Title: Clinico-pathological and survival profiles of orbito-ocular tumors in Enugu Nigeria. Is there an emerging trend?

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Abstract

Background: Orbito-ocular tumors are rare, but they cause significant morbidity and mortality. There are reported variations in their pattern of presentation and frequency of occurrence.

Objective: To evaluate the occurrence, clinicopathologic spectrum, and patterns of orbito-ocular neoplasms as well as the treatment and outcome profiles.

Methods: A 5-year retrospective analysis of consecutive patients treated for orbito-ocular tumors. We evaluated patterns of occurrence, clinicopathological concordance, and outcome of treatment. Associations were evaluated with chi square and confidence interval. Data analysis was performed using SPSS for windows version 23 and inferences were judged using the 95% level of significance.

Results: Among 100 patients with orbito-ocular masses, 62 were histologically confirmed. The female to male ratio (F:M) was 1.0. Their ages ranged from 7 months to 93 years, mean = 33.4 ± 2.7 years. There was an age variation among tumor types. Patients with squamous cell carcinoma (SCC) had a mean age of 46.4 years, while for retinoblastoma the mean age was 3.09 years. All patients with retinoblastoma had proven macroscopic orbital extension. SCC was the most common tumor type (n = 19), however, among children, retinoblastoma (n = 11) was more common. Melanocytic nevus, sebaceous gland carcinoma, and adenocarcinoma of lacrimal gland (n = 6, n = 5, n = 5), respectively, among other tumors were treated. Concordance between clinical and histopathological diagnoses was obtained among 30 (48.3%) cases. 1-year and 3-year survival for retinoblastoma was 90% and 72.9%, respectively, and 78.9% and 68.4% for SCC.

Conclusion: SCC is currently the most common orbito-ocular tumor in our setting.

Keywords
Orbito-ocular Tumors, clinical diagnosis, histopathology, profile, trends

Introduction

The management of orbito-ocular tumors present significant challenges to ophthalmologists practicing in the developing countries.¹,² The mean reported incidence of these lesions among African countries varies between 0.5 and 1.4 per 100,000 population.¹–³ Most cases of orbito-ocular tumors reported among the underdeveloped nations are malignant.¹–⁵ Studies from different parts of Nigeria have documented
Materials and Methods: We performed a 5-year single institution, retrospective analysis of the clinical and laboratory data of consecutive patients treated for orbito-ocular tumors from June 2013 to May 2018. Data was obtained from case notes, laboratory, and theater and follow-up records. Our unit protocol of obtaining consent from patients for publication of results during admission and follow-up records. Our unit protocol of obtaining consent from patients for publication of results during admission and follow-up records. Ethical approval was obtained from the Health and Research Ethics Committee of our hospital for the index study.

Inclusion criteria

All cases of orbito-ocular tumor with a clinical diagnosis made by an ophthalmologist in our center.

Cases must be registered and treated in our center.

All cases with histopathologic confirmation.

Exclusion criteria

Cases surgically treated in other centers and referred to our center for adjuvant treatment cases in which clinical diagnosis was uncertain and histopathologic review negative for orbito-ocular tumor. Based on the presentation and tumor type, treatment varied from excisional biopsy, enucleation to exenteration. Our current protocol of care includes a multidisciplinary tumor board review of cases, determination of appropriate adjuvant treatment for malignant cases, follow-up review, and outcome evaluation.

Data obtained from above records were analyzed to determine patterns of occurrence, clinic-pathological concordance, and outcome of treatment. Associations were evaluated with chi square and confidence interval. Data analysis was performed using SPSS for windows version 23 and inferences were judged using the 95% level of significance.

Follow-up: Duration of follow up varied from 1 month to 3.3 years with a mean of 1.1 ± 0.7 years. Major survival indices recorded during follow up include, visual status, recurrence profile, and performance status.

