such as headache, tingling sensations, and loss of vision may lead to delayed or incorrect diagnoses, with an impact on prognosis.[8] The tumor is thought to arise from the olfactory neuroepithelium, which lines the uppermost part of the nasal septum, the horizontal portion of the cribriform plate, and the upper and medial surface of middle and superior turbinates.[2,6] Basal cells and olfactory sensory neurons have been surmised as the potential cells of origin of ONB.[9] Cases of ONB originating outside the olfactory cleft area are extremely rare and are referred to as "ectopic" (eONB), in contrast to "orthotopic" tumors (oONB). The first reported instance of eONB dates to 1955[10] and subsequent cases have been documented in the literature.[11,12]

Moreover, ONB has been associated with paraneoplastic syndromes (PNSs), including the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and adrenocorticotropic hormone (ACTH) or Cushing's syndrome, as well as neurologic PNS.[13]

Due to its rarity, current understanding of the clinical presentation and characteristics of PNS associated with eONB remains limited. This study presents four new cases of eONB alongside with a systematic review of the literature under the hypothesis that eONB is associated with an increased incidence of SIADH compared to oONB. In addition, we analyzed pooled data to investigate the prognosis of eONB and oONB.

2 | MATERIALS AND METHODS

2.1 | Protocol registration

The protocol of this systematic review and meta-analysis was registered on PROSPERO,[14] an international database of prospectively registered systematic reviews in health and social care (Center for Reviews and Dissemination,

University of York, York, UK) in April 2024 with registry number CRD42024535483.

2.2 | Search strategy

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[15] The electronic databases Scopus, PubMed, and Embase were searched from database inception to May 10, 2024. A combination of MeSH terms and free-text words were utilized to search for: "olfactory neuroblastoma" or "esthesioneuroblastoma," and "ectopic," "maxillary," "ethmoid," "sphenoid," "sphenoclival," "sellar," and "nasopharynx" (Supporting Information A). The reference lists of all the included articles were thoroughly screened to find other relevant studies. References were exported to Zotero bibliography manager (v6.0.10, Center for History and New Media, George Mason University). After removal of duplicates, two reviewers (A.D. and M.F.) independently screened all titles and abstracts and then evaluated the full texts of eligible articles based on the inclusion criteria. Any disagreement between the reviewers involved in the literature search was resolved through discussion with all authors to reach a consensus.

2.3 | Selection criteria

The following articles were included in the systematic review:

- Articles on eONB, whether (eONB-SIADH$^+$) or not (eONB-SIADH$^-$) associated with SIADH.
- Articles on oONB with SIADH (oONB-SIADH$^+$).

ONB was considered orthotopic when the extracranial portion of the tumor was centered on the olfactory cleft. Any origin outside the olfactory cleft, including lower nasal cavity, paranasal sinuses, and non-sinonasal sites was considered ectopic. Ethmoidal ectopic origin was defined only when the ipsilateral olfactory cleft was clearly uninvolved. ONB with both olfactory cleft and ethmoidal involvement were considered as orthotopic tumors extending to the ethmoidal complex.

Exclusion criteria were as follows: (1) inaccessibility to full text; (2) articles with unclear primary tumor attachment and/or unclear PNS; (3) lack of relevant clinicopathological data; (4) non-original studies (i.e., letters, congress abstract, editorials, or book chapters); (5) animal model studies; and (6) non-English studies. The papers were thoroughly screened for duplicates.

2.4 | Data extraction and quality assessment

Extracted data were collected in an electronic database including first author, year of publication, country of origin, patient age, sex, primary attachment site, Hyams grading,[16] Kadish-INSICA[17] staging, management, initial clinical presentation, evaluation of SIADH after treatment, follow-up, and status at latest evaluation. The quality of the studies eligible for inclusion was categorized as poor, fair or good, in agreement with the National Institutes of Health quality assessment tool for Observational Cohorts and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, accessed on May 10, 2024).[18] Two reviewers (A.D. and M.F.) independently evaluated the papers, and any disagreement was resolved by discussion.

With institutional review board approval (codes: 433n/AO/23, NP3616, and RCR04-0636 for "Azienda Ospedale-Università Padova," "Spedali Civili Brescia," and "MD Anderson Cancer Center," respectively), a retrospective chart review of patients with eONB treated at three tertiary academic centers (University of Padova, University of Brescia, The University of Texas MD Anderson Cancer Center) in the 2021–2024 period was performed.

2.5 | Statistical analysis

The primary objective of this study was to evaluate whether the rate of SIADH differs significantly between eONB and oONB. In absence of a comprehensive reference for the total number of oONB cases, the prevalence of SIADH in oONB was obtained with the following three methods:

- Referring to the estimate reported by Gabbay et al.[19];
- Measuring the rate of oONB-SIADH$^+$ in the "MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers" (MUSES) Brescia-Paris-Varese dataset[20–22];
- Calculating the proportion between oONB-SIADH$^+$ (from this systematic review) and overall number of cases of ONB, measured as the largest calculated sample size among the 10 most recent PRISMA-based systematic reviews published in the English literature.[23–32]

Adoption of the numerosity of the afore-mentioned articles[19,23–32] as approximation of the overall oONB population was based upon the assumption that all ONB cases included were orthotopic. Anonymized single-patient information on oONB without SIADH (oONB-SIADH$^-$) cases were extracted from the MUSES database[20–22] to

compare clinicopathological information between the different ONB groups.

Statistical analyses were performed using XLSTAT (add-on for Microsoft Excel, version 2021.4.1, Addinsoft SARL) and RStudio (version 4.3.1, https://www.rstudio.com/). Descriptive statistics for continuous variables were presented as median (95% confidence interval [95% CI]). Differences in continuous variables were assessed using the Mann–Whitney *U*-test. Chi-square or Fisher's exact test was used to test for association between categorical variables, as appropriate. The following time-to-event prognostic outcomes were analyzed: (1) overall survival (OS), considering the death of any cause as event and patients alive at the latest evaluation as censors; (2) recurrence-free survival (RFS), considering recurrence of disease and death of any cause as events and patients who were disease-free and alive at the latest evaluation as censors; (3) time-to-recurrence (TTR), considering recurrence of disease as event and disease-free patients (either alive or dead) as censors; (4) disease-specific survival (DSS), considering the death due to the disease as event and patients alive at the latest evaluation or dead of other cause as censors. OS, RFS, TTR, and DSS were evaluated with the Kaplan–Meier method and the log-rank test was employed to test for relevant prognosticators. A multivariable Cox proportional hazards model with a priori selection of covariates was used to check for independent prognostic effects.

To check for trends in outcomes over time, a maximally selected rank statistics was run and the cutoff year of publication determining the best stratification of OS was identified. A subgroup of patients was selected by excluding cases published before the aforesaid cutoff year of publication and those from studies defined of "low quality" as per criteria reported above.[18] Prognostic analyses were repeated on this subgroup.

A multivariable model including only eONB cases was built in order to quantify the protective effect of the treatment pattern (non-surgical vs. surgery alone vs. surgery followed by adjuvant radiotherapy [RT]).

The results are expressed as *p*-value and hazard ratio (HR) with 95% CI. Statistical significance was defined at 0.05.

3 | RESULTS

3.1 | Padova–Brescia–Houston series of eONB

In the Padova–Brescia–Houston series, four cases of eONB-SIADH$^+$ were identified. A detailed description of these cases is reported in Supporting Information B.

Brief summary of cases:

- Case #1: A 20-year-old woman with SIADH (severe hyponatremia) and a right ethmoidal mass, successfully treated with endoscopic resection; disease-free and asymptomatic 37 months after surgery (Figure 1A).
- Case #2: A 43-year-old woman with SIADH (history of prolonged hyponatremia) and a right nasal cavity mass. She was treated with endoscopic resection and adjuvant RT, which was recently completed (Figure 1B).
- Case #3: A 25-year-old woman with a small right nasal mass and history of seizures due to SIADH (severe hyponatremia). After partial removal in another institution, complete surgical resection led to full recovery from SIADH, with no recurrence after 6 months (Figure 1C).
- Case #4: A 34-year-old woman with SIADH determining a profound hyponatremia that was difficult to control. Complete tumor resection, which was recently performed, achieved a reversal of her SIADH and a return of serum sodium to normal levels (Figure 1D).

