ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF RADIOLOGY

Imaging and Histopathologic Correlation of PediatricOculo-Orbital Tumors Evaluated in a Tertiary Level Teaching Hospital in Ethiopia: Three Years Retrospective Study

By: SemiraAbrar (M.D, Radiology resident)

Jan, 2021

Addis Ababa, Ethiopia

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

DEPARTMENT OF RADIOLOGY

Imaging and Histopathologic Correlation of PediatricOculo-Orbital Tumors Evaluated in a Tertiary Level Teaching Hospital in Ethiopia: Three Years Retrospective Study

By: SemiraAbrarIssa (Radiology resident)

Advisors: Prof. GetachewAssefa (MD, subspecialty in Neuroradiology)

AmalSaleh (MD, subspecialty in Neuroradiology)

A Thesis Proposal Submitted to the Department of Radiologyof Addis Ababa University in Partial Fulfillment of the Requirements for the Specialization Degree in Radiology

Dec, 2020

Addis Ababa, Ethiopia

Acknowledgement

Iwouldliketo extend my deepest gratitude to my advisors Prof. GetachewAssefaand Dr.AmalSalehfor their expertise and consultation in each step of my research work and the radiology department as a whole for giving me the opportunity to come with this academic research work.

I also want to acknowledge the whole pediatric oncology and the pediatric team in TASH for their cooperation during the data collection process.

Furthermore,Iwouldbehappytorecognizethecontributionofmyfriendsand family fortheirassistance.

Thank you GOD for being here in every step of my life.

Acronyms /Abbreviations

AAU	Addis Ababa University
CT	Computed tomography
DCE	dynamic contrast enhanced
DCE-MRI	dynamic contrast enhanced magnetic resonance imaging
DCMRI	dynamic contrast enhanced magnetic resonance imaging
DW MRI	Diffusion weighted magnetic resonance imaging
FNAB	Fine needle aspiration biopsy
FNAC	Fine needle aspiration cytology
IIRC	International intraocular retinoblastoma classification
IRSS	International retinoblastoma staging system
MDCT	Multidetector computed tomography
MRI	Magnetic resonance imaging
RMS	Rhabdomyosarcoma
TASH	TikurAnbessa Specialized Hospital
TIC	Time intensity curve

Abstract

Objective: This study is conducted to assess the cross sectional (CT and MRI) imaging pattern of pediatricoculo-orbital tumors and correlate with histopathologic finding and there is also general discussion on sociodemographic characteristics and clinical profileof these patients. Retinoblastoma is discussed in further detail.

Method: In a retrospective cross sectional studyconducted in a period of 3 years from February 2017 to January 2020 G.C, The medical records of all pediatric patients with orbital tumors evaluated at TASH oncology unit were reviewed.All Patients with initial pretreatment cross sectional imaging study and histopathologic analysis and patients who were conservatively treated for retinoblastoma with diagnosis established through evaluation under general anesthesiawere included in the study.
DatawascollectedusingapreparedchecklistandenteredusingMicrosoftexcelsoftwareandlatertransferredtoSPSSversion 20 foranalysis.

Result: Malignant tumors represented 96.1% of the total 101 cases in our series. The most common origin of orbital tumor was secondaryextension(69.6%) followed by primary orbital tumors 11(16.6%) and metastasis 9(13.6%).The most common primary oculo-orbital tumor was retinoblastoma followed by RMS and optic glioma. Neuroblastoma and leukemiawere the most common origins of orbital metastasis. The patients commonly presented withproptosis(78%) followed by leukocorea(16%). There was correlation between imaging and histologic finding in 89.7% of the oculo-orbital tumors in our study. The highest concordance rate was seen for retinoblastoma and optic glioma. The most common orbital subspace involved was the intraconal site. Patients with retinoblastoma commonly presented at an advanced stage with orbital and intracranial extension.

Conclusion: Pediatric orbital tumors are diagnosed at an advanced stage in our setup with grave complications which can be attributed to the late presentation from the parents' side and late referral from the primary care physicians. Thus, it is utmost importance to create awareness within the health care workers and the society at large for early detection with can salvage the vision and the life of this patients. Imaging plays an important role in the diagnosis and management of patients with oculo-orbital tumor. Communication between radiologist, pathologist and treating ophthalmologist is important in reaching the final diagnosis and for a better outcome in these patients.

Table of Contents

1. Introduction

1.1. Background

The orbits are bilateral bony cavities composed ofmultiple bones containing and protecting the eyeballs, extraocular muscles, lacrimal apparatus, fascial sheaths,nerves, vessels, and the fat in whichall is embedded.[1]All these anatomical structures can give rise to neoplasms and given the variety of these structures inside the relatively confined orbit, a systematic approach is important to understand the classification and diagnosis of orbital tumors.

Lesions of the orbit are classified into the intraconal and extraconal spacedepending on their relationship with the muscle cone. The muscle cone is formed by the extraocular muscles of the eye and their intermuscular septae.[2]

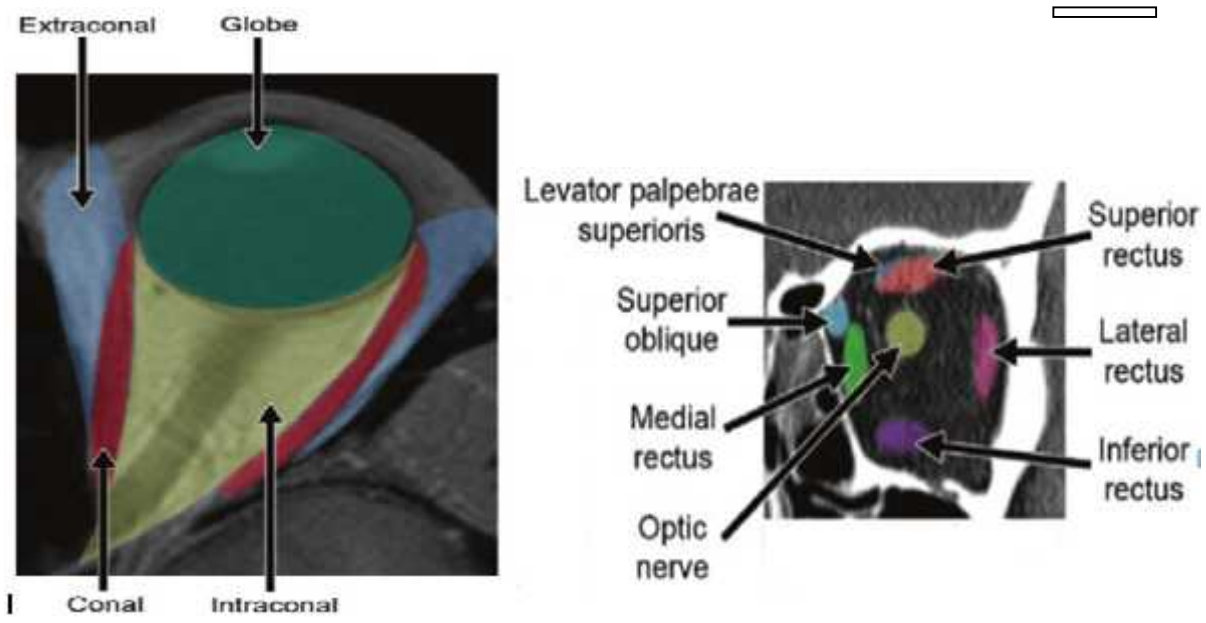


Fig 1:Normal orbital anatomy. Axial CT image (left) with color overlays shows the orbit divided into intraocular and extraocular spaces by the muscle cone.Coronal CT images (right) with color overlays show the configuration of the extraocular muscles.[2]

Orbital tumors canalso be classified based on origin:1) primary lesions, that originate from the orbit 2) secondary lesions, that extend to the orbit from adjacent structures; and3) metastatic tumors. [3]

The frequency of different orbital tumors varies in different literature which is likely attributed to the geographic location where the study is performed, the type of study performed and the difference in the study population.[4-7]

Various literatures in developing countries reported malignant lesions as the most common cause of pediatric orbital tumors with most of this representing retinoblastoma.[6-8]This is in contradiction to the reports from some of the developed nations with lower percentages of malignant tumors in the pediatric age group within the range of 10-32%.[5, 9]

Despite the fact that retinoblastoma remains the most common intraocular malignancy of pediatric age group, secondary orbital retinoblastoma is significantly reduced in developed countries with RMS becoming the most prevalent orbital malignant tumor.[4, 5, 10]

The most common clinical presentation of pediatric patients with primary orbital tumors is protrusion of the eyeball(proptosis). [4, 11]followed by swelling and reddening of conjunctivae and eyelids. Patients also present with blepharophimosis, limitation of eyeball movement, dysopsia (diplopia), visual acuity attenuation, pain in the eyeball, headache and blindness. [4, 5, 11]

In the diagnosis and management of orbital tumors adequate clinical history, ophthalmologic evaluation, laboratory investigations & imaging studies have their own complementary roles.

