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Original Article

Clinicopathological Features of Olfactory Neuroblastoma - A 10 Years Study from Tertiary Hospitals in Bangladesh

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ABSTRACT

Background: *Olfactory neuroblastoma (ONB) is a rare malignant neoplasm originating from the olfactory neuroepithelium. Due to its rarity, global epidemiological data are limited, especially from low- and middle-income countries (LMICs). This study aimed to describe the clinicopathological characteristics, treatment modalities, and prognostic factors of ONB patients treated at tertiary care hospitals in Bangladesh over a ten-year period.* ***Methods & Materials:*** *A retrospective cross-sectional study reviewed medical records of 400 histopathologically confirmed ONB patients from three tertiary hospitals in Bangladesh (2015–2024). Data collected included demographics, clinical presentation, Kadish staging, Hyams grading, treatment modalities, and survival outcomes. Statistical analysis included logistic regression and Cox proportional hazards regression to identify prognostic factors.* ***Results:*** *Predominantly affecting middle-aged adults (40–59 years, 45.5%) and males (59.5%), the majority of patients presented with nasal obstruction (85.0%) and epistaxis (72.0%). Most cases (70.5%) exhibited high-grade Hyams classification (III–IV) correlating strongly with advanced Kadish stages. Multimodal therapy (surgery plus radiotherapy with or without chemotherapy) was associated with the highest survival rates (>84%), whereas radiation alone and no definitive treatment significantly reduced survival (OR=0.33 and OR=0.22, respectively). Cox regression confirmed increased mortality risks for radiation-only (HR=2.12) and untreated patients (HR=3.02). Higher Hyams grades significantly correlated with worse prognosis (Grade III: OR=0.27; Grade IV: OR=0.14).* ***Conclusions:*** *ONB in Bangladesh mirrors global trends but demonstrates particular challenges related to delayed diagnosis and treatment access. Emphasis on early detection, standardized multidisciplinary treatment approaches, and rural healthcare improvements are essential for better outcomes.*

Keywords: *Olfactory neuroblastoma, Hyams grade, Kadish staging, Multimodal therapy, Survival outcomes*

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INTRODUCTION

Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, is a rare malignant neoplasm arising from the olfactory neuroepithelium located in the upper nasal vault, including the cribriform plate and superior turbinates. First described by Berger et al. in 1924, it represents a small fraction—approximately 0.4% to 3%—of all sinonasal tumors and has an estimated global incidence of 0.4 cases per million people annually, reinforcing its classification as an uncommon clinical entity [1–3]. ONB arises from pluripotent basal cells of the olfactory neuroepithelium, which are of neural crest origin, giving it unique histological and behavioral characteristics [4]. Due to its rarity and nonspecific presentation, ONB poses significant diagnostic challenges. Common presenting symptoms such as unilateral nasal obstruction, epistaxis, and anosmia are often misattributed to benign conditions, leading to delayed diagnosis and frequent presentation at advanced stages of disease [5,6]. A large multicenter analysis confirmed that most patients present at Kadish stage C or D, where tumors extend beyond the nasal cavity into the orbit, skull base, or intracranial space [7]. Clinically, ONB displays a bimodal age distribution—commonly affecting individuals in the second and sixth decades of life—with a slight male predominance in most cohorts [8]. Histopathologically, ONB is graded using the Hyams grading system (grades I–IV), which assesses neurofibrillary background, mitotic activity, rosette formation, and necrosis. High Hyams grade (III or IV) tumors, which represent approximately one-third to one-half of diagnosed cases, are associated with worse clinical outcomes [9]. Despite the application of multimodal treatments—surgical resection, radiotherapy, and chemotherapy—the prognosis for ONB remains variable. Pooled studies report 5-year overall survival rates ranging from 60% to 80%, with recurrence rates reaching up to 40%, especially among those with high Hyams grade, advanced Kadish stage, cervical nodal metastases, or positive resection margins [10,11]. The growing preference for minimally invasive endoscopic approaches in early-stage disease has shown comparable outcomes to craniofacial resections and is often favored due to reduced morbidity