3.2 | Systematic review

3.2.1 | Search results and quality assessment

A total of 3783 titles were collected from the literature search. After removal of duplicates and exclusion of 1985 records, 126 articles relevant to the topic were examined. Two studies were unavailable for retrieving. After including additional 14 articles identified from citation searching, 98 were included in the present review: 13 studies in the eONB-SIADH$^+$ group,[10,33–44] 56 in the eONB-SIADH$^-$ group,[10–12,45–97] and 30 studies in the oONB-SIADH$^+$ group.[19,98–126] A detailed PRISMA flowchart of the search process is shown in Figure 2.[15] One study reported on three cases and was included in both the eONB-SIADH$^+$ and eONB-SIADH$^-$ groups.[11]

In accordance with the National Institute of Health Quality Assessment Tool for Observational Cohorts and Cross-Sectional Studies,[18] 18 (18.4%) studies were deemed of *good* quality, 57 (58.2%) as *fair*, and 23 (23.4%) as *poor* due to the lack of clinical details (Supporting Information C).

3.2.2 | Series description and differences among groups

All the studies included had adequate relevance to the subject of this systematic review. None were randomized controlled trials or prospective studies and all the papers included were case reports and

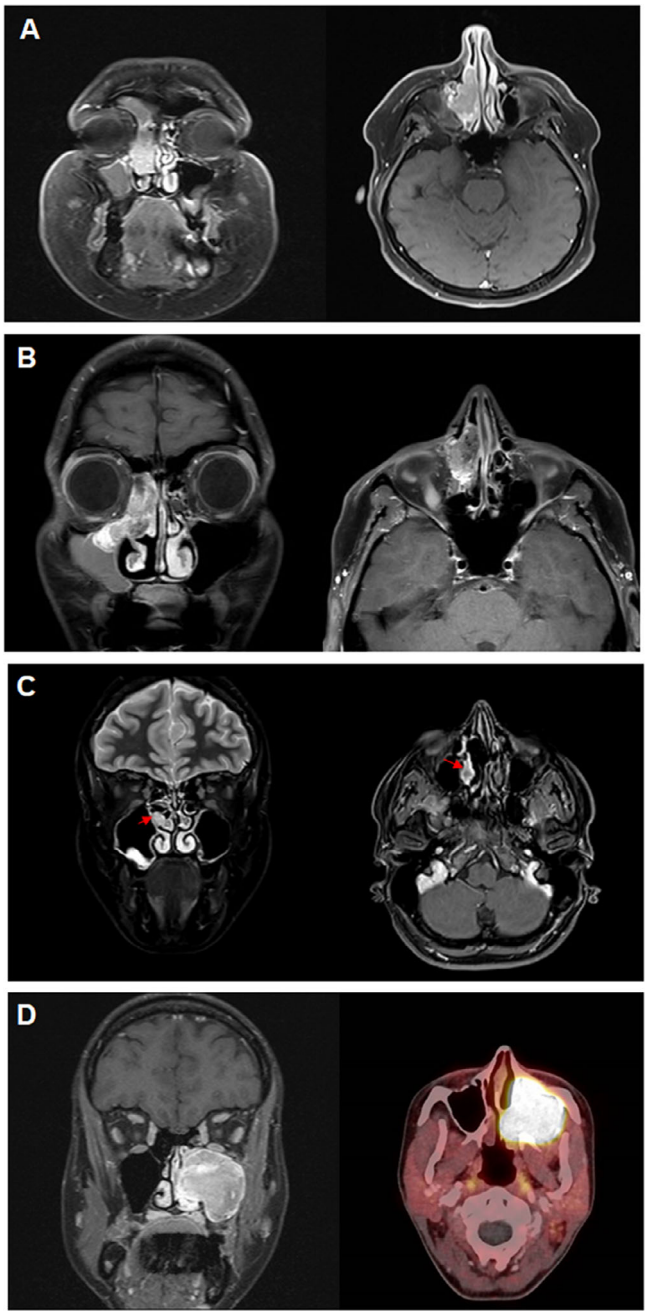

FIGURE 1 (A) Case 1: contrast-enhanced magnetic resonance imaging (MRI) scan (T1 coronal and axial) shows an hyperenhancing lesion centered on the right ostiomeatal complex, with no relation to the skull base and olfactory fissure. (B) Case 2: contrast-enhanced MRI scan (T1 coronal and axial) shows an hyperenhancing lesion centered on the right lacrimal bone, with no relation to the skull base and olfactory fissure. (C) Case 3: contrast-enhanced MRI scan (coronal, STIR, and axial, T1) acquired before incomplete resection of the tumor performed elsewhere shows an hyperenhancing lesion (arrows) centered in posterior portion of the right ostiomeatal complex, with no relation to the skull base and olfactory fissure. (D) Case 4: T1 coronal contrast-enhanced MRI scan and axial ^{68}Ga-DOTATOC PET-CT show a lesion centered in the left maxillary sinus, with no relation to the skull base and olfactory fissure.

case series. Studies were published between 1955 and 2024.

The total number of patients was 17, 76, and 39 in the eONB-SIADH$^+$, eONB-SIADH$^-$, and oONB-SIADH$^+$ groups, respectively. From the MUSES database,[20–22] 107 oONB with sufficient information to establish the presence or absence of SIADH were extracted; all were oONB-SIADH$^-$. Median age was 27.5 (range 11–79), 43 (range 11–89), 36 (range 17–61), and 52 years (range 13–80), respectively, with significant differences between groups ($p < 0.001$, Figure 3). No significant differences were found in sex ($p = 0.064$), although females were noticeably more frequent in the eONB-SIADH$^+$ group (70.6%) and slightly more prevalent in the oONB-SIADH$^+$ group (56.8%). A balanced male-to-female ratio was observed in the other groups.

The distribution of tumor epicenter for eONB is summarized in Table 1. The most common attachment site was the maxillary sinus (26/93, 27.9%) when both eONB subgroups were considered together, whereas it was the maxillary sinus (11/17, 64.6%) and sphenoid sinus (22/76, 28.9%) for eONB-SIADH$^+$ and eONB-SIADH$^-$ considered separately, respectively.

Kadish-INSICA stage is reported in Table 1. The most typical stage was Kadish-INSICA B and no significant differences was observed between groups ($p = 0.065$). When analyzing Hyams grade, grade I was the most represented in eONB-SIADH$^+$ (8/14, 57.1%), grade II in eONB-SIADH$^-$ (10/26, 38.5%) and oONB-SIADH$^-$ (42/78, 53.8%), and grade III in oONB-SIADH$^+$ (7/17, 41.2%) ($p < 0.001$).

Treatment modality is detailed in Table 1. Briefly, the proportion of patients treated with surgery and adjuvant (chemo)RT was significantly higher in the oONB-SIADH$^-$ group (81.3%, $p < 0.001$) compared to other groups, in which the frequency of surgery alone (31%–41%), surgery with adjuvant (chemo)RT (33%–54%), and definitive non-surgical treatment (6%–10%) was similar.

Margin status was available for 21/100 (21.0%) patients who underwent surgery, of whom 9/16 (56.3%), 9/51 (17.6%), and 3/33 (9.1%) affected by eONB-SIADH$^+$, eONB-SIADH$^-$, and oONB-SIADH$^+$, respectively. The rate of positive margins in patients with available margin status was 33.3%, 33.3%, and 33.3%, respectively. The rate of positive margins in oONB-SIADH$^-$ patients from the MUSES[20–22] was 17/106 (16.0%).

After surgery, PNS resolved in 15 (88.2%) patients of the eONB-SIADH$^+$ group. In one patient SIADH persisted after surgery, whereas in one study there was no information in this regard. In oONB-SIADH$^+$, complete PNS remission was observed in 31 (79.6%) patients, four (10.2%) had persistent SIADH, and for four (10.2%) no inherent data were available ($p = 0.761$).