Ultrasonography is popular and readily available modality with high diagnostic accuracy in localizing and characterizing orbital pathologies without the risk of ionizing radiation which is particularly useful for pediatric patients. The main limitation of ultrasonography for orbital pathologies is its inability to image the bony architecture, lack of detailed visualization of the orbital apex and for intracranial extension of tumors. [12]

CT and MRI have brought about a major advance in the evaluation of orbital tumors. Imaging can be used to precisely localize a lesion, to help establish a diagnosis, generate a differential diagnosis that guides management and also to follow a known lesion for progression. [2]

In patients with ocular neoplasm, MDCT is the modality of choice for evaluation of the bony orbit and for calcifications.[13]It can be rapidly obtained at most medical centers in comparison with MRI. The disadvantage of CT is the radiation dose to the body. Another important disadvantage of CT particularly in the imaging of the orbit is the presence of beam-hardening artifacts making the differential diagnosis of small pathologies difficult. [14]

MRI on the other hand with its high tissue contrast resolution is superior for evaluation of the visual pathways, the globe and soft tissue. [13]MR imaging is particularly important for evaluation of orbital tumors because it provides essential anatomic information about ocular structures involved, perineural spread and intracranial extension. [2]One of the disadvantages of MRI in the imaging of orbital tumors is the long acquisition time resulting in motion artifacts from eye movement. [14]

Whenimaging of retinoblastoma is considered, currently the diagnosis is usually made by fundo-scopy under general anesthesia and ultrasonography.[15]CT is no longer the preferred imaging modality because of similar sensitivity for calcification when MR, ophthalmoscopy, and ultrasound were combined compared with CT with the advantage of avoiding the ionizing radiation.[16]Pathologyremains the gold standard to assess high-risk features ofretinoblastoma. [15]

Common standard in determining extent of disease is important in retinoblastoma to identify whether differences in response to specific therapeutic approaches are due to differences in staging practices or to variations in tumor biology. Using a common staging system is also important in determining risk factors for recurrence and identify patients who require adjuvant chemotherapy. [17]

The IIRC scheme for intraocular retinoblastoma groups tumors from A-E, depending on their size, location, and additional features. It has better treatment and prognostic significance compared with Reese and Ellsworth (R-E) system which was initially introduced in the 1960s. [18]

Chantada and colleagues developed the International Retinoblastoma Staging System(IRSS). It sub-classifies the disease stage 0–IV based on the management, pathologic and imaging findings.[18]

In this study, the sociodemographic characteristics, clinical features, the imaging patterns of orbital tumors will be evaluated with emphasis on retinoblastoma with histopathology correlation.Retinoblastoma is given emphasis because of the predominance of the disease in our setup with further details given on staging of these patients based on the IRSS and IIRC staging systems.

1.2. Statement of the problem and significance of the study

Orbital tumors represent approximately 0.1% of all body tumors and approximately one-fifth of all orbital diseases. [19]Pediatric oculo-orbital tumors are unique with different clinical and imaging characteristic features peculiar to this age group that demands proper recognition for prompt detection and early management.

Many oculo-orbital tumors are not at first suspected and thus initially misdiagnosed due to the lack of proper diagnostic methods and lack of knowledge of such tumors from the clinicians side.Knowing the clinical features and imaging pattern of these tumors will significantly reduce delay in the diagnosis and avoid potential complications including visual loss, deformities and cost to the life of the patient.

Cross-sectional imaging plays a valuable role in characterization of these lesions and in evaluation of disease extent, supplementing clinical ophthalmologic examination and providing additional information to reach to the final diagnosis.

Determination of tumor staging can also be performed in oculo-orbitalpathologies using cross sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). Advancement in cross sectional imaging techniques also allows an integration of CT and MRI images into radiation planning systems. [14]

In source limited countries like Ethiopia, proper utilization of such imaging techniques like CT and MRI in the pediatric population should be tailored to the patients' maximum benefit. Knowledge of the most common oculo-orbitallesions, their typical clinical presentation and typical imaging appearance allows for the best use of such imaging modalities. This research aims to serve as additional input in achieving this goal.

The diagnostics and treatment of the different orbital tumors require the close co-operation of specialists including ophthalmologists, ENT (ear, nose, and throat) surgeons, endocrinologists, radiologists, neuroradiologists,neurosurgeons, plastic surgeons, and maxillofacial surgeons. This study also strives to show how radiologists can largely contribute in the diagnosis and management plan of these patients.

As to our knowledge, the present study is the first survey of the imaging pattern of pediatricoculo-orbital tumors in our locality, represented by a tertiary university hospital in Ethiopia.

2. Literature Review

In pediatric patients presenting with oculo-orbitaltumors, the proportion of benign and malignant tumor varies in different literatures. Shields et al in a series of 1264 patients referred for a suspected orbital mass over a 30-year period identified that benign orbital tumors are predominant in the pediatric age with malignant cases accounting for 16%. [5]Bullock et al[9] in his series reported even lower incidence of malignant lesions around 10.6%.

There are also different reports on the common tumor types affecting the pediatric orbit. In an analysis of 2480 space occupying lesions of the orbit,the most frequent benign tumors in the pediatric age were reported to be dermoid cyst (14%) and cavernous hemangioma (9%).[20]

In a cross sectional study conducted in Ethiopia evaluating the pattern and frequency of orbital tumors in Menilik tertiary referral hospital in Ethiopia showedthe most common ocular and orbital tumor was retinoblastoma in younger than 15years of age followed by dermoid cyst. [7]Suleiman et al[6] in a Nigerian study reported similar findings with Retinoblastoma being the most common oculo-orbital tumor.

A study done in Philippines eye research institute including a total of 1551 histologically confirmed orbital tumors revealed RMS was the most common specific malignancy in pediatrics age.[8] Shields et al. also reported similar findings. [5]

Incidence of orbital tumors also differs based on the origin of the lesion and the location. Regarding this, there was a retrospective case series done at a comprehensive cancer center in United States reviewing the medical records of 268 patients with orbital mass. In this study, 64% of the tumors were primary orbital, 26% were secondary orbital, and 10% were metastatic tumors. Of the tumors,16% were intraconal, 84% were extraconal. [3]

The choice of imaging modality between CT and MRI for the evaluation of orbital neoplasmsdiffers widely in different centers depending on the indication, the location and the availability.

A study analyzing the accuracy of CT in the diagnosis of orbital tumors shows accurate diagnosis can be made based on contrast enhanced CT of benign lesions with a sensitivity of 90.3%, and less accurate in diagnosing malignant tumors with a sensitivity of 78.9% with Overall the diagnostic accuracy of CT in diagnosing orbital tumors being 86%. [21]

In the same study only those patients for whom CT yielded insufficient information for making the diagnosis or insufficient anatomical detail for future surgical management underwent MRI.The research concluded CT scan can be considered as a cost effective, noninvasive, reliable diagnostic tool for evaluation of orbital tumors. [21]

Another prospective cross-sectional study conducted in Koirala Institute of Health Sciences, over the period of one year shows even better sensitivity(around 95%) of MDCT in diagnosing ocular and orbit lesions than the previous study. [22]

A study analyzing the value of MRI in the differentiation of benign and malignant orbital tumors revealed the most predictive features for orbital malignancywere isointense mass on T2-weighted imaging and a washout-type TIC. [23]Other supportive evidences for malignancy were the location, shape, andmargin of the mass, molding around orbital structures,and pattern of enhancement. [23]

The accurate interpretation of orbital imaging is a challenge and histopathologic examination remains the gold standard for diagnosis. While orbital imaging is a valuable diagnostic tool the interpretation of these studies is most accurate when conducted in the context of the patient's medical history, clinical exam, and with the physician most familiar with various orbital lesions. [24]

Retinoblastoma is the most common intraocular malignancy of infancy and childhood; with an incidence of 1/15,000–20,000 live births. [25] The most common clinical presentation of retinoblastoma in developed nations is leukocoria (56.2%), strabismus (23.6%) and poor vision (7.7%). [25]