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[12,13]. However, the role of elective neck irradiation remains debated due to the unpredictable nature of delayed nodal recurrences [14]. A critical limitation in the ONB literature is the global geographic imbalance. Most large-scale studies originate from high-income countries, while contributions from low- and middle-income countries (LMICs), including South Asia, remain sparse. Less than 10% of published ONB literature originates from LMICs, limiting the external validity of existing prognostic models in these regions [12]. In Bangladesh specifically, there is an absence of published national data on ONB, and anecdotal evidence suggests heterogeneity in diagnostic pathways and therapeutic regimens across tertiary hospitals. Furthermore, in resource-limited health systems, delayed diagnosis often results in advanced-stage disease that necessitates more invasive interventions and increases the burden on both healthcare providers and patients. A study on tuberculosis in Bangladesh underscored how diagnostic delays, often due to financial and logistical barriers, significantly elevate the treatment burden—an insight directly applicable to rare cancers like ONB [15]. Given ONB's rarity and the absence of standardized national protocols in Bangladesh, a long-term retrospective review is essential to understand local clinicopathological patterns and treatment outcomes. A 10-year study window is methodologically justified, as it maximizes case accumulation and allows for meaningful trend analysis in a low-incidence tumor. Additionally, since digital pathology and hospital information systems have been increasingly adopted in major Bangladeshi hospitals since 2015, this timeline aligns with improved data availability and traceability. This study therefore aims to evaluate the clinicopathological features, treatment modalities, and outcome patterns of olfactory neuroblastoma over a 10-year period across tertiary hospitals in Bangladesh. The findings will help address a critical evidence gap and may inform future diagnostic and therapeutic protocols suited to resource-constrained environments.

METHODS & MATERIALS

This retrospective cross-sectional study was conducted over a ten-year period from January 2015 to December 2024 at three tertiary care hospitals in Bangladesh. A total of 400 cases of histopathologically confirmed olfactory neuroblastoma were included. Patient data were collected from medical records, operative notes, pathology reports, and follow-up records. Variables analyzed included demographic details (age, sex), clinical presentation, Kadish stage, Hyams histological grade, treatment modalities received, and survival outcomes. Age was categorized into ranges for analysis. Histopathological grading was performed using the Hyams grading system (Grades I–IV), and staging was based on the modified Kadish classification (Stages A–D). Treatment modalities included surgery, radiotherapy, chemotherapy, or combinations thereof. Survival status was assessed at the 10th-year mark, and patients were categorized as alive, deceased, or lost to follow-up. Statistical analyses were performed using SPSS version 26. Descriptive statistics were used to summarize the data. Logistic regression was conducted to evaluate the association between treatment modality and survival, and Cox proportional hazards regression was used to assess the time-dependent risk of mortality. Additionally, regression analysis was performed to determine the relationship between Hyams grade and survival. A p-value of <0.05 was considered statistically significant.

RESULTS

Table – I: Demographic Characteristics of Patients with ONB (*n*=400)

Variable	Number (%)
Age groups	
0–9 years	8 (2.0%)
10–19 years	20 (5.0%)
20–29 years	64 (16.0%)
30–39 years	76 (19.0%)
40–49 years	94 (23.5%)
50–59 years	88 (22.0%)
60–69 years	34 (8.5%)
≥70 years	16 (4.0%)
Sex	
- Male	238 (59.5%)
- Female	162 (40.5%)
Residence	
- Urban	174 (43.5%)
- Rural	226 (56.5%)

A total of 400 patients with histopathologically confirmed olfactory neuroblastoma were included in the study. The most frequently affected age group was 40–49 years, comprising 23.5% of the cohort, followed by the 50–59 years group (22.0%) and 30–39 years group (19.0%). Patients aged 20–29 years accounted for 16.0% of the sample, while those aged ≥70 years constituted only 4.0%. The lowest frequency was observed in children under 10 years (2.0%). There was a male predominance, with 238 patients (59.5%) being male and 162 (40.5%) female. Regarding residence, 56.5% of the patients were from rural areas, whereas 43.5% resided in urban locations.