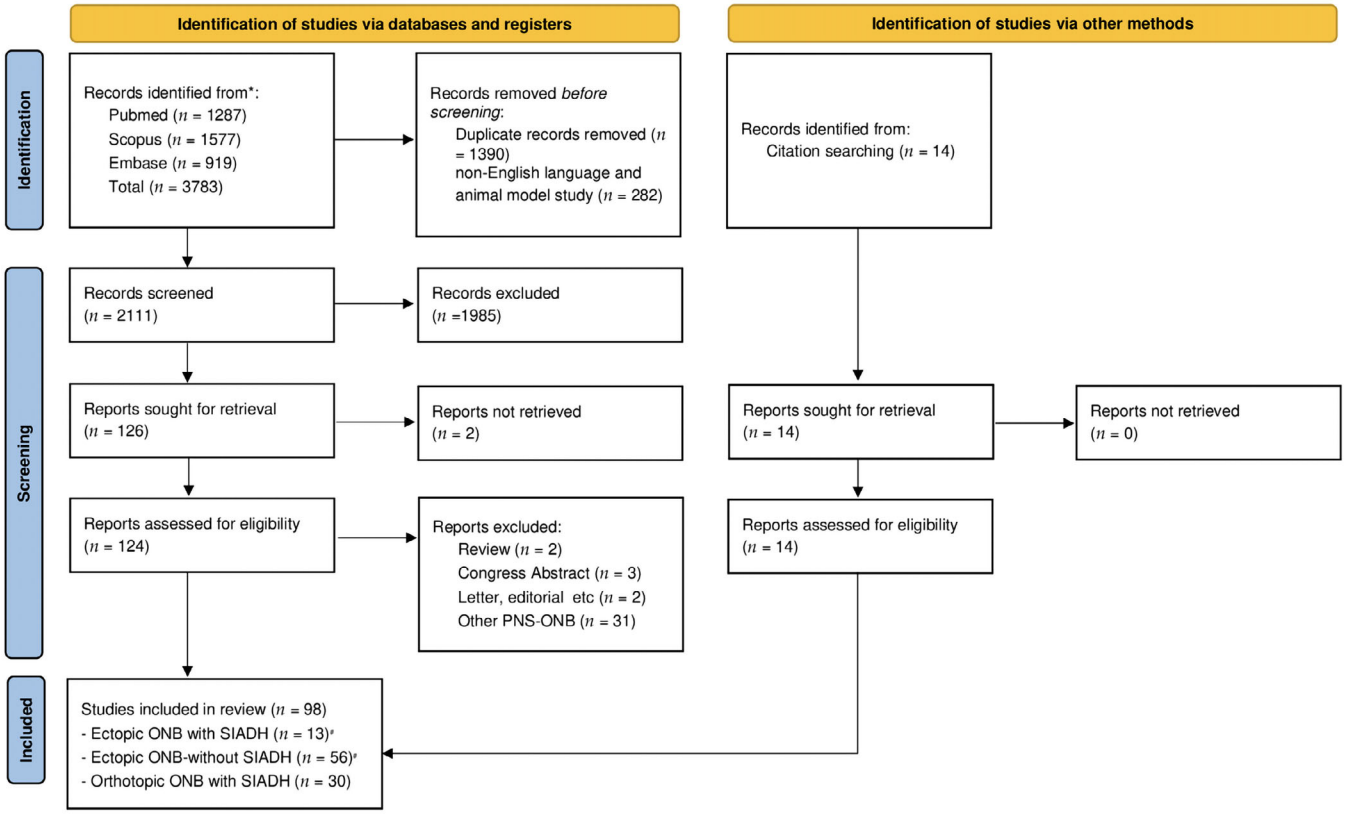

FIGURE 2 PRISMA[15] diagram resembling electronic database search and inclusion/exclusion process of the review. Legend: *Date of last search May 10, 2024. #One study has patients included in both groups.

Raw data on patient demographics, tumor features, clinical presentation, and outcomes are reported in Tables 2, 3, 4 for the eONB-SIADH$^+$, eONB-SIADH$^-$, and oONB-SIADH$^+$ groups, respectively.

3.2.3 | Prevalence of SIADH in ectopic versus orthotopic ONB

The prevalence of SIADH at presentation in eONB was 17/93 (18.3%; 95% CI: 10.9–26.8). Compared to the estimated proportion reported by Gabbay et al.[19] in ONB (26/1300, 2.0%; 95% CI: 1.2–2.8), the difference was statistically significant ($p < 0.0001$). Among the 10 most recent PRISMA-based systematic reviews on ONB,[23–32] that by Henson et al.[28] had the largest sample size (1829 patients). Using the Henson et al. population[28] as a reference and considering the cases of oONB-SIADH$^+$ identified in the present study (39 patients), the proportion was 2.1% (39/1829; 95% CI: 1.5–2.9), which is significantly different to the prevalence in eONB ($p < 0.0001$). Considering the MUSES dataset as reference,[20–22] there were no oONB-SIADH$^+$ (0/107, 0.0%; 95% CI: 0.0–3.6), which is significantly different to the measured prevalence in eONB ($p < 0.0001$).

3.2.4 | Association between clinicopathological variables and ONB prognosis in the four groups

Five-year OS for oONB-SIADH$^+$, oONB-SIADH$^-$, eONB-SIADH$^+$, and eONB-SIADH$^-$ were 100.0%, 93.6%, 87.5%, and 77.2% ($p = 0.040$), respectively; 5-year DSS were 100.0%, 95.8%, 100.0%, and 80.0% ($p = 0.020$), RFS 79.2%, 80.3%, 50.0%, and 47.9% ($p = 0.003$), and TTR 100.0%, 83.9%, 75.0%, and 66.8% ($p = 0.058$), respectively (Table 5). The presence of SIADH irrespective of orthotopic versus ectopic localization was not associated with prognosis ($p = 0.353$). The Kaplan–Meier curves are shown in Figure 4.

The results of multivariable analysis are presented in Table 6. Of note, eONB were associated with significantly worse RFS and TTR compared to oONB (HR = 3.36, $p = 0.002$; HR = 3.81, $p = 0.004$, respectively), independently of age, grade, stage, and treatment.

Maximally selected rank statistics identified 2003 as the cutoff publication year that best segregates OS (Figure S1). Considering the entire cohort, 146 patients (61.1%) underwent an endoscopic approach and 60 (25.1%) an open approach. Among patients treated before 2003, 12 (32.4%) underwent an endoscopic approach and 18 (48.7%) an open approach, whereas among patients treated from 2003