Retinoblastoma is bilateral in about 40% of cases with a median age at diagnosis of one year. [25]All bilateral and multifocal unilateral forms are hereditary and 15% of patients with unilateral retinoblastoma are known to have hereditary disease. [25]The occurrence of the disease in the two eyes is thought to be due to independent foci; the tumor in the second eye does reach it neither by direct extension along the optic nerves nor by dissemination via the blood stream.[26]

Trilateral retinoblastoma refers to a primary midline intracranial tumor in the presence of unilateral or bilateral retinoblastoma. [27, 28] The presence of an additional midline tumor in the suprasellar or parasellar region signifies a quadrilateral retinoblastoma. [27]An associated separate midline intracranial tumor is not a metastasis; it represents multifocal disease. [28]

When staging of retinoblastoma is concerned, The IRSS system is found to be superior than the other extraocular retinoblastoma staging systems in terms of grouping of patients with increasing risk of extraocular relapse for stage assignment and the fact than it is the only system that considers all unequivocally significant pathological prognostic factors.This includes postlaminar optic nerve invasion (PLONI), massive choroidal invasion, or any degree of scleral invasion.[29]

Table 1: IRSS Classification of Retinoblastoma

Stage 0	Patients treated conservatively
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumour
Stage III	Regional extension
	a. Overt orbital disease
	b. Preauricular or cervical lymph node extension
Stage IV	Metastatic disease a. Hematogenous metastasis (without CNS involvement) 1. Single lesion 2. Multiple lesions
	b. CNS extension (with or without any other site of regional or metastatic disease) 1. Prechiasmatic lesion 2. CNS mass 3.Leptomeningeal and CSF disease

For intraocular retinoblastoma, the first classification system was introduced by Reese and Ellsworth (R-E) in the 1960s to predict the chances of saving the eye following external beam radiotherapy. Later this was largely replaced by the International Intraocular Retinoblastoma Classification (IIRC) scheme. [18]

Considering the current trend and the considerable treatment and prognostic significance, we used the IRSS and the IRCC classification schemes in our study.

3. Objectives

3.1 General objectives

- To evaluate the imaging pattern of pediatric oculo-orbital tumors and correlate imaging findings with histopathologic findings.

3.2 Specific objectives

1. To determine pattern and the correlation between imaging and histopathology findings of oculo-orbital tumors.
2. To assess the clinical presentation of pediatric oculo-orbitaltumors.
3. To classify pediatric oculo-orbitaltumors based on origin of the lesion and the location within the orbital subspaces.
4. Staging of retinoblastoma into different categories based on the IRSS and IIRC system.

4. Methods and Materials

4.1 Study Design

An institutional based cross sectional study design was employed to assess the imaging pattern of oculo-orbital tumors evaluated in TASH oncology unit and correlate with histopathologic findings whenever possible.

4.2 Study area and period

The study will be conducted atTASH oncology unit, starting from February 2017 – January 2020. TikurAnbessa Specialized Hospital is the largest tertiary referral hospital in Ethiopia located in Addis Ababa which is a capital city of the country. It is one of the greatest & oldest public hospitals of the country providing high level of clinical care for more than 5 million of catchment area population and training health science students in joint venture.

The oncology unit in TASH is the oldest and largest oncology unit in the country having the highest number of patients among other hospitals in the country.

4.3 Source population

The source population for this study was all pediatric patients who were evaluated in the oncology department of TASH during the study period.

4.4 Study Population

The study population was all pediatric patients withoculo-orbital tumor who have both cross sectional imaging and pathology result being evaluated at TASH oncology unit during the study period.

4.5 Inclusion and exclusion criteria

4.5.1 Inclusion criteria

- ✓ All pediatric patients under the age of 14with confirmed oculo-orbital tumorvisiting the oncology unit of TASH during the study period and having pretreatment cross sectional imaging and pathology results during the study period.
- ✓ All patients with retinoblastoma visiting the oncology unit of TASH who are on conservative management and having pretreatmentcross sectional imaging and fundoscopic evaluation under general anesthesia.

4.5.2 Exclusion criteria

- ✓ Patients who didn't fulfill the inclusion criteria.
- ✓ Patients whose medical records were lost.

4.6 Sampling technique

All medical records of 134 pediatric patients who have oculo-orbitaltumor from the registry were reviewed. Of this, 101 patients were included in the study as they fulfilled the inclusion criteria. Data was retrieved from patient's chart including the sociodemographic characteristics, CT and MRI results and histopathology findings.

4.7Operational definition

- **Oculo orbital tumor:** refers to any benign or malignant lesion involving either the ocular or the orbital space.
- **IRSS Stage 0:**Childrendiagnosed with retinoblastoma with only intraocular disease and treated conservatively even if they were later enucleated.
- **IRSS Stage II:**The TNM stage T4a and T4b are considered as stage II (microscopic residual disease) on IRSS.
- **IRSSStage IIIa:**overt orbital disease was considered when there is involvement outside the ocular space as seen on CT and MRI imaging.

4.8 Data collection procedures and quality control

Data was collected from oncology unit of TASHstarting from February, 2017 up to January, 2020 using a structured questionnaire. The questionnaire was prepared by reviewing

literatures used in this study and related studies done in other countries and try to assess socio-demographic characteristics, clinical and systemic findings, imaging findings and histopathologic results from the patient charts.For patients with bilateral disease, information was taken for the most severely affected eye.

The data was collected from the patients chart by trained health professionals under close supervision by the principal investigator.

4.9 Methods of data analysis

Dataentering,codingandclearingforthe quantitativedataandtheanalysiswasperformed using Microsoft exceland SPSS version 20. After checking its completenessandconsistencyofthetool,furtherclearancewasmadeusingthissoftware.Thesocio-demographic& clinicalcharacteristics ofparticipantswerecomputedbyusingsimpledescriptivestatistics(mean,percentage,frequencies). RelationshipsbetweendependentandtheselectedindependentVariableswereanalyzedusingcross tabulation.P-value of <0.05 and 95% confidence level will be used as a difference of statistical significance. Finally, the study finding was presented using diagrams, tables and figures.

4.10 Ethical Considerations

Ethicalclearancewasobtainedfrom InstitutionalReview Board ofthecollege of health sciences, Addis Ababa University.Permissionletterwas submitted tothemedicalrecordunittoretrieveandreviewtheCharts.

RESULTS

Pediatric oculo-orbital tumors

Among 101 pediatric patients with oculo-orbital tumors included in ourstudy, malignant tumors represented 97(96.1%) with benign lesions representing only 4(3.9%) of the cases. Based on the origin of the mass, secondary orbital tumor represented 45(70.3%) of the cases followed by primary orbital tumors 11(15.6%) and metastasis 9(14%).

Retinoblastoma represented 77.1% of the oculo-orbital tumors diagnosed in our study and 43(42.5%) of the orbital tumors from secondary extension. Nasopharyngeal Carcinoma 2(1.9%) is the other causes of orbital secondary in our series**.** From the primary orbital tumors, RMS is the most common 8 (8.2%) followed by optic glioma2(1.9%).

Table 2: Frequency of pediatric oculo-orbitaltumors in patients evaluated at TAH during the period of February 2017-January 2020.

Oculo-orbital tumor types	Frequency(n)	Percent (%)
Retinoblastoma	78	77.2
RMS	8	7.9
Optic glioma	2	1.98
Orbital lymphangioma	1	0.99
NPC	2	1.98
capillary hemangioma	1	0.99
Neuroblastoma	5	4.95
Leukemia	4	3.96

When gender distribution was considered, male patients were 48 (47.5%) and the remaining 53(52.5%) were female.88(87.1%) of patients in our series were below 5yrs of age with mean age at presentation being 3.6 yrs.

Table 3: Age characteristics of pediatric patients diagnosed with oculo-orbitaltumors at TAH from February 2017-January 2020.