Results

Among 100 patients with lesions suggestive of ocular neoplasms, 62 patients satisfied the inclusion criteria. 38 patients were excluded because their histopathology showed inflammatory mass lesions (n = 21) and pterygium (n = 17). 32 were female with F:M ratio = 1. There was no gender variation among tumor subtypes. Patients’ ages ranged from 7 months to 93 years with a mean of 33.4 ± 2.7 years. There was a significant age variation among tumor types (F = 11.3, p = 0.003). Patients with squamous cell carcinoma (SCC) had a mean age of 46.4 ± 1.9 years, while for retinoblastoma the mean age was 3.1 ± 0.4 years. Among the 62 patients with histopathological diagnosis, SCC was the most common tumor type (n = 19), followed by retinoblastoma (n = 11). However, squamous cell carcinoma (SCC) was the most common tumor among adults and retinoblastomas were the most common among children. Other tumors treated were melanocytic nevus in six patients, sebaceous gland carcinoma, and adenocarcinoma of lacrimal gland in five patients, respectively (Table 1). Three (3) patients had rhabdomyosarcoma, melanoma of uveal tract, and squamous papilloma of the conjunctiva, respectively. Two patients had Rosai Dorfman’s and fibroma. Basal cell carcinoma, trichilemmal carcinoma, and dermoid cyst occurred in one patient, respectively. 17 (27.4%) patients had comorbidities with hypertension in 11 patients, diabetes mellitus in four patients, and peptic ulcer disease in two patients accounting for the comorbidities. Premorbid history of hypertension was associated with increased risk of a malignant orbito-ocular tumor (X² = 7.07, p = 0.004) (Table 1). Concordance between clinical and histopathological diagnoses occurred in 30 (48.3%) cases (Figure 1). Microsurgical local excisional biopsy was performed in 33 (53.2%) patients, enucleation was performed in 10 (16.1%) patients, whereas exenteration was performed for 19 (30.6%) patients. Early post-operative mortality occurred in 1 (1.6%) patient from postoperative sepsis. Local recurrence was noted in 8 (12.9%) patients. 4 cases of recurrence were SCC, 2 cases were rhabdomyosarcoma, while 1 case each of sebaceous gland adenocarcinoma and lacrimal gland carcinoma also recurred. Time to recurrence varied from 3.5 months in rhabdomyosarcoma to 12 months in SCC with a mean of 6.5 ± 0.2 months. For retinoblastoma, (RB) patients treated with enucleation (8) or chemotherapy with external beam radiotherapy without enucleation (3) had a mean progression free interval of 4.7 ± 0.5 months (range of 3.1–7.3 months). In one RB (1.6%) patient, tumor regression occurred with resultant globe salvage. 10 RB (90 ± 3.0%) patients survived for 1 year and 8 (72.9 ± 2.7%) survived for 3 years. The 1-year survival ranged from 50% in rhabdomyosarcoma to 78.9(SCC), whereas the 3-year survival was 50% in rhabdomyosarcoma and 68.4% in SCC (Table 2).
Discussion

In our current series, a significant proportion of clinically suspected orbito-ocular neoplasms were histologically confirmed as non-tumor lesions highlighting the role of histopathological examination in verifying clinically suspected mass lesions. Among histologically proven cases, the clinico-pathological concordance was low suggesting that reliance on clinical suspicion for diagnosis may be deceptive or inaccurate in our setting. Ocular tumors in our series showed no gender bias, however, there was a significant variation in the histological profile of tumors between adults and children. Squamous cell carcinoma was the most common tumor overall but it was predominantly reported among adults, whereas retinoblastoma was the most commonly diagnosed tumor in children. History of hypertension in a setting of ocular mass lesion among adults was associated with an increased occurrence of a malignant orbito-ocular pathology. Rhabdomyosarcoma was associated with the worst survival profile among malignant tumors. In a previous study on orbito-ocular tumors from Lagos, Southwest Nigeria, Anunobi and co-workers found retinoblastoma the most common orbito-ocular tumor in general, whereas rhabdomyosarcoma was the most common orbital malignancy. 9 This is corroborated by a previous study from our center almost two decades ago which also reported retinoblastoma as the most common orbito-ocular neoplasm followed by squamous cell carcinoma. Another

Table 1. Tumor subtypes and association with premorbid diseases.

| Characteristics | Frequency (% Frequency) |
|-----------------|------------------------|
| A. Tumor histology | N (%) |
| Squamous cell carcinoma (SCC) | 19 (30.6) |
| Retinoblastoma | 11 (17.7) |
| Melanocytic nevus | 6 (10.0) |
| Sebaceous gland carcinoma | 5 (8.1) |
| Lacrimal gland carcinoma | 5 (8.1) |
| Rhabdomyosarcoma | 3 (5.0) |
| Uveal tract melanoma | 3 (5.0) |
| Squamous papilloma of the conjunctiva | 3 (5.0) |
| Rosai Dorfman’s | 2 (3.0) |
| Fibroma | 2 (3.0) |
| Basal cell carcinoma (BCC) | 1 (1.5) |
| Trichilemmal carcinoma | 1 (1.5) |
| Dermoid cyst | 1 (1.5) |
| Total (N) | 62 (100.0) |
| A. Associated premorbid conditions | N (%) |
| Hypertension | 11 (64.7) |
| SCC | 5 (29.4) |
| Uveal tract melanoma | 2 (11.8) |
| Sebaceous gland melanoma | 2 (11.8) |
| BCC | 1 (5.9) |
| Fibroma | 1 (5.9) |
| Diabetes mellitus | 4 (23.6) |
| SCC | 1 (5.9) |
| Squamous papilloma of the conjunctiva | 2 (11.8) |
| Rosai Dorfman’s | 1 (5.9) |
| Peptic ulcer disease | 2 (11.8) |
| Lacrimal gland carcinoma | 1 (5.9) |
| Melanocytic nevus | 1 (5.9) |

A. Association between hypertension and malignant orbito-ocular tumor

Chi Square($X^2 = 7.07$, $p = 0.004$)

Figure 1. Concordance between clinical and histopathological diagnosis ($n = 48.4\%$).