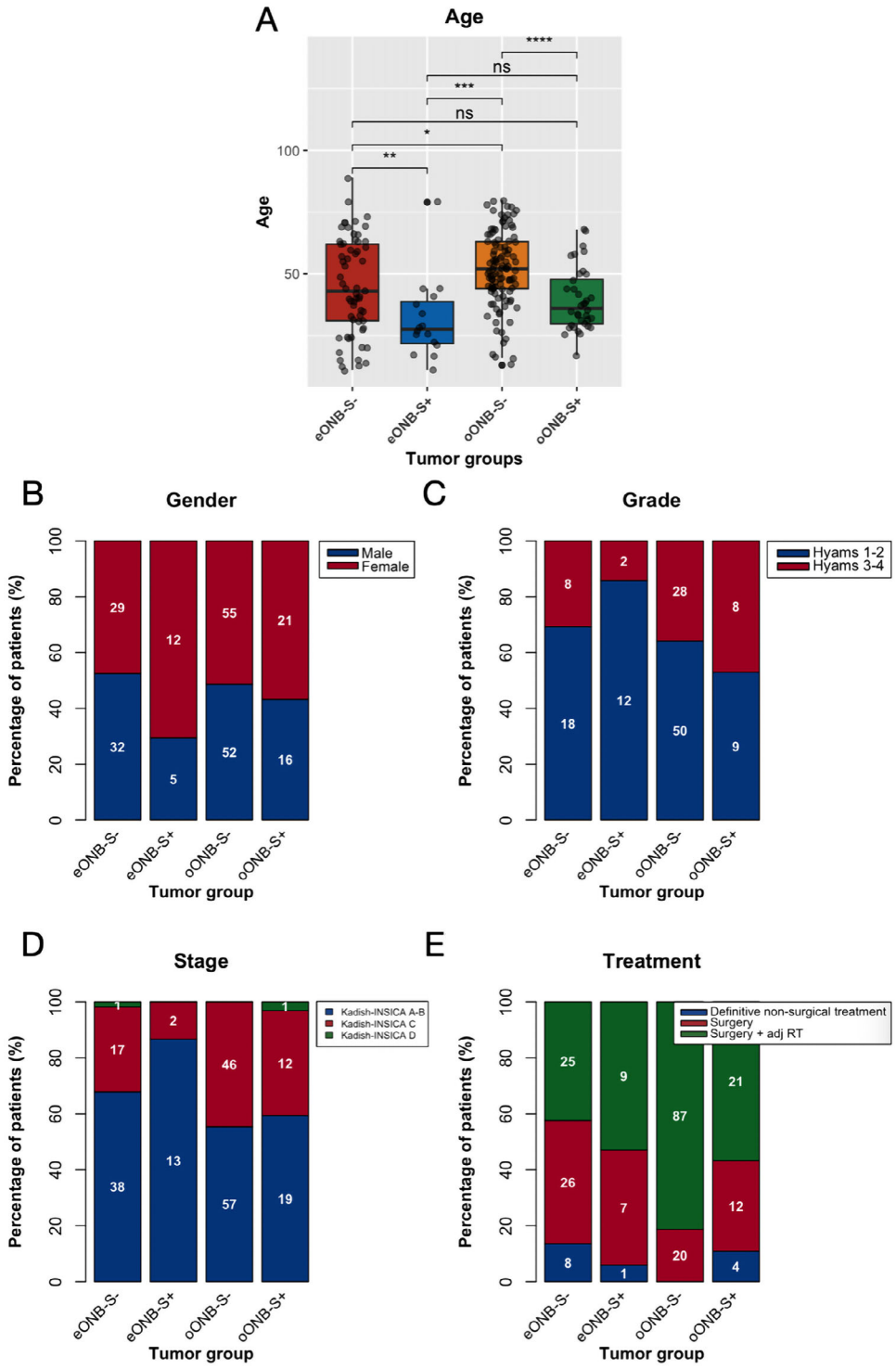

FIGURE 3 Comparison of clinical features across tumor groups. (A) Boxplot illustrating age differences across tumor groups; (B) barplot showing the gender distribution across tumor groups (ns, not significant difference; *, $p<0.05$; **, $p<0.01$; ***, $p<001$; ****, $p<0.0001$); (C) barplot depicting the distribution of Hyams grades across tumor groups; (D) barplot comparing the Kadish-INSICA stage distribution among tumor groups; (E) barplot comparing the treatment modalities across tumor groups.

TABLE 1 Summary of clinicopathological information of the studies included.

	Orthotopic SIADH-ONB, *N* (IQR)	Orthotopic non-SIADH-ONB, *N* (IQR)	Ectopic SIADH-ONB, *N* (IQR)	Ectopic non-SIADH-ONB, *N* (IQR)	*p*-value
Age (median)	36.0 (29.7–47.7)	52.0 (43.7–63.0)	27.5 (21.7–38.8)	43.0 (31.0–62.0)	**<0.001**
Gender					
Male	16 (41.0%)	52 (48.6%)	5 (29.4%)	32 (42.1%)	0.064
Female	21 (53.9%)	55 (51.4%)	12 (70.6%)	29 (38.2%)	
Not available	2 (5.1%)	0 (0.0%)	0 (0.0%)	15 (19.7%)	
Kadish-INSICA stage					
A–B	19 (48.7%)	57 (53.3%)	13 (76.4%)	38 (50.0%)	0.065
C	12 (30.8%)	46 (43.0%)	2 (11.8%)	17 (22.4%)	
D	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
Not available	7 (17.9%)	4 (3.7%)	2 (11.8%)	20 (26.3%)	
Hyams grade					
I	6 (15.4%)	8 (7.5%)	8 (47.1%)	8 (10.5%)	**<0.001**
II	3 (7.7%)	42 (39.2%)	4 (23.5%)	10 (13.1%)	
III	7 (17.9%)	23 (21.5%)	2 (11.8%)	3 (4.0%)	
IV	1 (2.6%)	5 (4.7%)	0 (0.0%)	5 (6.6%)	
Not available	22 (56.4%)	29 (27.1%)	3 (17.7%)	50 (65.8%)	
Treatment					
No surgery	4 (10.3%)	0 (0.0%)	1 (5.9%)	8 (10.5%)	**<0.001**
Surgery	12 (30.8%)	20 (18.7%)	7 (41.2%)	26 (34.2%)	
Surgery + adjuvant RT	21 (53.8%)	87 (81.3%)	9 (52.9%)	25 (32.9%)	
Other	2 (5.1%)	0 (0.0%)	0 (0.0%)	17 (22.4%)	
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Tumor insertion					
Maxillary sinus	–	–	11 (64.6%)	16 (21.1%)	**0.001**
Sellar/parasellar	–	–	2 (11.8%)	8 (10.6%)	
Lacrimal sac/bone	–	–	2 (11.8%)	1 (1.3%)	
Lateral wall/ostiomeatal complex	–	–	2 (11.8%)	5 (6.6%)	
Sphenoid	–	–	0 (0.0%)	22 (29.0%)	
Nasopharynx	–	–	0 (0.0%)	5 (6.5%)	
Ethmoid	–	–	0 (0.0%)	14 (18.4%)	
Pterygopalatine fossa	–	–	0 (0.0%)	1 (1.3%)	
Posterior nasal septum	–	–	0 (0.0%)	1 (1.3%)	
Inferior meatus/turbinate	–	–	0 (0.0%)	2 (2.6%)	
Nasal floor	–	–	0 (0.0%)	1 (1.3%)	
Status at latest evaluation					
No evidence of disease	20 (51.3%)	85 (79.5%)	13 (76.5%)	34 (44.7%)	**<0.001**
Alive with disease	2 (5.1%)	12 (11.2%)	1 (5.9%)	6 (7.9%)	
Died of disease	2 (5.1%)	6 (5.6%)	1 (5.9%)	8 (10.5%)	
Died of other causes	0 (0.0%)	3 (2.8%)	0 (0.0%)	1 (1.3%)	
Not available	15 (38.5%)	1 (0.9%)	2 (11.7%)	27 (35.6%)	
SIADH after treatment					
Remission	31 (79.6%)	–	15 (88.2%)	–	0.761
Persistence	4 (10.2%)	–	1 (5.9%)	–	
Not available	4 (10.2%)	–	1 (5.9%)	–	

(Continues)

TABLE 1 (Continued)

	Orthotopic SIADH-ONB, *N* (IQR)	Orthotopic non-SIADH-ONB, *N* (IQR)	Ectopic SIADH-ONB, *N* (IQR)	Ectopic non-SIADH-ONB, *N* (IQR)	*p*-value
Primary treatment					
Surgery alone	10 (25.6%)	14 (13.1%)	6 (35.3%)	15 (19.7%)	**<0.001**
Surgery + RT	11 (28.2%)	66 (61.7%)	9 (52.9%)	24 (31.6%)	
Surgery + CT	0 (0.0%)	0 (0.0%)	1 (5.9%)	2 (2.6%)	
Surgery + CRT	4 (10.2%)	7 (6.5%)	0 (0.0%)	3 (4.0%)	
RT + surgery	1 (2.6%)	2 (1.9%)	0 (0.0%)	3 (4.0%)	
CT + surgery	0 (0.0%)	2 (1.9%)	0 (0.0%)	1 (1.3%)	
CT + surgery + RT	5 (12.8%)	10 (9.3%)	0 (0.0%)	1 (1.3%)	
RT alone	1 (2.6%)	0 (0.0%)	1 (5.9%)	1 (1.3%)	
CT alone	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
CT + RT/RT + CT/CRT	1 (2.6%)	0 (0.0%)	0 (0.0%)	5 (6.5%)	
Other	4 (10.3%)	6 (5.6%)	0 (0.0%)	3 (4.0%)	
Not available	2 (5.1%)	0 (0.0%)	0 (0.0%)	17 (22.4%)	
Surgical approach					
Open	25 (64.1%)	0 (0.0%)	1 (5.9%)	26 (34.2%)	**<0.001**
Endoscopic	6 (15.4%)	107 (100.0%)	11 (64.7%)	22 (29.0%)	
Combined	0 (0.0%)	0 (0.0%)	3 (17.6%)	2 (2.6%)	
Not available	8 (20.5%)	0 (0.0%)	2 (11.8%)	26 (34.2%)	
Margin status					
Positive margins	1 (2.5%)	17 (15.9%)	3 (17.6%)	3 (4.0%)	0.143
Negative margins	2 (5.3%)	89 (83.2%)	6 (35.3%)	6 (7.9%)	
Unknown	32 (82.0%)	1 (0.9%)	7 (41.1%)	59 (77.6%)	
Non-surgical treatment	4 (10.2%)	0 (0.0%)	1 (6.0%)	8 (10.5%)	

Note: Bold *p*-values are statistically significant.