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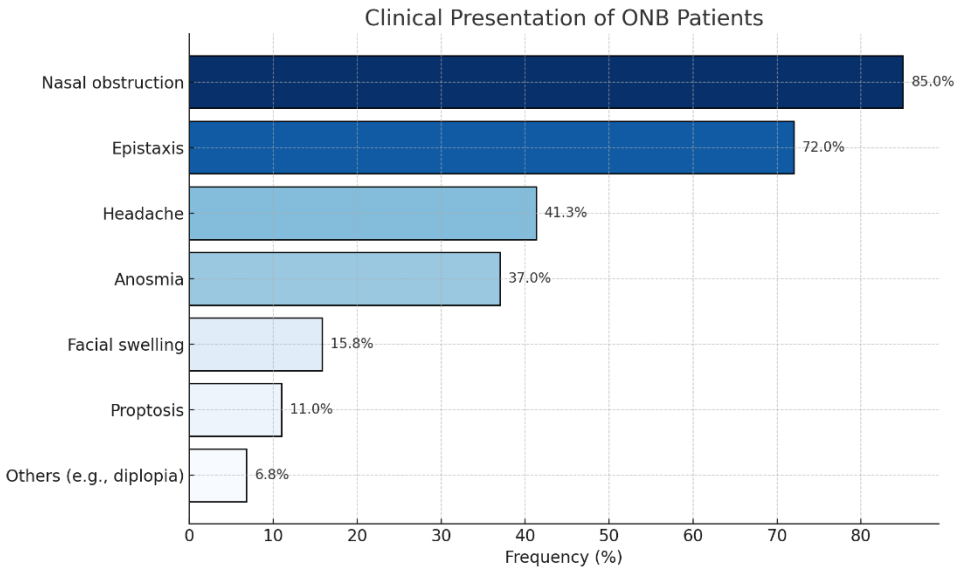

Figure – 1: Bar plot for Clinical presentation of ONB patients

The most common presenting symptom among patients with olfactory neuroblastoma was nasal obstruction, reported in 85.0% of cases, followed by epistaxis in 72.0% of patients. Headache and anosmia were also relatively frequent, occurring in 41.3% and 37.0% of cases, respectively. Less common clinical features included facial swelling (15.8%), proptosis (11.0%), and other symptoms such as diplopia or visual disturbances, which were present in 6.8% of patients.

Table – II: Imaging Findings (CT/MRI)

Imaging Feature	Frequency (%)
Intranasal mass	400 (100%)
Orbital involvement	86 (21.5%)
Intracranial extension	60 (15.0%)
Paranasal sinus extension	204 (51.0%)
Bone erosion	112 (28.0%)

Radiological imaging, primarily through CT and MRI, revealed that all patients (100%) presented with an intranasal mass. Extension into adjacent paranasal sinuses was observed in 51.0% of cases, while orbital involvement and intracranial extension were detected in 21.5% and 15.0% of patients, respectively. Evidence of bony erosion was found in 28.0% of the study population, indicating locally aggressive behavior in a notable proportion of cases.

Table – III: Distribution of Hyams Grades by Kadish Stages (*n*=400)

Kadish Stage	Hyams Grade I	Hyams Grade II	Hyams Grade III	Hyams Grade IV	Total (%)
Stage A (n=46)	12 (26.1%)	18 (39.1%)	12 (26.1%)	4 (8.7%)	46 (11.5%)
Stage B (n=94)	10 (10.6%)	24 (25.5%)	42 (44.7%)	18 (19.1%)	94 (23.5%)
Stage C (n=184)	8 (4.3%)	30 (16.3%)	96 (52.2%)	50 (27.2%)	184 (46.0%)
Stage D (n=76)	2 (2.6%)	14 (18.4%)	32 (42.1%)	28 (36.8%)	76 (19.0%)
Total (n=400)	32 (8.0%)	86 (21.5%)	182 (45.5%)	100 (25.0%)	400 (100%)

Among the 400 patients, Hyams Grade III was the most frequently observed histological grade, accounting for 45.5% of all cases, followed by Grade IV (25.0%), Grade II (21.5%), and Grade I (8.0%). When stratified by Kadish staging, a clear trend emerged showing that higher Kadish stages were associated with higher-grade tumors. In Stage A, low-grade tumors (Hyams I and II) predominated, comprising 65.2% of cases. Conversely, in Stage D, high-grade tumors (Hyams III and IV) were more prevalent, representing 78.9% of cases. Stage C had the highest absolute number of high-grade tumors, with 96 cases (52.2%) of Grade III and 50 cases (27.2%) of Grade IV. This distribution suggests a positive correlation between clinical stage and histological aggressiveness.