Table 2. Treatment options and outcome.

| Characteristics | Frequency |
|-----------------|-----------|
| A. Treatment modality | N (%) |
| Enucleation | 10 (16.1) |
| Excisional biopsy | 33 (53.2) |
| Exenteration | 19 (30.6) |
| A. Early post-operative mortality (First 30 days) | 1 (1.6) |
| A. Local recurrence | 8 (12.9) |
| SCC | 4 (6.5) |
| Rhabdomyosarcoma | 2 (2.2) |
| Sebaceous gland Ca | 1 (1.1) |
| Lacrimal gland Ca | 1 (1.1) |
| A. Survival (retinoblastoma) (%) |
| 1-year | 90 ± 3.0 |
| 3-year | 72.9 ± 2.7 |
| Survival (other malignant tumors) Range (%) |
| 1-year | 50–78.9 mean = 69.7 ± 2.5 |
| 3-year | 50–68.4 mean = 60.1 ± 2.1 |
publication by Olurin and Williams almost five decades ago also reported retinoblastoma as the most common orbito-ocular malignancy in our country. In contrast, however, we found squamous cell carcinoma more common than retinoblastoma. This may be the result of a true change in secular trends with respect to the epidemiology of orbito-ocular neoplasms over time in our setting. However, retinoblastoma remains from our study the most common orbito-ocular tumor among children as was reported in previous clinical and histopathological series from our sub region. Our suspicion of the role of secular trends in the current profile of orbito-ocular neoplasms is corroborated by the results of a more recent morphological study performed by Onwubuya and coworkers in a center from North central Nigeria which showed a preponderance of squamous cell carcinoma in their series similar to our index study. Beyond elucidating the current status of the distribution of tumors, our findings suggest a possible association between premorbid hypertension and increased occurrence of malignant orbito-ocular disease. Although many ocular conditions such as hypertensive retinopathy, glaucoma, vitreo-retinal hemorrhages, age-related macular degeneration, and retinal detachment among others have been associated with hypertension, no previous study has reported a specific association between orbito-ocular neoplasms and hypertension. We believe the association between hypertension and ocular tumors will need to be further evaluated through a large multicenter prospective observational study. A previous report on the role of plasma vascular endothelial growth factor as a marker for early vascular damage in hypertension may further lend support to a possible link between the up regulation of growth factor activity and neoplastic initiation or proliferation. Our study is the first from our country to report survival profiles of cohorts with malignant orbito-ocular tumors. It is interesting to note that the 1-year and 3-year survival rates of patients with retinoblastoma were better than those of other malignant tumors. However, the patient survival rates for retinoblastoma in our series were significantly less than the rates reported from other developing nations such as Jordan and Iran as well as the developed western nations. The globe survival rate in our series of 1.6% poorly contrasts with 44% in Iran and 62.1% reported from Jordan. We did not find the globe survival rates from other sub-Saharan countries in the literature. Apart from the role of poor health systems leading to late diagnosis, lack of infrastructure for multimodality care and the slow pace of oculoplastic subspecialty development in our setting, the survival disparity between our patients, and those of the other nations cited above may also be related to the high burden of orbital extension which was found among all our retinoblastoma patients. Orbital retinoblastoma has been previously associated with poor survival. Although we found a low early postoperative mortality rate in this series from postoperative sepsis and meningitis in a patient with squamous cell carcinoma. The possible risk of a life threatening systemic post-surgical infection should be considered in the work-up of patients with malignant orbito-ocular neoplasms. Local recurrence was experienced mostly with squamous cell carcinoma (SCC) and rhabdomyosarcoma in our study. The recurrence rate of SCC found in our study differs from a previous report from Germany although their study was limited to advanced SCC of the conjunctiva. The poor concordance between clinical and histopathological diagnosis may highlight the need for more collaborations between anatomic pathologists and ophthalmologists caring for patients with orbito-ocular tumors. One of the ways this could be achieved is by establishment of a separate orbito-ocular tumor board.

**Conclusion:** Squamous cell carcinoma is currently the most orbito-ocular tumor in our setting. Premorbid history of hypertension is associated with increased occurrence of malignant orbito-ocular tumor phenotype. The survival rates for malignant orbito-ocular tumors are variable and patients with retinoblastoma were found to experience better survival profiles. A low concordance exists between clinical and histopathological diagnoses suggesting the need for an orbito-ocular tumor board to foster closer collaboration.

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**Informed Consent**

Our unit protocol for retrospective studies involves obtaining consent from patients regarding the publication of results during admission and follow up. This was applied to all our study cases.

**Ethical Approval**

Ethical Approval was obtained from our institution’s Health and Research Ethics Committee (HREC).
**Contributorship**

UNJ designed the study concept, acquired and analyzed data, drafted the initial manuscript, OOn discussed core concepts, analyzed data and revised initial draft, OOb discussed core concepts, and revised the draft, OI discussed study concepts, contributed to data acquisition, UEO participated in study design, analyzed data, revised the initial draft manuscript. All authors approved the final draft for publication.

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