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; INSICA, international network for sinonasal cancer research; IQR, interquartile range; ONB, olfactory neuroblastoma; RT, radiotherapy; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

onwards, 134 (66.3%) were operated on with an endoscopic approach and 42 (20.8%) with an open approach. Distribution of surgical technique was significantly different before 2003 and after 2003 (included) ($p < 0.001$). Excluding studies published before 2003 and/or classified as of "poor quality,"[18] 5-year OS for oONB-SIADH$^+$, oONB-SIADH$^-$, eONB-SIADH$^+$, and eONB-SIADH$^-$ was 100.0%, 92.7%, 100.0%, and 86.5% ($p = 0.203$), respectively; 5-year DSS were 100.0%, 95.1%, 100.0%, and 86.2% ($p = 0.073$), 5-year RFS 80.0%, 79.8%, 66.7%, and 71.9% ($p = 0.224$), and 5-year TTR 100.0%, 83.9%, 100.0%, and 84.0% ($p = 0.303$), respectively (Figure S2). In the same subgroup of patients, surgical approach (classified as endoscopic vs. open vs. combined) did not significantly impact prognosis (Figure S3).

In patients affected by eONB, the multivariable model analysis demonstrated that pattern of treatment impacted OS irrespective of age, Hyams grade, and Kadish-INSICA stage, with surgery followed by RT being associated with the highest protective effect (HR = 0.04; vs. non-surgical treatment [reference] and surgery alone [HR = 0.17], $p = 0.008$) (Table S1).

4 | DISCUSSION

The present study revealed that the prevalence of SIADH at presentation in eONB was significantly higher than in oONB, suggesting that the biological mechanisms underlying ONB to arise ectopically might facilitate inappropriate secretion of antidiuretic hormone by neoplastic tissue. This result was confirmed with multiple methods. To the best of our knowledge, this is the first study that has specifically compared eONB and oONB in terms of their association with SIADH.[11,12]

Various hypotheses have been proposed to elucidate the pathogenesis of eONB, including the origin from tissues such as the sphenopalatine ganglion, ectodermal olfactory placode, Loci's ganglion, autonomic ganglia in nasal mucosa, Jacobson vomeronasal organ, and ectopic olfactory epithelium.[11] Among these, the notion that primary eONB may arise from basal cells of the olfactory mucosa,[9] which were demonstrated outside of the olfactory cleft, appears to be the most plausible.[127] Another theory suggests that accessory olfactory structures, such

TABLE 2 Summary of studies included in ectopic olfactory neuroblastoma (ONB) with syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Author	Year	Country	Age	Sex	Location	Hyams grade	Kadish-INSICA stage	Initial presentation	Reason for seeking medical attention	Management	SIADH after treatment	Follow-up (months)	Status
al Ahwal et al.[33]	1994	Canada	27	M	Maxillary sinus	NA	B	Nausea and vomiting	SNS	S	Resolved	12 RM → RT	NA
Myers et al.[37]	1994	Canada	79	F	Maxillary sinus	NA	C	Maxillary ridge swelling, loss of consciousness	SIADH + SNS	RT	NA	8	DOD: IM
Radotra et al.[38]	2010	UK	29	M	Sellar region	III	C	Fatigue, lethargy, headache, and progressive visual loss	SIADH + SNS	ER + S + RT	Resolved	14	NED
Dupuy et al.[34]	2012	France	44	F	Sellar region	NA	NA	Left temporal hemianopsia, secondary amenorrhea	SIADH + SNS	ER	Persisted	36	AWD
Sejling et al.[42]	2014	Denmark	38	M	Maxillary sinus	I	B	SIADH diagnosis 12 years before	SIADH	ER	Resolved	7	NED
Jiang et al.[36]	2015	USA	NA	M	Maxillary sinus	I	B	Vomiting, dizziness, unstable gait, headache	SIADH	ER + S + RT	Resolved	NA	NED
Fosbol et al.[35]	2018	Denmark	17	F	Maxillary sinus	I	B	Hypomania, hallucinations, emesis	SIADH	ER + RT	Resolved	6	NED
Rasool et al.[39]	2018	Canada	28	F	Maxillary sinus	III	B	Nasal congestion, postnasal discharge, headache	SIADH + SNS	ER + RT	Resolved	6	NED
Wong et al.[44]	2019	Australia	17	F	Maxillary sinus	I	B	1-Year history of lethargy, nausea, pre-syncopal symptoms	SIADH	ER + RT	Resolved	84	NED
Tudor et al.[43]	2021	Croatia	11	F	Maxillary sinus	I	NA	Epistaxis abdominal pain	SNS	ER + CT	Resolved	NA	NA
Turri-Zanoni et al.[11]	2022	Italy	41	M	Lacrimal sac	II	B	Mental confusion episode, dysphoria	SIADH	ER + RT	Resolved	12	NED
Saad et al.[40]	2023	Tunisia	26	F	Maxillary sinus	II	B	Recurrent headaches, abdominal pain, and vomiting	SIADH	ER	Resolved	24	NED

(Continues)

TABLE 2 (Continued)

Author	Year	Country	Age	Sex	Location	Hyams grade	Kadish-INSICA stage	Initial presentation	Reason for seeking medical attention	Management	SIADH after treatment	Follow-up (months)	Status
Saffarzadeh et al.[41]	2023	Canada	22	F	Lamina Papyracea	I	B	Nasal obstruction, congestion, and epiphora	SNS	ER + RT	Resolved	NA	NED
Our cases	2024	Italy/USA	21	F	Ostiomeatal complex	I	B	Fatigue, headaches, insomnia, nocturia	SIADH	ER	Resolved	37	NED
			44	F	Lacrimal bone	II	B	2–3 year history of hyponatremia	SIADH	ER + RT	Resolved	1	NED
			25	F	Maxillary sinus	I	B	Hyponatremia with seizures lasting for 6 years	SIADH	ER	Resolved	6	NED
			34	F	Maxillary sinus	II	B	Severe hyponatremia	SIADH	ER + RT	Resolved	1	NED

Abbreviations: AWD, alive with disease; CT, chemotherapy; DOD, died of disease; ER, endoscopic resection; F, female; IM, intracranial metastasis; M, male; NA, not available; NED, no-evidence-of-disease; RM, regional metastasis; RT, radiotherapy; S, surgery; SNS, sinonasal symptoms.

as the vomeronasal organ of Jacobson and the terminal nerve, persist beyond fetal life and could potentially give rise to eONB.[53] In ONB, both endocrinological (such as SIADH, ectopic ACTH syndrome, humoral hypercalcemia of malignancy, and hypertension from tumor-produced catecholamines) and neurological PNS (such as opsoclonus-myoclonus-ataxia and cerebellar degeneration) may arise.[13] Signs and symptoms in PNS do not result from direct tumor invasion or compression, but are related to tumor secretion.[128] SIADH involves excessive release or activity of antidiuretic hormone, resulting in persistent hyponatremia and elevated urine osmolality,[129] and has been reported in 1.5%–3% of patients with head and neck cancer.[130] Symptoms of SIADH are predominantly neurological and vary based on the severity and speed of development of hyponatremia. Slow-onset hyponatremia may cause mild or nonspecific symptoms such as anorexia, nausea, vomiting, irritability, headaches, and abdominal cramps, whereas rapid onset leads to more severe manifestations including brain edema and coma.

The data collected suggest that eONB, with special reference to eONB-SIADH$^+$, presents a typical clinical profile, often affecting younger patients, with slight female predominance, and most frequently displaying a low grade. Whether this clinical phenotype owes to the effect of PNS on early diagnosis or is related to an underlying biological mechanism remains an unanswered question. Of note, a remarkable proportion of eONB-SIADH$^+$ patients underwent surgery alone, whereas most orthotopic cases received surgery followed by adjuvant RT. A large majority of ONB patients affected by SIADH experience a complete PNS remission following locoregional treatment. The persistence of SIADH after treatment might be due to the presence of residual tumor[34] and/or incomplete response to non-surgical therapies.[100,109,121] The fact that adjuvant RT was used less frequently in eONB than oONB might partially explain the worse prognostic outcomes in the former group. However, multivariable analysis showed poorer RFS and TTR in eONB, independently of age, grade, stage, and treatment. The Kaplan–Meier curves shown in Figure 4 provide a visual representation of these prognostic differences, highlighting the worse outcomes of eONB compared with oONB. Interestingly, the prognostic disadvantage of eONB was not influenced by the presence of SIADH. OS of eONB included in the systematic review was similar to what is reported in a multi-institutional, international series of 404 ONB[17] (78.9% vs. 82.3% at 5 years, respectively), whereas it was remarkably lower than that reported in a series of 114 ONB treated with endoscopic surgery (94.0% at 5 years).[20] Thus, the comparison may be biased by selection. However, when focusing on RFS, eONB showed worse outcomes compared to both the aforementioned series (47.2% vs. 67.6%[17] vs. 81.9%[20] at 5 years, respectively). Based on these findings, one cannot

TABLE 3 Summary of studies included in the ectopic olfactory neuroblastoma (ONB) without syndrome of inappropriate antidiuretic hormone secretion (SIADH) group.