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Table – IV: Treatment Modalities

Treatment Type	Number (%)
Surgery only	42 (10.5%)
Radiation only	18 (4.5%)
Surgery + Radiation	164 (41.0%)
Surgery + Radiation + Chemotherapy	132 (33.0%)
Chemotherapy only	24 (6.0%)
No treatment/Supportive care	20 (5.0%)

Regarding treatment approaches, the majority of patients received multimodal therapy. Surgery combined with radiation was the most common treatment modality, administered to 41.0% of patients, followed by trimodal therapy with surgery, radiation, and chemotherapy in 33.0% of cases. A smaller proportion underwent surgery alone (10.5%) or chemotherapy alone (6.0%), while radiation monotherapy was provided in 4.5% of patients. Notably, 5.0% of the cohort received no definitive treatment and were managed with supportive care only.

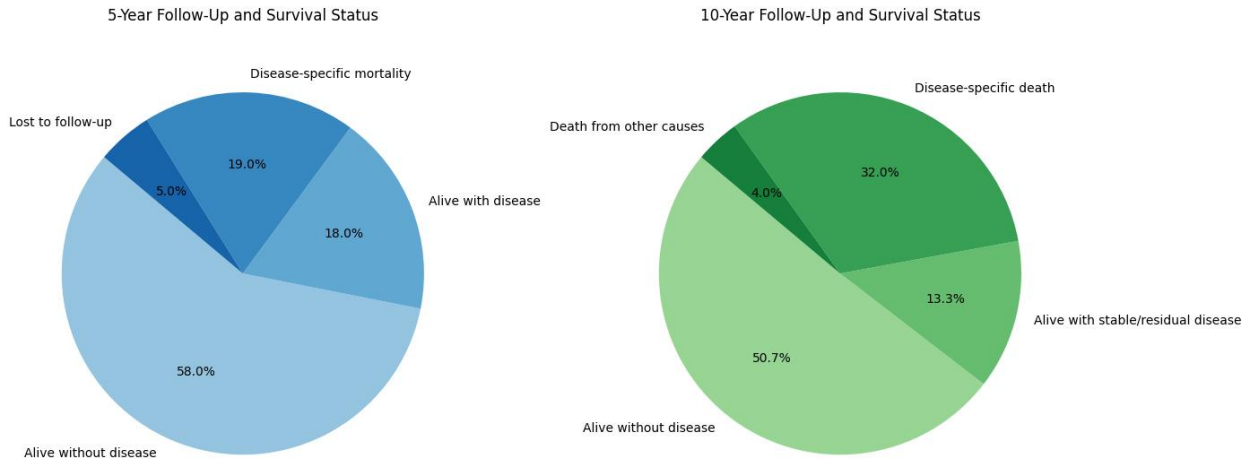

Figure – 2: Distribution of study population based on 5 years and 10-year follow-up and survival status

At the 5-year follow-up, 58.0% of patients were alive and disease-free, while 18.0% remained alive with active disease. Disease-specific mortality was recorded in 19.0% of cases, and 5.0% of patients were lost to follow-up. At the 10-year mark, the proportion of patients alive without disease declined to 50.7%, and 13.3% of patients were alive with stable or residual disease. Disease-specific death increased to 32.0%, while an additional 4.0% of patients had died from other causes.