Age range(in yrs)	Frequency(n)	Percent (%)
0 – 23 (months)	32	31.7
2-5 yr	56	55.4
6-10 yr	11	10.9
>11 yr	2	2.0

Protrusion of the eyerepresented 78(78%) of the primary complaint of patients at presentation to healthcare institution followed by leukocoria(16. 16%) and discharge from the eye(2, 2%). Other complaints include blurring of vision 1(1%), visual loss 1(%) and reddish color change of the eye 1(1%)

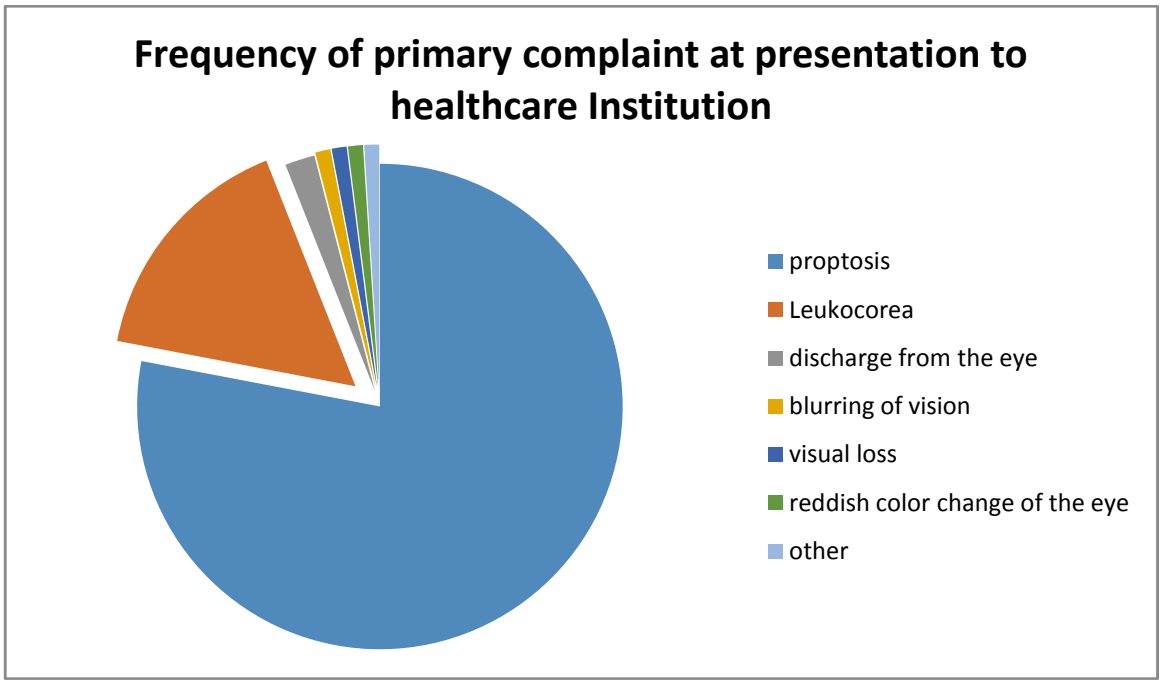


Fig 2: Primary Complaint at Presentation to healthcare institution of pediatric patients diagnosed with oculo-orbitaltumors evaluated at TAH from February 2017-January 2020.

Pathology specimen was performed from the orbital mass either by excisional biopsy (72.2%)or incisional biopsy(15.5%) representing 87.7% of the patients.Peripheral smear (PS)/bone marrow aspiration (BMA) rendered diagnosis in 5.2% of patients. Biopsy/ FNAC from enlarged lymphnodes confirmed the diagnosis in 7.2% of the cases.

MRI was the commonly used imaging modality 61(60.4%) in our study. CT scan was done for 34(33.7%) with 6(5.9%) of patients having both CT and MRI scans at initial diagnosis.

Based on the imaging findings, both the intraocular and extraocular space are involved in 45(44.6%) of the cases followed by isolated intraocular space tumors in 35(34.7%) and with isolated extraocular space involvement in 21(20.8%) of the cases. See table 6 below for further details on orbital subspace involved.

Table 4: Location of tumor within the orbit on MRI and CT imaging in pediatric patients evaluated with oculo-orbitaltumors in TAH from February 2017-January 2020.

Location of tumor within the orbit	Frequency(n)	Percent(%)
1 Intraocular	35	34.7
2 Extraocular	21	20.8
3 Intraocular and extraocular	45	44.6
Subspace within the extraocular space		
1 intraconal	34	51.6
2 extraconal	4	6.0
3 conal	2	3.0
4 Multicompartmental involvement	26	39.4

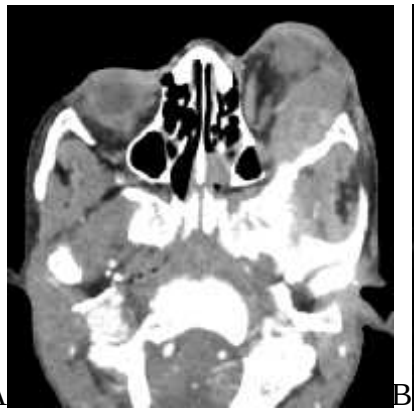
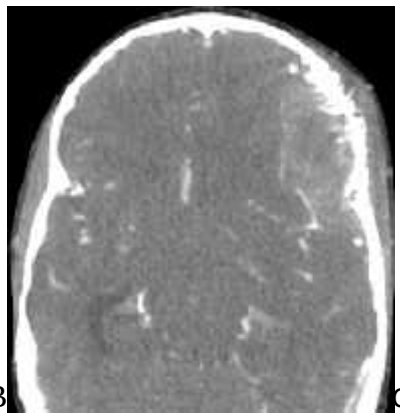
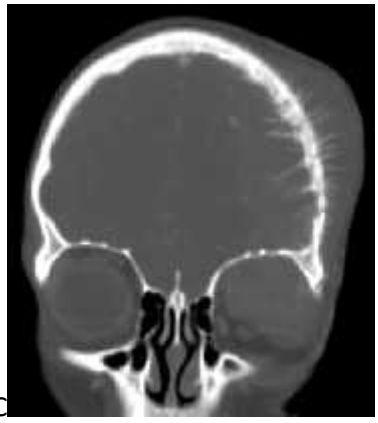
A  B  C 

Fig 3: Axial soft tissue window CT images of 10yrs old male patient with neuroblastoma metastasis who presented with left eye proptosis of 1month duration. A)Shows left superior and lateral wall of the orbit huge soft tissue mass causing anterior displacement of the left

globe B) Another enhancing extra cranial and intracranial extra axial soft tissue in the left frontal and parietal bone with aggressive hair on end type of periosteal reaction(C)

There was concordance rate of 88(89.7%) between imaging and pathologic diagnosis with discordance seen in the remaining10 (10.3%). Please see table 7 for further details.

Table 5: Correlation between radiologic and pathologic findings in pediatric patients with orbital tumors evaluated in TAH from February 2017-January 2020

Radiologic and pathologic concordance	No concordance
88(89.7%)	10(10.3%)
Retinoblastoma(n 72) RMS(5) Neuroblastoma metastasis(4) Leukemia metastasis(3) NPC(1) Cavernous hemangioma secondary(1) Optic glioma(2)	Retinoblastoma(n 1) RMS(3) Neuroblastoma metastasis(1) Leukemia metastasis(1) NPC(1) Secondary(1) Phtisis bulbi(2) Orbital lymphangioma(1)

Retinoblastoma

In patients with retinoblastoma, there was similar distribution between male and female patients with 1:1 ratio. The mean age at presentation to health care institution was 3.2yrs. The mean age of patients at the detection of the first symptom was 2.6yrs**.** Considering the detection of initial symptom, it takes a mean time of 11.7 months to present to health care institution.

Patients with retinoblastoma had protrusion of the eye as a primary complaint at presentation in 56(73.7%) of cases and Leucocoria in 16(21.1%). There were also patients who presented

with discharge from the eye 1(1.3%), loss of vision 1(1.3%) and reddish color change of the eye1(1.3%. There was mean age difference between unilateral and bilateral retinoblastomawas 1yr and 5months.