Author	Year	Country	Age	Sex	Location	Hyams grade	Kadish-INSICA stage	Management	Follow-up (months)	Status
McCormack et al.[10]	1955	USA	56	M	Lateral nasal wall	NA	NA	S	24	DOD: DM
Mashberg et al.[73]	1960	USA	24	M	Maxillary sinus	NA	NA	S	12	NED
Lindström et al.[69]	1975	Sweden	44	M	Maxillary sinus	NA	B	S	24	NED
Schochet et al.[88]	1975	USA	31	F	Parasellar	II	B	S + RT	12	NED
Oberman et al.[78]	1976	USA	69	F	Sphenoid sinus	NA	NA	S + RT	12	AWD: T + DM
Sarwar[87]	1979	USA	31	F	Sellar	NA	C	S + RT	60	AWD
Appelblatt et al.[48]	1982	USA	69	F	Sphenoid sinus	NA	C	RT	12	DOD: DM
Meyrowitz et al.[75]	1984	Israel	71	F	Maxillary sinus	NA	B	S + RT	18 R	DOC
Berman et al.[52]	1992	USA	11	F	Sphenoid sinus	NA	B	S + CRT	NA	NA
Chacko et al.[54]	1998	India	62	F	Sphenoid sinus	IV	C	None	NA	DOD
Roy et al.[85]	2000	UK	44	F	Sellar	NA	C	ER + RT	12	NED
Sharma et al.[90]	2002	India	40	M	Sphenoid sinus	NA	B	CRT	11	NED
Argiris et al.[49]	2003	USA	53	M	Maxillary sinus	I	B	S + CT	52.8 R → S + CT	NED
			24	M	Nasopharynx	III	C	RT + S	8 R	DOD
Chirico et al.[56]	2003	Italy	59	F	Sphenoid sinus	II	C	CRT	NA	NA
Mariani et al.[72]	2004	Germany	35	F	Sellar	III	B	S	25	NED
Morris et al.[77]	2004	USA	63	M	Sphenoid sinus	NA	B	ER	15	NED
Oyama et al.[79]	2005	Japan	33	M	Sellar	NA	C	ER + S + GK + RT	NA	NED
Sajko et al.[86]	2005	Croatia	57	F	Sellar	NA	C	S + RT	NA	NA
Unal et al.[92]	2006	Turkey	14	F	Middle turbinate (inferior portion)	NA	B	CT + S	24	NED
Lee et al.[64]	2007	Canada	49	M	Left lateral nasal + right maxillary sinus	II	B	RT + S	NA	NA
Lee et al.[65]	2007	South Korea	89	M	Inferior meatus	NA	B	RT + ER	6	NED
Chan et al.[55]	2009	Taiwan	79	M	Sphenoid sinus	NA	B	ER + RT	16	NED
Lin et al.[67]	2009	Taiwan	64	F	Sphenoid sinus	NA	B	Died before treatment	0	DOD
Lin et al.[68]	2009	Taiwan	40	M	Sellar	NA	B	ER	12	NED
Cho et al.[57]	2010	South Korea	58	F	Posterior nasal septum	I	A	ER	25	NED
Seccia et al.[89]	2010	Italy	69	F	Pterygopalatine fossa	NA	NA	ER + RT	36	NED

(Continues)

TABLE 3 (Continued)

Author	Year	Country	Age	Sex	Location	Hyams grade	Kadish-INSICA stage	Management	Follow-up (months)	Status
Wormald et al.[94]	2011	Ireland	15	F	Lateral nasal wall	II	B	S + RT	18	NED
			60	M	Sphenoid sinus	II	B	S + RT	120	NED
			61	M	Nasopharynx	I	A	S + RT	120	NED
			12	M	Nasal floor	NA	A	S	276	NED
Akinfolarin et al.[47]	2012	USA	33	M	Sphenoid sinus	NA	B	ER + CT	5	DOD
Kumar et al.[62]	2013	India	35	F	Middle meatus	NA	B	S + RT	10	NED
Lopez et al.[71]	2013	France	73	F	Maxillary sinus	NA	C	S + ND + RT	NA	NA
Abdel-Rahman et al.[46]	2014	Egypt	55	M	Sphenoid sinus	NA	B	ER + CRT	NA	NA
von Zeidler et al.[93]	2014	Brazil	24	F	Inferior turbinate	III	A	S + RT	12 R → S; 22 R → CT	AWD
Jankowski et al.[61]	2015	France	39	M	Anterior ethmoid	NA	C	CT + ER + ND + RT	24	NED
			40	M	Anterior ethmoid	NA	B	ER	6	NED
Matsunaga et al.[74]	2015	Japan	46	M	Sphenoid sinus	NA	B	ER + RT	16	NED
Purohit et al.[83]	2015	Switzerland	62	F	Sphenoid sinus	IV	C	CT	9	DOD: DM
Yamamuro et al.[95]	2015	Japan	71	M	Sellar	NA	C	ER + S + GK	18	NED
Belliveau et al.[51]	2016	Canada	18	F	Nasolacrimal duct	I	B	ER + RT	17	NED
Holmes et al.[60]	2016	USA	63	F	Maxillary sinus	IV	B	S + ND	NA	NA
Leon-Soriano et al.[66]	2016	Spain	41	M	Bilateral ethmoid	II	B	ER + RT	48	NED
Raj et al.[84]	2016	India	24	F	Maxillary sinus	NA	NA	S + RT	NA	NA
Zahedi et al.[96]	2017	Malaysia	71	M	Sphenoid sinus	NA	B	ER	NA	NED
Peng et al.[80]	2018	China	66	M	Sphenoid sinus	I	C	S + RT + CT	13 R → RT + CT; 36	AWD
Caldwell et al.[53]	2019	USA	15	M	Nasopharynx	NA	D	CT + RT + ND	15	DOD
Familiar et al.[58]	2019	Spain	31	M	Sphenoid sinus	I	C	CT + RT	12	AWD
Mims et al.[76]	2020	USA	13	M	Lateral nasal wall	II	B	S + ER + PBRT	6	NED
Pérez-Sayáns et al.[81]	2020	Spain	39	M	Maxillary sinus	NA	B	NA	NA	NA
Peyneshki et al.[82]	2020	Switzerland	66	M	Sphenoid sinus	II	C	ER + S	NA	AWD
Abdelmeguid et al.[46]	2021	USA	NA	NA	Maxillary sinus ($n = 5$)	NA	NA	NA	NA	NA
			NA	NA	Sphenoid sinus	NA	NA	NA	NA	NA
			NA	NA	Nasopharynx	NA	NA	NA	NA	NA
Arosio et al.[50]	2022	Italy	NA	NA	Maxillary sinus	NA	NA	NA	NA	NA

(Continues)

TABLE 3 (Continued)

Author	Year	Country	Age	Sex	Location	Hyams grade	Kadish-INSICA stage	Management	Follow-up (months)	Status
Lohar et al.[70]	2022	India	20	F	Lateral nasal wall	IV	B	S + RT	6	NED
Turri-Zanoni et al.[11]	2022	Italy	37	F	Bulla ethmoidalis	I	B	ER	60	NED
			28	M	Maxillary sinus	II	B	ER + CRT	24	NED
Lui et al.[12]	2023	USA	20	F	Maxillary sinus	II	B	ER	60	NED
			43	F	Lateral nasal wall	I	B	ER + RT	144 R → S + ER + RT; 24	NED
Touihmi et al.[91]	2023	Morocco	27	M	Sphenoid sinus	NA	C	RT + CT	NA	NA
Kumaria et al.[63]	2023	UK	42	F	Sphenoid sinus	NA	B	ER	NA	NA
Zhong et al.[97]	2023	China	55	M	Nasopharynx	IV	B	ER	14 R → RT; 96	NED
Hirunpat et al.[59]	2024	Thailand	NA	NA	Middle nasal cavity ($n = 7$)	NA	NA	NA	NA	NA
			63	F	Sphenoid sinus	NA	C	NA	NA	NA