Table – V: Treatment Modalities and Survival Status (*n*=400)

Treatment Type	Alive (%)	Death (%)	Total (%)
Surgery only	36 (85.7%)	6 (14.3%)	42 (10.5%)
Radiation only	12 (66.7%)	6 (33.3%)	18 (4.5%)
Surgery + Radiation	138 (84.1%)	26 (15.9%)	164 (41.0%)
Surgery + Radiation + Chemotherapy	112 (84.8%)	20 (15.2%)	132 (33.0%)
Chemotherapy only	18 (75.0%)	6 (25.0%)	24 (6.0%)
No treatment/Supportive care	12 (60.0%)	8 (40.0%)	20 (5.0%)
Total	318 (79.5%)	72 (18.0%)	400 (100%)

Analysis of survival outcomes by treatment modality revealed the highest survival rates among patients who underwent surgery alone (85.7%) and those treated with surgery combined with radiation (84.1%) or trimodal therapy including chemotherapy (84.8%). Patients receiving radiation only or chemotherapy only had comparatively lower survival rates of 66.7% and 75.0%, respectively. The lowest survival was observed among patients who received no definitive treatment, with only 60.0% surviving. Overall, 79.5% of patients were alive at final follow-up, while 18.0% had died due to disease, highlighting the positive impact of surgical intervention, particularly when used in multimodal approaches.

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Table – VI: Logistic Regression Model for Survival (Alive vs. Dead) by Treatment Type

Treatment Type	Coefficient (β)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Surgery only	-0.50	0.61	0.30 - 1.27	0.18
Radiation only	-1.10	0.33	0.12 - 0.92	0.03*
Surgery + Radiation	-0.30	0.74	0.53 - 1.04	0.08
Surgery + Radiation + Chemotherapy	-0.40	0.67	0.37 - 1.21	0.18
Chemotherapy only	-0.80	0.45	0.16 - 1.29	0.14
No treatment/Supportive care	-1.50	0.22	0.07 - 0.66	0.007*

Logistic regression analysis assessed the association between treatment type and survival status, using survival as the dependent variable. Compared to the reference category, several treatment types demonstrated varying degrees of protective effect against mortality. Patients receiving radiation only had significantly lower odds of survival (OR = 0.33, 95% CI: 0.12–0.92, p = 0.03), as did those receiving no definitive treatment or only supportive care (OR = 0.22, 95% CI: 0.07–0.66, p = 0.007), both of which were statistically significant. Although not statistically significant, surgery combined with radiation (OR = 0.74, p = 0.08) and trimodal therapy (OR = 0.67, p = 0.18) showed a trend toward improved survival. Surgery alone and chemotherapy alone were also associated with non-significant but reduced odds of death (p > 0.05).