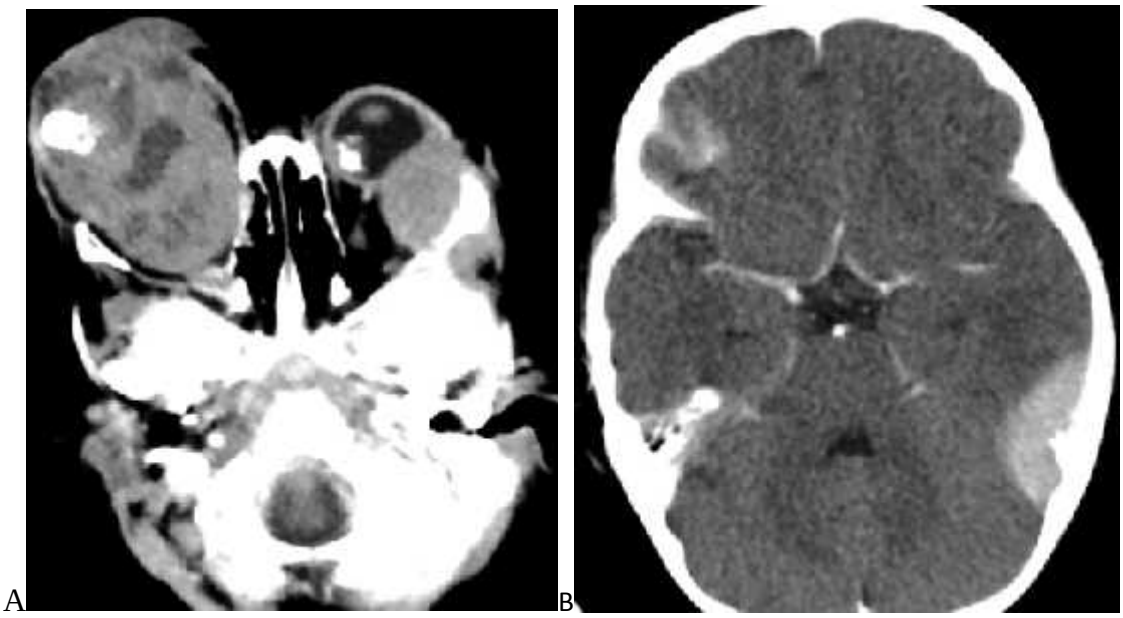


Fig 4: Axial soft tissue window contrast enhanced CT images of 2yrs old female patient diagnosed with bilateral retinoblastoma after she presented with proptosis of 1yr duration. A) Heterogeneously enhancing mass replacing the globe and involving all the subspaces of the orbit having internal areas of dense calcification. There is also focal lesion in the posteromedial wall of the left eye globe. There are homogenously enhancing lesions involving extraconal space in the left orbit (A) and extra-axial space in the left occipitotemporal convexity (B) suggestive of intracranial metastasis.

One patient had family history in an older sibling which makes it 1.28%. The lesions were unilateral in 59(75.6%) and bilateral in 19(24.4%). Trilateral retinoblastoma was found in 3(3.8%) of the cases.

From 78 patients with retinoblastoma, 43(55.1%) had extraocular extension with site of extraocular involvement being the intraconal space in 71.1% followed by multicompartmental involvement 17.8%.

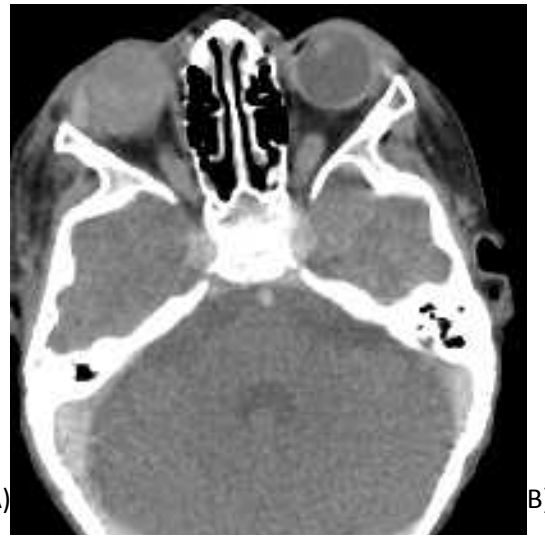
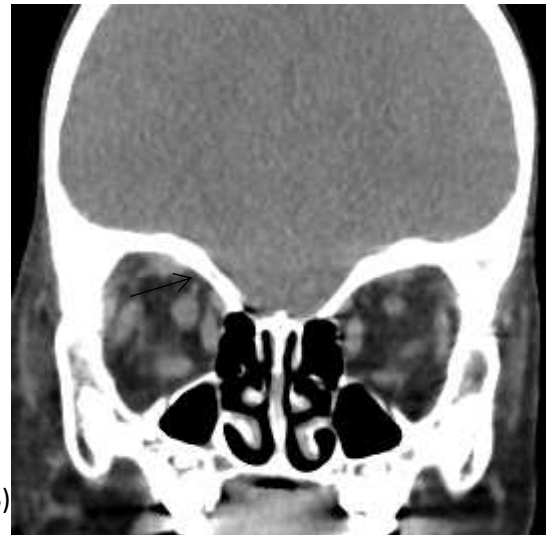
A)  B) 

Fig 5: 4yrs old male patient who presented with proptosis of 4month duration with a diagnosis of right retinoblastoma. A) Soft tissue attenuating lesion filling the right eye globe with no internal calcification B) The intra-orbital part of optic nerve (arrow) is thickened on the right compared with the contra lateral side having similar attenuation.

There were 23(29.4%) patients with intracranial extension. This include, intracranial mass 15(19.2%), prechiasmatic lesion 5(6.4%) and leptomeningeal involvement 5(6.4%).

Table 6: Intracranial sites of involvement as evaluated on CT and MRI of pediatric patients with retinoblastoma evaluated in TAH from February 2017-January 2020.

Intracranial site involved		Frequency(n)	Percent (%)
Prechiasmatic lesion		5	6.4
Intracranial mass	Suprasellar	8	10.2
	Pineal	3	3.8
	Dura based	2	2.5
	Other site	3	3.8
Leptomeningeal metastasis		5	6.4

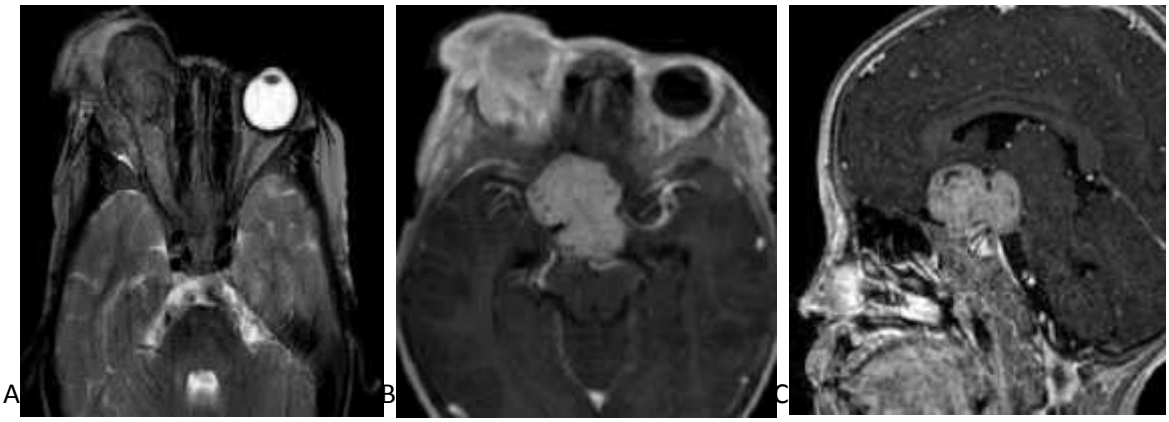


Fig 6: 4yrs old female patient presented with right eye swelling of 2month duration.There is right intraocular ill-defined mass replacing most of the globe with proptosis. The mass is intermediate signal which is hyperintense to vitreous on T1W and hypointense on T2 W with intense contrast enhancement. There are similar signal intensity change following the right optic nerve and optic chiasm forming a suprasellar mass.

We used the IIRC staging system for intraocular retinoblastoma and the IRSS staging system for both extraocular and intraocular retinoblastoma. Based on IIRC staging system, 33(91.4%) of the intraocular retinoblastoma were found to be stage E followed by stage D (5.7%) and stage C(2.9%). There were no patients with stage A and Stage B.

Based on the IIRS staging system, patients are staged as IVb in 25(33.3%) of cases and stage IIIa in 20(26.7%) of cases. There are close proportions of patients with stage I(11,14.7%) and stage II(10, 13.3%). Stage IIIb was found in 2(2.7%) and stage IVa in 4(5.3%) of the patients.

Table 9: IIRC staging of intraocular pediatric patients with intraocular retinoblastoma evaluated in TAH from February 2017-January 2020.