Abbreviations: AWD, alive with disease; CRT, chemoradiotherapy; CT, chemotherapy; DOC, dead of other causes; DOD, dead of disease; DM, distant metastasis; ER, endoscopic resection; F, female; GK, Gamma Knife r; M, male; NA, not available; ND, neck dissection; NED, no-evidence-of-disease; PBRT, proton beam radiotherapy; R, disease relapse; RT, radiotherapy; S, surgery; T, local recurrence.

exclude that eONB is biologically more aggressive than oONB despite the lower grade in the former group. On the other hand, the doubt that a large proportion of eONB were undertreated through a unimodal approach and/or less aggressive surgery cannot be dispelled. One should consider the role of postoperative RT that has been demonstrated for ONB in general, thus underlying the importance of bimodal treatment in this disease.[131,132] On the other hand, the lack of neoadjuvant chemotherapy cannot be considered as a reason for worse prognosis, as patients with low-grade ONB have no indication to be treated with such an approach.[132–134] The fact that also eONB mandates a combination of surgery and adjuvant RT is corroborated by the present study, since this treatment strategy was associated with the highest protective effect in terms of OS, irrespective of age, tumor grade, and stage. Another contributing factor may be related to the rarity and atypical presentation of eONB. Due to their unusual locations and presentations, eONB are often more challenging to diagnose, which can lead to initial misdiagnosis. In turn, misdiagnosis of sinonasal cancers was demonstrated to negatively impact outcomes irrespective of other relevant prognosticators.[135] This represents a further potential explanation for the relatively low RFS of eONB and mandates considering it in the differential diagnosis of non-olfactory-cleft-centered sinonasal lesions. To achieve an accurate diagnosis, immunohistochemical staining is imperative, including markers such as synaptophysin, chromogranin A, CD56, neuron-specific enolase, and S-100 protein.[136] Furthermore, given the rarity of eONB, surgical technique may vary significantly among different centers and deviate from the standard surgical technique that is adopted in patients with nasoethmoid-centered lesions,[20] thus contributing to treatment heterogeneity. However, although an increase in survival outcomes over time was observed in the present study, the increasing use of endoscopic surgery does not seem to be the driving reason for such an improvement. Overall, the heterogeneity in surgical approaches (especially in terms of extent of resection), variability in adjuvant therapies, large period of inclusion, and lack of information on margin status prevent drawing definitive conclusions on outcomes and mandate cautious interpretation of prognostic findings reported for eONB.

4.1 | Limitations of the study

The present study has several limitations that are worthy of mention:

- Case reports: The review primarily included case reports, which can limit the generalizability of findings due to variability and heterogeneity.

TABLE 4 Summary of studies included in the orthotopic olfactory neuroblastoma (ONB) with syndrome of inappropriate antidiuretic hormone secretion (SIADH) group.

Author	Year	Country	Age	Sex	Hyams grade	Kadish-INSICA stage	Initial presentation	Reason for seeking medical attention	Management	SIADH after treatment	Follow-up (months)	Status
Pope et al.[118]	1980	USA	50	F	NA	A	Gastroduodenitis	SIADH	S + RT	Resolved	2	NED
Singh et al.[121]	1980	Scotland	17	F	II	B	Nasal obstruction	SNS	RT + CT	Persisted	NA	DOD
Srigley et al.[122]	1983	Canada	33	F	NA	NA	Mucopurulent drainage	SIADH + SNS	S + RT	Resolved	12	AWD
Wade et al.[124]	1984	USA	59	F	NA	B	Confusion, nausea, and vomiting	SIADH + SNS	S + RT + CT	Resolved	12	NED
Cullen et al.[98]	1986	Ireland	26	F	NA	NA	Malaise and lethargy, hyponatremia	SIADH + SNS	ER + RT	Resolved	12	NED
Osterman et al.[115]	1986	Columbia	28	M	NA	B	Syncope	SIADH	S + RT	Resolved	NA	NA
Morris et al.[110]	1994	USA	NA	F	NA	B	Nasal obstruction and SIADH	SIADH	S	Resolved	24	NED
Koka et al.[108]	1998	France	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Müller et al.[111]	2000	Germany	47	M	NA	B	Major depressive episode	SIADH	S	Resolved	NA	NA
Iliades et al.[106]	2002	Greece	57	F	NA	NA	Sudden onset of coma	SIADH + SNS	S + RT	NA	108	NED
Vasan et al.[123]	2004	USA	30	F	NA	A	Anosmia and neck mass	SNS	CT + RT + ND	Resolved	22	NED
Freeman et al.[102]	2005	UK	51	F	I	B	15-year history of hyponatremia	SIADH + SNS	S	Resolved	84	NED
			42	F	I	B	7-year history of hyponatremia	SIADH + SNS	S	Resolved	24	NED
Nabili et al.[113]	2006	USA	27	F	NA	B	Nasal obstruction, sinus infections, epistaxis, headaches, hyponatremia	SIADH + SNS	S + RT	Resolved	NA	NA
Plasencia et al.[117]	2006	Spain	34	F	I	B	Paraureteral cyst planned resection	Incidental diagnosis	S + RT	Resolved	12	NED
Maeda et al.[109]	2007	Japan	61	M	NA	C	Right cervical lymph node swelling	SNS	RT	Persisted	NA	DOD
Renneboog et al.[119]	2008	Belgium	28	F	NA	B	Hyponatremia and vomiting	SIADH	S + RT	Resolved	NA	NA
Ward et al.[125]	2009	USA	NA	NA	NA	NA	NA	NA	S + NA	NA	NA	NA

(Continues)

TABLE 4 (Continued)

Author	Year	Country	Age	Sex	Hyams grade	Kadish-INSICA stage	Initial presentation	Reason for seeking medical attention	Management	SIADH after treatment	Follow-up (months)	Status
Senchak et al.[120]	2012	USA	28	F	I	C	Emesis, malaise, and diarrhea over a 3-year time period	SIADH	ER	Resolved	24	NED
Gray et al.[103]	2012	USA	29	M	III	C	Mental status changes and hyponatremia	SIADH	S	Resolved	28	NED
			25	F	III	B	Mental status changes and hyponatremia	SIADH	CT + S + PBRT	Resolved	23	NED
			32	F	III	B	Mental status changes and hyponatremia	SIADH	S + PBRT	Resolved	29	NED
Gabbay et al.[19]	2013	Israel	50	M	NA	NA	16-year history of hyponatremia	SIADH + SNS	S	Resolved	156	NED
Yumusakhuylu et al.[126]	2013	Turkey	38	M	II	A	Epistaxis, nasal obstruction	SNS	ER + CRT	Resolved	NA	NA
Hoorn et al.[105]	2015	Netherlands	29	F	I	B	Hypertension and hyponatremia	SIADH + SNS	ER	Resolved	16	NED
Nakano et al.[114]	2017	Japan	31	F	NA	C	Stomach ache and hyponatremia	SIADH	S + CRT	Resolved	14	NED
Parrilla et al.[116]	2017	Italy	31	M	II	B	Nausea, dizziness, and weakness	SIADH	S + RT	Resolved	60	NED
Klironomos et al.[107]	2018	Canada	44	M	IV	D	NA	NA	RT + ER	NA	110	NED
Diamond et al.[101]	2019	USA	40	M	NA	NA	Hyponatremia	SIADH + SNS	S + ND + CRT	Resolved	NA	NA
Mzaiti et al.[112]	2022	Belgium	39	F	I	A	Hyponatremia	SIADH	S	Resolved	NA	NA
Heiland et al.[104]	2023	USA	35	M	NA	B	Syncope due to SIADH	SIADH + SNS	ER	Resolved	60	AWD
Devaraja et al.[100]	2023	India	33	M	NA	C	NA	SIADH + SNS	Palliation	Persisted	NA	NA
			38	M	NA	C	NA	SIADH + SNS	NA	Persisted	NA	NA
			68	F	NA	C	NA	SIADH + SNS	S + RT	Resolved	30	NED
			58	F	NA	C	NA	SIADH + SNS	S + CRT	Resolved	8	NED
Dang et al.[99]	2024	China	44	M	III	C	NA	NA	CT + S + RT	Resolved	NA	NA
			37	M	III	C	NA	NA	CT + S + RT	Resolved	NA	NA
			67	M	III	C	NA	NA	CT + S + RT	Resolved	NA	NA
			35	M	III	C	NA	NA	CT + S + RT	Resolved	NA	NA

Abbreviations: AWD, alive with disease; CRT, chemoradiotherapy; CT, chemotherapy; DOD, died of disease; ER, endoscopic resection; F, female; M, male; NA, not available; ND, neck dissection; NED, no-evidence-of-disease; PBRT, proton beam radiotherapy; RT, radiotherapy; S, surgery; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNS, sinonasal symptom.

