

# Rare Head and Neck Malignancies Focusing on Olfactory Neuroblastoma

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## ABSTRACT

**Background:** Olfactory neuroblastoma (ONB) is a rare malignant tumor arising from the olfactory epithelium and remains poorly characterized in low- and middle-income countries. This study aimed to evaluate the clinicopathological spectrum, treatment approaches, and outcomes of ONB among patients with rare head and neck malignancies in Bangladesh. **Methods & Materials:** A retrospective review was conducted on 100 rare head and neck cancer cases diagnosed from July, 2023 to June, 2024, including 25 ONB patients. Data on demographics, clinical features, histopathology, treatment, and follow-up were analyzed. Logistic regression and Cox proportional hazards models were used to identify predictors of recurrence and mortality. **Results:** ONB constituted 25% of all rare malignancies. Most patients were aged 30–50 years (48%) and male (56%). Nasal obstruction (80%), epistaxis (60%), and anosmia (48%) were common symptoms. Hyams grade II was most frequent (32%). Surgery followed by radiotherapy was the predominant treatment. Disease-free survival at  $\geq 2$  years was 72%. Hyams grade III–IV was the only significant predictor of recurrence (OR = 4.75,  $p = 0.018$ ) and mortality (HR = 5.10,  $p = 0.009$ ). **Conclusion:** High-grade ONB is strongly associated with poor prognosis. Tumor grade was the most reliable predictor of both recurrence and mortality, underscoring the importance of early detection and multimodal therapy in ONB management in low-resource settings.

**Keywords:** Olfactory Neuroblastoma, Head and Neck Cancer, Hyams Grading, Recurrence, Survival Analysis

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## INTRODUCTION

Head and neck cancers (HNCs) represent a significant oncologic burden globally, ranking as the sixth most common cancer type worldwide, with over 630,000 new cases and more than 350,000 deaths annually [1]. Despite improvements in diagnostic and treatment strategies, the mortality burden continues to rise, particularly in low- and middle-income countries (LMICs), with an estimated economic loss of USD 535 billion projected between 2018 and 2030 due to HNC-related productivity loss and premature death [2]. Within this broader cancer group lies a much smaller, clinically distinct category of rare head and neck malignancies—defined as those with an incidence of  $\leq 6$  cases per 100,000 per year [3]. Among these rare malignancies, olfactory neuroblastoma (ONB), also referred to as esthesioneuroblastoma, is a rare and aggressive neoplasm originating from the olfactory neuroepithelium in the superior nasal cavity. First described by Berger et al., ONB accounts for approximately 2% of all sinonasal tumors, with an estimated annual incidence ranging between 0.4 to 1 case per 2 to 2.5 million population [4]. Clinically, ONB often presents with nonspecific symptoms including nasal obstruction, epistaxis, and anosmia, leading to

delayed diagnosis in many patients. Its neuroectodermal origin and bimodal age distribution—commonly affecting individuals in the second and sixth decades of life—make it an uncommon but important consideration in the differential diagnosis of nasal masses [1]. The Kadish staging system (A–D) and the Hyams histological grading system (I–IV) remain the most widely used tools for clinical and pathological stratification of ONB. Higher Kadish stages and Hyams grades have consistently been associated with poorer outcomes. A Korean multicenter study involving 195 patients found that modified Kadish stage and Hyams grade were statistically significant predictors of 5-year overall survival (OS: 78.6%) and disease-free survival (DFS: 62.4%), using both Kaplan–Meier and Cox regression analyses [5]. These findings were reinforced by a large North American cohort ( $n = 256$ ), where the incorporation of Hyams grade into existing staging systems enhanced survival prediction accuracy, particularly for locally advanced tumors [6]. The treatment of ONB typically involves surgical resection—either endoscopic or craniofacial—followed by adjuvant radiotherapy. For unresectable or advanced-stage tumors, chemotherapy and immunotherapy are occasionally employed, although evidence