IIRC stages	Frequency(n)	Percent (%)
A	0	0
B	0	0
C	1	2.9
D	2	5.7
E	32	91.4

Table 10: IRSS staging of pediatric patients retinoblastoma evaluated in TAH from February 2017-January 2020

IIRS stages	Frequency(n)	Percent (%)
0	3	3.9
I	11	14.3
II	12	15.6
IIIa	22	28.6
IIIb	3	3.9
IVa	3	3.9
IVb	23	29.9

Other common pediatricorbital tumors

In patients diagnosed with RMS, 5(62.5%) were female and 3 (37.5%) were male. The mean age at presentation was 3.3yrs.The most common symptom at presentation was proptosis seen in 7(87.5%). From the RMS patients we had, the subtype was mentioned in 7 patients from which 4 had alveolar type of RMS, 2 embyonal type and 1 pleomorphic type.

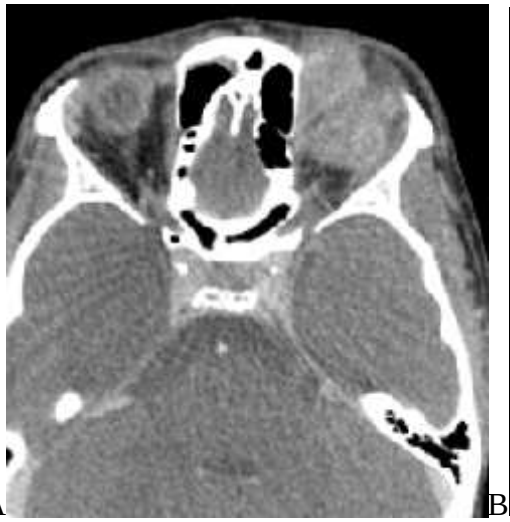
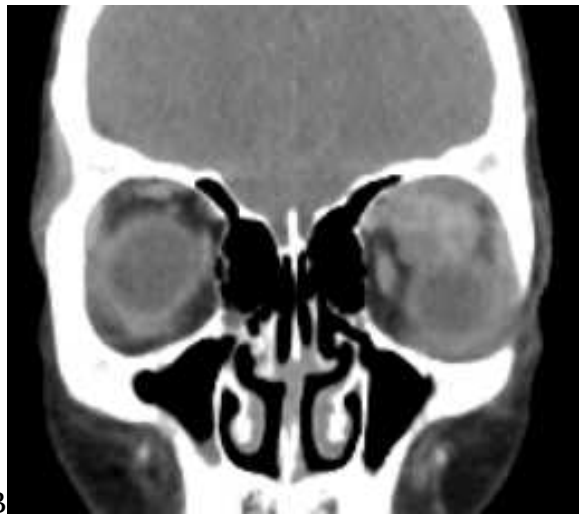
A  B 

Fig 8: axial and coronal soft tissue window CT images of 13yrs old male who presented with proptosis of the left eye of 1month duration with a diagnosis of left orbital RMS. There is a heterogeneous predominantly hyper dense soft tissue attenuating lesions with internal areas of hypodensity involving the superior and medial aspect of the left orbit causing inferolateral displacement of the globe. The superior rectus muscle is not separately visualized.

In patients with orbital metastasis, the mean age at presentation was 5yrs 3month and 7(77.8%) of the patients were in the age range of 5 to 10yrs. The origin of orbital metastasis in our series was from Neuroblastoma (5,4.9%) and leukemia (4,3.9%).

Discussion

As to my knowledge, there are very few researches done in Ethiopia concerning orbital tumors in general and there are no studies done pertaining to pediatric orbital tumors. The aim of this discussion is to assess the sociodemographic characteristics, imaging pattern and histopathologic correlation of pediatric oculo-orbitaltumors in Ethiopian setup with particular emphasis given to retinoblastoma.

Among 101 pediatric patients with oculo-orbital tumors included in our study, malignant tumors represented the vast majority of the cases (96.1%).The higher percentage of malignant tumor in our study is likely attributed to the study centrebeing the only referral hospital with radiotherapy unit and most of the patients referred comprise of malignant lesions.

When origin of the tumor is considered, secondary orbital tumors were common in our series (70.3%) followed by Primary orbitaltumors and Metastasis. Bakhshi et al [11]reported59.6% of the cases in his series being secondary orbital tumors in indian study. This is likely because in populations where advanced retinoblastoma is common, the proportion of secondary orbital tumors tends to be much higher. In western countries, primary malignant tumors are reported to be the most common followed by secondary orbital tumors and metastasis. [3, 5]

The most common oculo-orbital tumor in our study was retinoblastoma representing the entire ocular tumors diagnosed and 65.1% of the orbital lesions through secondary extension. The finding in our study compares favourably with the study done by Suleiman et al [6] in Nigeria who reported retinoblastoma as most common cause of oculo-orbital tumor accounting for 76% of the cases.

From the primary orbital tumors in our series, orbital RMS is the most common followed by optic glioma. A study done in Ethiopia analyzing a total of 144 patients with orbital tumors, the most prevalent primary malignant pediatric orbital tumor was RMS representing 12.2 of all cases. [7]With the advancement in the healthcare system and the early diagnosis of

retinoblastoma patients, RMS has become the most prevalent extraocular orbital malignancy in children particularly in developed nations. [4, 5, 8]

We have identified two cases of phthisis bulbi on histopathologic evaluation of enucleated specimen with clinical and imaging evidence of retinoblastoma which was bilateral in one of the patients. Different literatures reported retinoblastoma as one of the causes of Phthisis bulbi [30, 31]. Kashyap et al [30] reported phtisis bulbi in 3.5% of patients with retinoblastoma with most of the patients having advanced retinoblastoma cases.

The vast majority of patients were below 5yrs of age representing 87.1% of the cases with the mean age at presentation being 3yrs and 6months. This is in line with the study done by ModiPJ and his colleagues which shows that most of the paediatric orbital tumors are found below age of 6 years [32].

Proptosis was the most common complaint at presentation in our series followed by leukocoria. Alkatan et al [4]in Saudi Arabia reported similar findings with proptosis being the primary complaint in patients presenting with orbital tumors. Bakhshi et al [11] in a series of 104 cases found that 49.4% of patients with a malignant orbital mass had clinically documented proptosis.The higher number of proptosis encountered in our study can be explained by late presentation or delayed referral of patients through our health care system.

Based on the finding on MRI and CT scan of patients with orbital tumors in our study, both the intraocular and extraocular space are involved in the majority of the cases (44.6%) and isolated intraocular tumors were found in 34.7%. This trend was seen because of advanced retinoblastoma cases which extend to the orbital space.

From the orbital subspaces, intraconal space was the most common site of the lesions (50.9%). This is again explained by the large number of retinoblastoma cases which tends to involve the intraconal space than the other orbital subspaces.

In orbital RMS, the conal space was most commonly involved. The extraocular compartment was commonly involved in patients with leukemic metastasis. Bidar et al [33]reported similar finding.

The concordance rate for oculo-orbitaltumors in general was 89.7% with discordance seen in the remaining 10.3% of the cases. There was complete correlation seen for optic glioma. There was also strong correlationseen for retinoblastoma with concordance rate of 98.6%(72

out of 73 cases).One of the patients who were histologicallyconfirmed as retinoblastoma was diagnosed as orbital RMS on imaging. This patient had advanced disease with extensive orbital involvement.

The imaging and pathologic correlation showed disparity in orbital RMS with 3 out of 8 (37.5%) patients having other diagnosis with 2 casesconsidered hemangioma at initial imagingand one of the patient had the diagnosis unspecified.RMS may sometimes be highly vascular with internal flow voids masquerading with infantile hemangioma. Diffusion-weighted MRI is useful to differentiate orbital infantile hemangioma from RMS in pediatric patients. [34]

There was also disparity between imaging and MRI finding for metastasis with 2 out of 9 patients(22.2%) considered as orbital RMS and optic glioma on MRI. These two patients had primary tumourelsewhere and it shows importance of putting clinical findings into consideration during imaging patients with orbital tumours.

While orbital imaging is a valuable diagnostic tool the interpretation of orbital tumors, it is most accurate when conducted in the context of the patient's medical history and clinical exam.[24]Another studyemphasized the importance of communication between the clinician and the radiologist on the clinical suspicion.[35]The sample size was small for orbital RMS and metastasis in our series and further studies are recommended.

Retinoblastoma

Retinoblastoma being the most common intra-ocular and orbital tumor in our series, we have separately discussed the sociodemographic characteristics, clinical presentation, imaging findings andhistopathology of this patients.