TABLE 5 Univariate analysis for overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and time-to-recurrence (TTR).

Variable	5-Year OS	*p*-value	5-Year DSS	*p*-value	5-Year RFS	*p*-value	5-Year TTR	*p*-value
Tumor groups								
Orthotopic SIADH-ONB	100.0%	**0.040**	100.0%	**0.020**	79.2%	**0.003**	100.0%	0.058
Orthotopic non-SIADH-ONB	93.6%		95.8%		80.3%		83.9%	
Ectopic SIADH-ONB	87.5%		100.0%		50.0%		75.0%	
Ectopic non-SIADH-ONB	77.2%		80.0%		47.9%		66.8%	
Gender								
Male	85.4%	0.322	88.1%	0.175	81.6%	**0.050**	90.2%	**0.026**
Female	94.3%		96.7%		61.6%		72.4%	
Kadish-INSICA stage								
A–B	93.9%	0.270	96.2%	0.253	80.9%	**0.002**	85.3%	**0.005**
C	84.8%		88.5%		58.0%		74.6%	
Hyams grade								
I	95.8%	0.112	100.0%	**0.039**	79.7%	0.706	87.1%	0.498
II	100.0%		100.0%		85.3%		85.3%	
III	83.4%		88.6%		63.0%		67.8%	
IV	87.5%		87.5%		75.0%		75.0%	
Treatment								
No surgery	26.8%	**<0.001**	32.1%	**<0.001**	17.9%	**<0.001**	83.3%	0.248
Surgery	91.4%		91.3%		66.9%		75.8%	
Surgery + adjuvant RT	92.3%		95.4%		77.4%		84.8%	

Note: Bold *p*-values are statistically significant.

Abbreviations: ONB, olfactory neuroblastoma; RT, radiotherapy; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

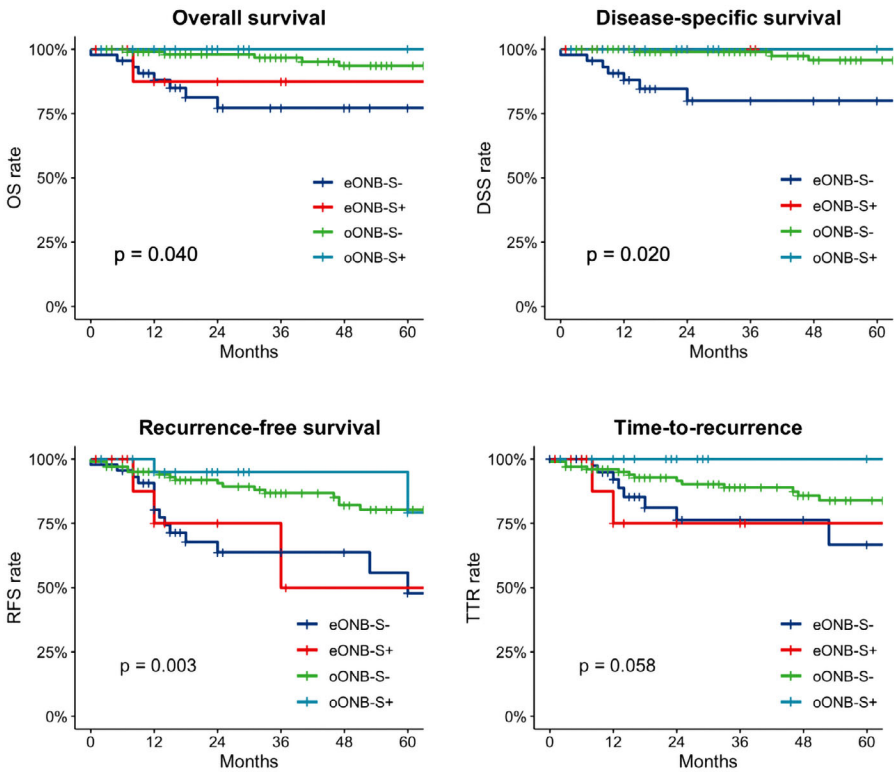

FIGURE 4 Kaplan–Meier curves estimating overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and time-to-recurrence (TTR) across tumor groups.

TABLE 6 Multivariable analysis of pooled data.

Variable	OS		DSS		RFS		TTR	
	HR (CI)	*p*-value	HR (CI)	*p*-value	HR (CI)	*p*-value	HR (CI)	*p*-value
Origin site								
Orthotopic	Ref		Ref		Ref		Ref	
Ectopic	3.03 (0.84–10.87)	0.089	2.34 (0.49– 11.27)	0.289	3.36 (1.55–7.32)	**0.002**	3.81 (1.55–9.33)	**0.004**
Age	1.05 (1.01–1.08)	**0.008**	1.03 (0.99–1.07)	0.124	1.03 (1.01–1.05)	**0.004**	1.04 (1.01–1.06)	**0.006**
Kadish-INSICA stage								
A–B	Ref		Ref		Ref		Ref	
C	1.18 (0.37–3.76)	0.777	1.51 (0.39–5.93)	0.553	3.03 (1.46–6.30)	**0.003**	4.10 (1.72–9.82)	**0.002**
Hyams grades								
I–II	Ref		Ref		Ref		Ref	
III–IV	3.68 (0.98–13.84)	0.054	7.39 (0.91–60.21)	0.062	1.19 (0.60–2.37)	0.622	0.90 (0.41–2.01)	0.802
Treatment								
Surgery	Ref		Ref		Ref		Ref	
Surgery + adjuvant RT	0.95 (0.27–3.36)	0.942	0.51 (0.12–2.22)	0.373	0.55 (0.27–11.13)	0.103	0.43 (0.19–0.97)	**0.041**
Definitive non-surgical treatment	7.10 (1.04–48.03)	**0.045**	5.01 (0.57–43.89)	0.145	2.72 (0.67–11.01)	0.160	0.56 (0.06–5.34)	0.613

Note: Bold *p*-values are statistically significant.

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy; TTR, time-to-recurrence.

- Staging: The Kadish-INSICA staging is intended for oONB, which makes application to eONB of limited utility, since most cases are by definition stage A/B and this might not adequately represent the complexity of neoplasm extension.
- Prevalence: The comparison of the prevalence of SIADH across different ONB groups, including those with different sample sizes and inclusion methodologies, involves a degree of extrapolation and potentially forced alignment. Additionally, in Gabbay et al.[19] and Henson et al.,[28] all ONB cases were assumed to be orthotopic, due to the rarity of eONB and the absence of specific data to suggest otherwise. This approximation introduces a potential assumption bias.
- Missing data: Some older articles lacked details relevant to the study, leading to the exclusion of some information from the analyses.
- Evolution of treatment: The evolution of surgical technique and overall management of sinonasal cancers that has taken place over the last decades may have improved outcomes, potentially affecting the comparability of older data with more recent data.
- Unknown margin status: Information on margin status was not available in several studies. This lack of data prevented the inclusion of this relevant information into the prognostic analysis.

5 | CONCLUSIONS

Overall, the present study suggests that eONB has a distinct clinical profile, with a higher prevalence of SIADH and a worse prognosis than oONB. These findings warrant further investigation to understand the underlying molecular mechanisms alongside with potential implications for management of eONB. The poorer disease control observed in eONB might be related to several factors, including initial misdiagnosis, enhanced aggressiveness, and undertreatment. Future research should focus on refining diagnostic and treatment strategies to improve outcomes for this unique group of patients.

AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The authors thank Rosalinda Russo for the literature search.

Open access publishing facilitated by Universita degli Studi di Padova, as part of the Wiley - CRUI-CARE agreement.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

FUNDING INFORMATION

The authors received no funds to perform the present research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The study was conducted in accordance with the principles of the Helsinki Declaration, the Italian and US privacy and sensitive data laws, and the internal regulations for retrospective studies of the Otolaryngology Section at Padova University and Brescia University (Italy) and The University of Texas MD Anderson Cancer Center (US). Patients signed a detailed informed consent form regarding the processing and publication of their data.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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How to cite this article: Daloiso A, Gaudioso P, Vinciguerra A, et al. Ectopic olfactory neuroblastoma is associated with increased frequency of syndrome of inappropriate antidiuretic hormone secretion and reduced disease control: Case series with systematic review and pooled analysis. *Int Forum Allergy Rhinol*. 2024;1-23. https://doi.org/10.1002/alr.23502