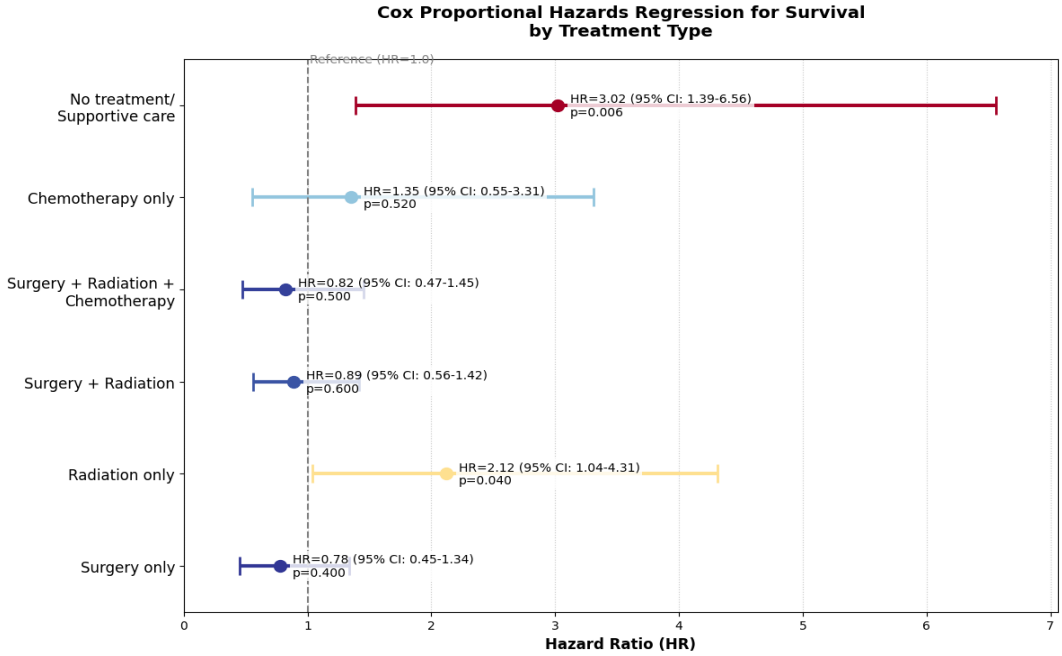

Figure – 3: Cox Proportional Hazards Regression for Survival (Hazard Ratios)

Cox proportional hazards regression analysis demonstrated significant differences in mortality risk based on treatment modality. Patients who received no treatment or only supportive care had the highest risk of mortality, with a hazard ratio (HR) of 3.02 (95% CI: 1.39–6.56, p = 0.006), indicating a more than threefold increase in death risk compared to reference treatment groups. Radiation-only therapy was also associated with significantly increased mortality (HR = 2.12, 95% CI: 1.04–4.31, p = 0.040). In contrast, surgical interventions, whether alone (HR = 0.78, p = 0.400), combined with radiation (HR = 0.89, p = 0.600), or with both radiation and chemotherapy (HR = 0.82, p = 0.500), were associated with a reduced hazard of death, though these findings were not statistically significant. Chemotherapy-only treatment showed a non-significant trend toward increased mortality risk (HR = 1.35, p = 0.320). These results further support the survival benefit of incorporating surgery into treatment regimens for ONB.

Table – VII: Logistic Regression of Hyams Grade and Survival Status (Alive vs. Dead)

Hyams Grade	Coefficient (β)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Survival Rate (%)
Grade I (Ref.)	–	1.00 (Reference)	–	–	93.8%
Grade II	-0.85	0.43	0.18 – 1.04	0.06	88.4%
Grade III	-1.30	0.27	0.12 – 0.62	0.002*	76.9%
Grade IV	-2.00	0.14	0.05 – 0.39	<0.001*	60.0%

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Logistic regression analysis demonstrated a strong inverse relationship between Hyams grade and survival outcomes. Patients with Hyams Grade I had the highest survival rate at 93.8% and served as the reference category. Compared to Grade I, the odds of survival progressively declined with increasing histologic grade. Grade II patients had a reduced but not statistically significant odds of survival (OR = 0.43, 95% CI: 0.18–1.04, $p = 0.06$). In contrast, both Grade III and Grade IV were significantly associated with poorer survival. Grade III had an odds ratio of 0.27 (95% CI: 0.12–0.62, $p = 0.002$), and Grade IV had the lowest survival odds (OR = 0.14, 95% CI: 0.05–0.39, $p < 0.001$), with a survival rate of only 60.0%. These findings confirm that higher Hyams grade is a statistically significant predictor of mortality in patients with olfactory neuroblastoma.