Considering age at initial presentation, patients with retinoblastoma in our series were below five years in 92.1% of the cases and mean age of 3.25 yrs. Nigerian study reported average age of occurrence of 3.4 years.[36]

The mean age at the detection of initial symptom is 2.6yrs in our series which is much lower than the age at presentationwith mean time of 11.7 months between initial detection of symptom and at presentation to health care institutions. This could be from poor awareness on the patient side on the important symptoms of retinoblastoma, socioeconomic reasons or

poor referral system. JZ Shifa et al has comparable finding in another study done at a tertiary referral hospital in Ethiopia [37]

Family history was reported only in 1 patient (1.28%) from the 78 patients included in the study. In a hospital based study in Egypt, Family history of retinoblastoma was reported in 5.7% of patients.[38]Abrahson et al reported 12.2% family history in New York hospital based study.[39] The percentage of patients with family history is very low in our series which could be related to higher mortality and few survivors of patients in our locality because of advanced disease at presentation.

The most common symptom at presentation was protrusion of the eye(73.7%) followed by Leucocoria(21.1%). This is comparable with the study by Antoneli et al who reported proptosis as primary presentation in 75.9% of retinoblastoma patients. [40] The Ethiopian study by JZ Shifa et al reported similar findings with lower percentage of proptosis(53.7%) and leukocoria(22%). [37]

Bilateral retinoblastoma was found in 24.4% of the cases and unilateral retinoblastoma in the remaining 75.6% of the cases in our series. JZ Shifa et al reported bilateral retinoblastoma in 22% of the cases. [37]

Trilateral retinoblastoma was found in 3, 3.8% of the cases in our series and all are pineal trilateral retinoblastoma. Potter et al in a series of 440 pediatric patients with retinoblastoma reported 3% incidence of trilateral retinoblastoma. [41] Another meta-analysis from selected 26 cohorts reported an adjusted incidence of 3.8% with 2.9% pineal and 0.7% non-pineal trilateral retinoblastoma among patients with bilateral retinoblastoma. [28]

Based on the IIRC scheme, majority of the patients in our study are grouped under category E(30,91.6%) because of the advanced stage at presentation with small percentage of stage D(2,5.5%) and C(1,2.7%).

The IRSS classification scheme is important when extraocular retinoblastoma is considered. The drawback in the IRSS system is its poor clarification of the term overt orbital disease in stage IIIa. [29]

Based on the IRSS staging system, patients in our study were most commonly staged as IVb (23, 29.9%) followed by stage IIIa (22,28.6%). This finding reaffirms the fact that patients in our series were late at presentation with an advanced stage.

Other common pediatric orbital tumors

Patients whichRMS in our series are presented with mean age of 3yrs 3month with all cases below the age of 10yrs. From those patients were the pathologic subtype of orbital RMS mentioned, 4patients (57%) have alveolar type of RMS, followed by embyonaltype 2 (28.5) and pleomorphic type1(14.2).

For patients with orbital metastasis, the mean age at presentation was 5yrs and 3month which was lower than the one reported by Bidar et al [33]which was 8yrs.The most common origin of orbital metastasis was neuroblastoma followed by leukemia (AML and ALL). Similar findings were seen in shields et al [5] and Johnson et al [36] with neuroblastoma and leukemia as the dominant cause of orbital metastasis in pediatric patients.

Strength and limitation of the study

Strength

- This study was the first one of its kind in our locality focusing on the imaging findings of patients and histopathology correlation of pediatric orbital tumorswhich is an additional input to the limited information we have on orbital tumors at large and retinoblastoma in particular in our setup. It can be taken as a baseline for other studies in the future.
- Retinoblastoma was discussed in detail including the IIRC and IRSS systems which was important in the management and follow up of these patients.

Limitation

- The study being retrospective in nature and includes patients only in a single institution with cases received in a referral system, it is subjected to bias.
- Information was taken from existing hospital records of patients and this has significant impact as there was a gap in the card keeping with lost medical records and incomplete data.
- The imaging and pathology reports were inconsistent with difficulty in the data collection process.

Recommendation

- While pediatric orbital tumors are most often managed in tertiary care centres, primary health care workers should be aware of the signs and symptoms of intraocular and orbital neoplasms for early identification and referral.
- Creating awareness within the society at large reduces late presentationto seek medical care.
- Screening of pediatric patients for retinoblastoma based on risk stratification improves early detection and management.
- Communication between radiologist, pathologist and treating ophthalmologist is important for a better outcome in these patients.

Reference

1. Wichmann, W., et al., *Imaging of orbital and visual pathway.* Heidelberg, 2006. **P25-60**.
2. Tailor, T.D., et al., *Orbital neoplasms in adults: clinical, radiologic, and pathologic review.* Radiographics, 2013. **33**(6): p. 1739-58.
3. Shinder, R., N. Al-Zubidi, and B. Esmaeli, *Survey of orbital tumors at a comprehensive cancer center in the United States.* Head Neck, 2011. **33**(5): p. 610-4.
4. Alkatan, H.M., F. Al Marek, and S. Elkhamary, *Demographics of Pediatric Orbital Lesions: A Tertiary Eye Center Experience in Saudi Arabia.* J Epidemiol Glob Health, 2019. **9**(1): p. 3-10.
5. Shields, J.A., C.L. Shields, and R. Scartozzi, *Survey of 1264 patients with orbital tumors and simulating lesions: The 2002 Montgomery Lecture, part 1.* Ophthalmology, 2004. **111**(5): p. 997-1008.
6. Suleiman DE, I.Y., Ahmed SA, Liman AA. , *Histopathologic spectrum of paediatric eye and ocular adnexal tumours: A 10-year review from a referral centre in Nigeria.* Niger J Clin Pract. , 2020. **23**(5): p. 654-659.
7. Y. Adamu, S.A., *Patterns of tumours involving the orbit in patients seen at Menellik II referral hospital, Addis Ababa, Ethiopia.* Ethiopian medical journal, 2019. **57**(1): p. 13-18.
8. Domingo RE, M.L., Castro RM, *Tumors of the eye and ocular adnexa at the Philippine Eye Research Institute: a 10-year review.* Clin Ophthalmol, 2015. **9**(9): p. 1239-47
9. Bullock JD, G.S., Rakes SM., *Orbital tumors in children.* Ophthalmic Plast Reconstr Surg, 1989. **5**(1): p. 13-6.
10. Bienvenido V Castillo, L.K., *Pediatric tumors of the eye and orbit.* Pediatric Clinics of North America, 2003. **50**(1): p. 149-72.
11. Bakhshi, S., P. Singh, and N. Chawla, *Malignant childhood proptosis: study of 104 cases.* J Pediatr Hematol Oncol, 2008. **30**(1): p. 73-6.
12. Nagaraju, R.M., et al., *Efficacy of High Frequency Ultrasound in Localization and Characterization of Orbital Lesions.* J Clin Diagn Res, 2015. **9**(9): p. TC01-6.
13. Hande, P.C. and I. Talwar, *Multimodality imaging of the orbit.* Indian J Radiol Imaging, 2012. **22**(3): p. 227-39.
14. Sagerman, R.H., Alberti, W.E. (Eds.), *Radiotherapy of Intraocular and Orbital Tumors* 2003, Berlin Heidelberg: Springer-Verlag.
15. Graaf, et al., *Guidelines for imaging retinoblastoma: Imaging principles and MRI standardization.* Pediatric radiology, 2011. **42**: p. 2-14.
16. Galluzzi, P., et al., *Is CT still useful in the study protocol of retinoblastoma?* AJNR Am J Neuroradiol, 2009. **30**(9): p. 1760-5.
17. Chantada, G., et al., *A proposal for an international retinoblastoma staging system.* Pediatr Blood Cancer, 2006. **47**(6): p. 801-5.
18. Fabian, I.D., A. Reddy, and M.S. Sagoo, *Classification and staging of retinoblastoma.* Community Eye Health, 2018. **31**(101): p. 11-13.
19. Blandford, et al., *Classification of Orbital Tumors*, in *clinical ophthalmic oncology*. 2019. p. 9-15.
20. Bonavolontà G, S.D., Grassi P, Comune C, Tranfa F, Uccello G, Iuliano A., *An analysis of 2,480 space-occupying lesions of the orbit from 1976 to 2011.* Ophthalmic Plast Reconstr Surg, 2013 **29**(2): p. 79-86.
21. Dr.B.Ushalatha and Dr.K.Sambasivarao, *Role of CT in the Evaluation of Orbital Tumors.* IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), 2016. **15**(4): p. 16-19.
22. Sha, P., et al., *Role of imaging (MDCT) in ocular and orbital lesions.* Health Renaissance, 2015. **13**(3): p. 24-36.