supporting their efficacy remains limited. In a population-based SEER study of 513 ONB cases, postoperative radiotherapy significantly improved OS for Kadish stage C and D patients, but not for earlier stages, while chemotherapy showed no statistically significant survival benefit [7]. Similarly, a long-term study of 85 Kadish C patients noted a 5-year OS of 83.7% with multimodal therapy, underscoring the importance of tailored treatment strategies based on stage, grade, and resection margins [8]. In the South Asian context, particularly in Bangladesh, ONB remains poorly characterized due to the rarity of the disease and the absence of national cancer registries for rare head and neck tumors. However, Bangladesh ranks among the highest globally in overall HNC incidence, with approximately 21 per 100,000 males affected annually—primarily driven by high prevalence of smokeless tobacco and betel nut use [9]. Unfortunately, ONB-specific data from Bangladesh is almost entirely absent in the literature, with only sporadic case reports appearing in institutional archives. This poses a significant public health and research gap, as the unique socio-epidemiologic features of LMICs—including delayed presentation, limited access to skull base surgical services, and poor HPV vaccination coverage—may influence ONB presentation and prognosis differently compared to high-income countries [10,11]. In light of these gaps, the present study aims to characterize the epidemiologic profile, clinicopathological features, treatment strategies, and short- to mid-term outcomes of ONB and other rare head and neck malignancies diagnosed and managed in tertiary hospitals across Bangladesh between 2015 and 2024. Specifically, we seek to: estimate crude incidence and hospital-based prevalence; describe demographic distributions by age, sex, and socioeconomic status; evaluate Kadish and Hyams staging distributions; assess treatment

modalities and survival outcomes; and explore statistical associations using Kaplan–Meier and Cox regression analyses.

## METHODS & MATERIALS

This retrospective study was conducted at Rajshahi Medical College, Rajshahi, Bangladesh from July, 2023 to June, 2024. Data were collected from medical records. Inclusion criteria included histologically confirmed cases of rare head and neck malignancies, with a subset of patients specifically diagnosed with ONB. Demographic information, clinical presentation, imaging findings, histopathological reports, treatment details, and follow-up outcomes were reviewed. Tumor grading for ONB cases was performed using the Hyams grading system. Recurrence and mortality were recorded as primary outcomes. Statistical analysis was carried out using SPSS version 26. Categorical variables were expressed as frequencies and percentages. Logistic regression was used to identify predictors of recurrence, and odds ratios (OR) with 95% confidence intervals (CI) were calculated. A Cox proportional hazards regression model was used to evaluate factors influencing overall survival, with hazard ratios (HR) and corresponding 95% CIs. A p-value of less than 0.05 was considered statistically significant

## RESULTS

Among the 100 patients diagnosed with rare head and neck malignancies, olfactory neuroblastoma (ONB) accounted for the highest proportion, comprising 25% of cases. This was followed by adenoid cystic carcinoma in 20% of patients and mucoepidermoid carcinoma in 15%. Sinonasal undifferentiated carcinoma represented 10% of the cohort, while NUT carcinoma was identified in 5% of cases. The remaining 25% included a variety of other rare tumor types, collectively grouped as “Other Rare Tumors.” [Table-I].

**Table – I: Distribution of Rare Head and Neck Malignancies (n = 100)**

Malignancy Type	Frequency (n)	Percentage (%)
Olfactory Neuroblastoma	25	25.0%
Adenoid Cystic Carcinoma	20	20.0%
Mucoepidermoid Carcinoma	15	15.0%
Sinonasal Undifferentiated Carcinoma	10	10.0%
NUT Carcinoma	5	5.0%
Other Rare Tumors	25	25.0%

Among the 25 patients diagnosed with olfactory neuroblastoma, the majority (48%) were between 30 and 50 years of age, followed by 36% over 50 years and 16% under

30 years. A slight male predominance was observed, with 56% of cases occurring in males and 44% in females. [Table-II]

**Table – II: Demographic Characteristics of Patients with Olfactory Neuroblastoma (n = 25)**

Category	Frequency (n)	Percentage (%)
<b>Age Group</b>		
<30 years	4	16.0%
30–50 years	12	48.0%
>50 years	9	36.0%
<b>Sex</b>		
Male	14	56.0%
Female	11	44.0%

The most common presenting symptom among patients with olfactory neuroblastoma was nasal obstruction, reported in 80% of cases. This was followed by epistaxis in 60% and anosmia in 48% of patients. Headache was noted in 32% of cases, while visual disturbances were reported by 12%, indicating varying degrees of local invasion or pressure effects. [Table-III]

**Table – III: Clinical Presentation of Olfactory Neuroblastoma (n = 25)**

Symptom	Frequency (n)	Percentage (%)
Nasal obstruction	20	80.0%
Epistaxis (nosebleed)	15	60.0%
Anosmia (loss of smell)	12	48.0%
Headache	8	32.0%
Visual disturbances	3	12.0%

Histopathological grading of olfactory neuroblastoma cases using the Hyams system revealed that Grade II was the most frequently observed, accounting for 32% of patients. Grade III was present in 28% of cases, while both Grade I and Grade IV were identified in 20% of patients each, indicating a fairly

balanced distribution across low- to high-grade tumors. [Table-IV]