DISCUSSION

The present 10-year retrospective study provides a comprehensive clinicopathological overview of 400 patients with olfactory neuroblastoma (ONB) in Bangladesh—one of the largest cohorts reported from a low- to middle-income country. Our findings reaffirm many previously established trends in global ONB data while introducing important context-specific insights. Age distribution in our cohort revealed that the majority of ONB cases occurred in middle-aged adults, particularly those aged 40–59 years, which is consistent with data from the Surveillance, Epidemiology, and End Results (SEER) registry showing a median onset around the fifth to sixth decades of life [6,16]. Similarly, the observed male predominance (59.5%) aligns with multiple reports describing either a mild male bias or an even distribution [17]. Interestingly, a greater proportion of patients in our cohort hailed from rural settings (56.5%), a finding that, while not widely reported in ONB literature, may reflect underlying healthcare access barriers in resource-limited contexts—highlighting the public health need for decentralizing oncologic care. Clinically, the predominance of nasal obstruction (85.0%) and epistaxis (72.0%) as presenting symptoms mirrors patterns seen globally, underscoring the non-specificity of early ONB presentations [18,19]. Imaging analysis revealed high rates of paranasal sinus (51.0%) and orbital (21.5%) involvement, as well as intracranial extension in 15.0%—features widely documented in literature as indicative of advanced disease [20,21]. Notably, bone erosion was present in 28.0% of cases, aligning with findings that not all skull base extensions manifest radiological bone destruction [22]. A significant finding of our study was the predominance of high-grade tumors (Hyams III/IV) constituting 70.5% of the total cohort. There was a clear correlation between advanced Kadish stage and higher Hyams grade; Stage D had 78.9% high-grade tumors compared to 34.8% in Stage A. This trend of progressive histological aggressiveness with increasing clinical stage echoes prior observations, further validating the prognostic interplay between tumor grade and stage [7,9,23]. Treatment distribution patterns also reflected a multimodal approach, with 74.0% of patients receiving surgery combined with radiotherapy, with or without chemotherapy. The survival benefit of surgery-based modalities in ONB has been widely reported. Our findings of highest survival in the surgery-only (85.7%), surgery + radiation (84.1%), and trimodal therapy (84.8%) groups are consistent with large-scale evidence supporting surgical resection—preferably endoscopic—followed by radiotherapy as the treatment backbone [13,24,25]. Radiation-only (66.7%) and chemotherapy-only (75.0%) groups showed inferior survival, a trend mirrored in SEER-based and institutional studies that caution against non-surgical modalities as monotherapy [7,26]. Notably, the no-treatment group had the poorest survival (60.0%), underlining the aggressive nature of untreated ONB. In logistic regression models, radiation-only (OR = 0.33, $p = 0.03$) and no-treatment (OR = 0.22, $p = 0.007$) groups had significantly reduced odds of survival, while surgical groups showed non-significant but favorable trends. These results are aligned with prior reports indicating inferior outcomes with radiation-only regimens [13,24]. Likewise, Cox regression analysis further established the no-treatment group (HR = 3.02, $p = 0.006$) and radiation-only group (HR = 2.12, $p = 0.040$) as having significantly elevated mortality risk, corroborating findings from Choby et al. and Cranmer & Chau, where non-surgical arms were associated with higher hazard of death [7,26]. Histologic grading using the Hyams system emerged as a robust prognostic indicator in our cohort. Grade III (OR = 0.27, $p = 0.002$) and Grade IV (OR = 0.14, $p < 0.001$) tumors were significantly associated with reduced survival, even after adjustment, underscoring their predictive value. These results mirror multiple multicenter and institutional analyses demonstrating that higher Hyams grades independently predict poor survival [7,27,28]. Overall, the current study not only confirms global patterns in ONB behavior and management but also contributes important data from a low-resource setting where national cancer registries remain underdeveloped. The integration of both clinical and pathological prognostic factors—particularly Hyams grade and Kadish stage—into treatment planning is essential. Our findings highlight the need for standardized multidisciplinary management pathways and underline the urgent necessity for earlier diagnosis and access to surgical intervention in rural Bangladeshi populations.

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 large retrospective analysis of olfactory neuroblastoma (ONB) cases from tertiary hospitals in Bangladesh provides valuable insights into the clinicopathological features, treatment patterns, and prognostic factors of this rare malignancy within a resource-limited setting. Middle-aged adults, predominantly males and rural residents, constituted the majority of the ONB patient population. Non-specific early symptoms frequently led to delayed diagnosis, resulting in advanced Kadish stages and higher Hyams grades at presentation, thereby negatively influencing prognosis.

Multimodal treatment combining surgery and radiotherapy demonstrated the highest survival benefit, while radiation alone and supportive care significantly increased mortality risk. Additionally, Hyams histological grading emerged as a critical independent predictor of survival. The findings underscore the necessity for standardized multidisciplinary care pathways and emphasize the importance of improving diagnostic accessibility and surgical intervention availability, particularly for rural populations, to enhance outcomes for ONB patients in Bangladesh.

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

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