23. Markowski, J., et al., *Primary orbital tumors: a review of 122 cases during a 23-year period: a histo-clinical study in material from the ENT Department of the Medical University of Silesia.* Med Sci Monit, 2014. **20**: p. 988-94.
24. Bacorn, C., K.K. Gokoffski, and L.K. Lin, *Clinical correlation recommended: accuracy of clinician versus radiologic interpretation of the imaging of orbital lesions.* Orbit, 2020: p. 1-5.
25. Aerts, I., et al., *Retinoblastoma.* Orphanet J Rare Dis, 2006. **1**: p. 31.
26. Kodilinye, H.C., *Retinoblastoma in Nigeria: problems of treatment.* Am J Ophthalmol, 1967. **63**(3): p. 469-81.
27. James, S.H., W.C. Halliday, and H.M. Branson, *Best cases from the AFIP: Trilateral retinoblastoma.* Radiographics, 2010. **30**(3): p. 833-7.
28. de Jong, M.C., et al., *The Incidence of Trilateral Retinoblastoma: A Systematic Review and Meta-Analysis.* Am J Ophthalmol, 2015. **160**(6): p. 1116-1126 e5.
29. Chantada, G.L., et al., *Comparison of staging systems for extraocular retinoblastoma: analysis of 533 patients.* JAMA Ophthalmol, 2013. **131**(9): p. 1127-34.
30. Kashyap, S., et al., *Phthisis bulbi in retinoblastoma.* Clin Exp Ophthalmol, 2011. **39**(2): p. 105-10.
31. Taha, H., et al., *Phthisis bulbi: clinical and pathologic findings in retinoblastoma.* Fetal Pediatr Pathol, 2015. **34**(3): p. 176-84.
32. PJ, M., et al., *Orbital tumors in children: a descriptive study at tertiary care centre.* Natl J Med Res

2013. **3**: p. 362–6.
33. Bidar, M., et al., *Clinical and imaging characteristics of orbital leukemic tumors.* Ophthalmic Plast Reconstr Surg, 2007. **23**(2): p. 87-93.
34. Kralik, S.F., et al., *Orbital infantile hemangioma and rhabdomyosarcoma in children: differentiation using diffusion-weighted magnetic resonance imaging.* J AAPOS, 2018. **22**(1): p. 27-31.
35. Kumar, A., et al., *The clinical radiological and histological correlation of orbital assessment in malignant lesions of the maxillo-ethmoid complex.* Indian J Otolaryngol Head Neck Surg, 2000. **52**(3): p. 230-4.
36. Thomas E. Johnson, S.H.S., Amin M. Nasr, Gudmund Bergqvist & John C. Cavender, *Pediatric orbital tumors in Saudi Arabia.* Orbit, 1990. **9**(4): p. 205-215.
37. Shifa, J.Z. and A.M. Gezmu, *Presenting signs of retinoblastoma at a tertiary level teaching hospital in Ethiopia.* Pan Afr Med J, 2017. **28**: p. 66.
38. El Zomor, H., et al., *Clinical presentation of intraocular retinoblastoma; 5-year hospital-based registry in Egypt.* J Egypt Natl Canc Inst, 2015. **27**(4): p. 195-203.
39. Abramson, D.H., et al., *Presenting signs of retinoblastoma.* J Pediatr, 1998. **132**(3 Pt 1): p. 505-8.
40. Antoneli, C.B., et al., *Extraocular retinoblastoma: a 13-year experience.* Cancer, 2003. **98**(6): p. 1292-8.
41. De Potter, P., C.L. Shields, and J.A. Shields, *Clinical variations of trilateral retinoblastoma: a report of 13 cases.* J Pediatr Ophthalmol Strabismus, 1994. **31**(1): p. 26-31.

Research questionnaire

Research topic: Imaging with histopathologic correlation of pediatric oculo-orbitaltumors evaluated in TikurAnbessa specialized hospital (Three years retrospective study)

Patient code(ID):____

I sociodemographic data

1. Age at presentation(in years): ____
2. Gender: 1. Male 2. Female
3. Address(Region) in Ethiopia: _____

II Patient clinical data:

1. Presenting symptom
   - 1.1 Swelling around the eye
   - 1.2 whitish color change of the eye
   - 1.3 blurring of vision
   - 1.4 pain
   - 1.5 discharge from the eye
   - 1.6 headache
   - 1.7 Loss of vision
   - 1.8 Other(specify)_____
1. Duration of symptom(in mnths)_____
2. Age at first recognition(in yrs)_____
3. Family history 1. Yes 2. No
4. Presenting sign
   - 4.1 Leukocorea
   - 4.2 Strabismus
   - 4.3 Proptosis
   - 4.4 Fungating mass
   - 4.5 echymosis
   - 4.6 Red eye
   - 4.7 Decreased vision
   - 4.8 diplopia
   - 4.9 Other(specify)
5. Staging on fundoscopic evaluation under ansthesia based on the international classification for intraocular retinoblastoma
   1. Group A 2. Group B 3. Group C 4. Group D 5. Group E

II Pathology findings

1. Pathology specimen 1. Incisional biopsy 2. excisional biopsy 3. FNAC
2. Necrosis 1. Yes 2. No
3. Calcification 1. Yes 2. No
4. Hemorrhage 1. Yes 2. No
5. Extraocular extension 1. Yes 2. No
6. Optic nerve invasion 1. Yes 2. No
7. Pathology diagnosis_____
8. Pathology staging (based on AJCC staging for retinoblastoma only)_____

9. Histologic subgroup(for orbital RMS only) 1. Pleomorphic 2. Embryonal 3.Alveolar
10. Origin of the mass 1. Primary 2. Secondary 3. Metastasis

III <u>Imaging studies</u>

1. CT scan of the orbit and brain: 1. Yes 2. No
   The protocol used 1orbital 2.brain 3 both
2. MRI of the orbit and brain: 1. Yes 2.No
3. If the answer to question 1 is yes and for primary orbital and metastasis to orbit
   3.1 Location1. Ocular 2.Extraocular 3. Both
   3.2 For tumors with extraocular involvement, orbital compartment involved
   1. Intraconal 2. Extraconal 3.Conal 4.multicompartmental
   3.3 Optic nerve invasion. 1. Yes 2. No

3.4 Lacrimal gland involvement1. Yes 2. No

3.5Preseptal compartment involvement 1. Yes 2. No

3.6 Eyeball involvement 1.no 2. Lytic 3.Sclerotic 4.mixed

3.7 Intracranial extension 1. Prechiasmaticlesion 2.leptomeningeal involvement 3. Pineal region mass 4. Other intracranial structures involvement(specify)_____

3.8 Other adjacent structures involved(specify)_____

3.9 Primary diagnosis_____

3.10 Staging of the tumor for retinoblastoma(based on the international classification of retinoblastoma)

1. Stage 0 2. Stage I 3. Stage II 4. Stage III 5. Stage IV

4. If the answer to question number 1 is yes and for secondary orbital tumors,

4.1 Origin of the mass 1. retinoblastoma 2.Nasopharyngeal carcinoma 3.other diagnosis, describe_____

5. If the answer for question number 2 is yes and for primary and metastatic orbital tumors,
   5.1 Location1. Ocular 2.Extraocular 3. Both
   5.2 For tumors with extraocular involvement, orbital compartment involved 1.Intraconal 2. Extraconal 3.Conal 4.1&2 5. 1&3 6.2&3 7. All three compartments
   5.3 Optic nerve invasion. 1. Orbital portion 2. Intracranial portion
   5.4 Lacrimal gland involvement
   5.5Preseptal compartment involvement
   5.6 Eyeball involvement 1. Lytic 2.Sclerotic 3. Mixed
   5.7 Intracranial extension 1. Parasellar involvement 2.dural involvement 3.Pineal gland involvement 4. Other intracranial structures involvement
   5.8 Other adjacent structure involvement
   3.9 Primary diagnosis_____
   3.10Staging of the tumor for retinoblastoma only(based on the international classification of retinoblastoma) 1. Stage 0 2. Stage I 3. Stage II 4.Stage III 5. Stage IV
6. If the answer to question number 2 is yes and for secondary orbital tumors,
   6.1 Origin of the mass 1. retinoblastoma 2.Nasopharyngeal carcinoma 3.other diagnosis, describe_____