**Table – IV: Histopathological Grade (Hyams Grade) of ONB Cases (n = 25)**

Hyams Grade	Frequency (n)	Percentage (%)
Grade I	5	20.0%
Grade II	8	32.0%
Grade III	7	28.0%
Grade IV	5	20.0%

Regarding treatment approaches among patients with olfactory neuroblastoma, the most common modality was surgery followed by radiotherapy, administered to 40% of patients. This was followed by surgery combined with chemoradiotherapy in 28%, and chemoradiotherapy alone in 20%. A small subset (12%) underwent surgery alone. At follow-up beyond two years, 72% of patients remained disease-free, while 20% experienced recurrence and 8% succumbed to the disease, indicating generally favorable outcomes with multimodal treatment. [Table-V]

**Table – V: Treatment Modalities and Outcomes in ONB (n = 25)**

Variable	Frequency (n)	Percentage (%)
<b>Treatment Modality</b>		
Surgery only	3	12.0%
Surgery + Radiotherapy	10	40.0%
Surgery + Chemoradiotherapy	7	28.0%
Chemoradiotherapy only	5	20.0%
<b>Outcome (Follow-up &gt;2 years)</b>		
Disease-free	18	72.0%
Recurrence	5	20.0%
Death	2	8.0%

Multivariate logistic regression analysis identified Hyams grade III–IV as a statistically significant independent predictor of recurrence in patients with olfactory neuroblastoma, with an odds ratio (OR) of 4.75 (95% CI: 1.30–17.40;  $p = 0.018$ ), suggesting that high-grade tumors were nearly five times more likely to recur compared to low-grade counterparts. Although not statistically significant, age over 50 years (OR =

2.45;  $p = 0.08$ ) and receiving chemoradiotherapy alone (OR = 3.30;  $p = 0.06$ ) showed a trend toward increased recurrence risk. Male sex (OR = 1.20;  $p = 0.72$ ) and treatment with surgery plus radiotherapy (OR = 0.45;  $p = 0.29$ ) were not significantly associated with recurrence. These findings highlight tumor grade as the most robust predictor of disease recurrence within this cohort. [Table-VI].

**Table – VI: Multivariate Logistic Regression – Predictors of Recurrence in ONB (n = 25)**

Predictor Variable	Odds Ratio (OR)	95% CI (Lower–Upper)	p-value
Age > 50	2.45	0.90–6.70	0.08
Male sex	1.20	0.45–3.22	0.72
Hyams Grade III–IV	4.75	1.30–17.40	0.018*
Chemoradiotherapy only	3.30	0.95–11.40	0.06
Surgery + Radiotherapy	0.45	0.10–1.95	0.29

\*Significant at  $p < 0.05$

Cox proportional hazards regression analysis revealed that Hyams grade III–IV was the only statistically significant predictor of mortality among patients with olfactory neuroblastoma. Patients with high-grade tumors had a hazard ratio (HR) of 5.10 (95% CI: 1.50–17.20;  $p = 0.009$ ), indicating a more than fivefold increased risk of death compared to those with low-grade tumors. Although patients aged over 50

years (HR = 2.20;  $p = 0.10$ ) and those treated with chemoradiotherapy alone (HR = 2.90;  $p = 0.11$ ) demonstrated elevated hazard ratios, these associations did not reach statistical significance. Similarly, male sex (HR = 1.40;  $p = 0.43$ ) and treatment with surgery plus chemoradiotherapy (HR = 0.55;  $p = 0.44$ ) were not significantly linked to overall survival. These findings underscore tumor grade as the most

impactful prognostic variable for both recurrence and mortality in ONB. [Table-VII].

**Table – VII: Cox Proportional Hazards Regression – Predictors of Mortality (n = 25)**

Predictor Variable	Hazard Ratio (HR)	95% CI (Lower–Upper)	p-value
Age > 50	2.20	0.85–5.70	0.10
Male sex	1.40	0.60–3.30	0.43
Hyams Grade III–IV	5.10	1.50–17.20	0.009*
Chemoradiotherapy only	2.90	0.80–10.50	0.11
Surgery + Chemoradiotherapy	0.55	0.12–2.50	0.44

\*Significant at  $p < 0.05$

## DISCUSSION

In this retrospective analysis conducted across tertiary care centers in Bangladesh, olfactory neuroblastoma (ONB) emerged as the most frequently encountered rare head and neck malignancy, constituting 25% of the 100 rare tumor cases identified. This proportion is notably high and consistent with institutional series where ONB predominated among rare sinonasal neoplasms [12]. While SEER-based population data suggest ONB has a lower overall incidence compared to other neuroendocrine sinonasal tumors, its relative frequency within specialized centers may reflect referral bias toward surgically manageable tumors [13]. The age distribution in our cohort was skewed toward middle-aged adults, with 48% aged 30–50 years and 36% over 50, aligning with prior studies indicating peak incidence between the fifth and sixth decades [1,14]. A modest male predominance (56%) was observed, mirroring sex distribution patterns reported in smaller institutional series [15]. The clinical presentation was characterized predominantly by nasal obstruction (80%), epistaxis (60%), and anosmia (48%), findings that strongly align with other observational series where these symptoms were cited as hallmark manifestations [14,16]. Less frequent symptoms such as headache and visual disturbances were also consistent with local extension, corroborating similar patterns in cases involving orbital or intracranial invasion [17]. Histopathological grading using the Hyams system revealed a fairly balanced distribution in our cohort, with Grade II being most common (32%), followed by Grade III (28%), and Grades I and IV at 20% each. This pattern closely parallels observations by Gram et al. and Fukushima et al., who also reported predominance of intermediate grades with variable outcome implications [18,19]. Treatment strategies in our study favored multimodal approaches, with surgery followed by radiotherapy being the most commonly employed (40%), consistent with the established paradigm that surgery-based combinations yield the best survival outcomes [20,21]. The 72% disease-free rate at  $\geq 2$ -year follow-up in our series compares favorably with Korean and Mexican cohorts reporting disease-free survival (DFS) rates ranging from 62–70% following surgery-based treatment [5]. Meanwhile, chemoradiotherapy alone was associated with poorer outcomes, consistent with large-scale studies showing no added survival benefit in non-surgical regimens, especially in advanced disease [22,23]. Importantly, multivariate logistic regression identified Hyams grade III–IV as the sole significant predictor of recurrence (OR = 4.75,  $p = 0.018$ ), underscoring the strong prognostic value of tumor grade. This is supported

by extensive literature, including Wolfe et al. and Choby et al., both of whom demonstrated that high Hyams grade independently predicted recurrence and worse survival [6,24]. Age >50 and chemoradiotherapy-only treatment showed elevated, though non-significant, odds ratios for recurrence, echoing findings from SEER and institutional cohorts where these factors trended toward poorer outcomes without reaching statistical significance [1,5]. In the Cox regression model for mortality, Hyams grade III–IV again emerged as the only statistically significant predictor (HR = 5.10,  $p = 0.009$ ), aligning with evidence from Van Gompel et al. and Wolfe et al., who demonstrated markedly lower survival in high-grade ONB [24,25]. Conversely, age >50 (HR = 2.20,  $p = 0.10$ ) and chemoradiotherapy-only (HR = 2.90,  $p = 0.11$ ) showed elevated but non-significant hazard ratios, a trend consistently noted across several retrospective cohorts [5,22]. Male sex and surgery combined with chemoradiotherapy were not significantly associated with survival outcomes, consistent with findings from Okafor et al. and Veyrat et al., who reported no sex-based survival differences and variable efficacy for chemoradiation across different tumor grades and stages [4,14]. Overall, our study reinforces that histological tumor grade remains the most reliable prognostic indicator for both recurrence and mortality in olfactory neuroblastoma, while age and treatment modality contribute variably. The predominance of intermediate-grade disease, frequent use of multimodal therapy, and relatively favorable short- to mid-term outcomes support international trends but also emphasize the urgent need for regional data consolidation. In resource-limited settings like Bangladesh, early-stage identification and structured surgical oncology pathways could significantly improve outcomes, especially as high-grade ONB continues to portend a markedly worse prognosis despite aggressive multimodal treatment.

## Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

## CONCLUSION

This study highlights olfactory neuroblastoma (ONB) as a leading entity among rare head and neck malignancies diagnosed in tertiary hospitals in Bangladesh. The findings underscore the predominance of ONB in middle-aged adults, with common symptoms including nasal obstruction, epistaxis, and anosmia. Histopathologically, Hyams grade II



was the most frequently observed, though high-grade tumors (III–IV) significantly correlated with increased risks of recurrence and mortality. Multimodal treatment approaches, particularly surgery followed by radiotherapy, were associated with favorable short- to mid-term outcomes, whereas chemoradiotherapy alone showed poorer trends. Logistic and Cox regression analyses confirmed high tumor grade as the strongest prognostic factor, while age, sex, and treatment modality did not show statistically significant associations with survival or recurrence. The study adds valuable regional epidemiologic and outcome data to the limited global literature on ONB and reinforces the need for early-stage diagnosis and standardized multimodal care in resource-limited settings. Larger multicenter prospective studies are recommended to validate these findings and optimize treatment algorithms.

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**Ethical approval:** The study was approved by the Institutional Ethics Committee

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