Ethiopian National Retinoblastoma Guidelines for Care

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ABSTRACT

Retinoblastoma is a rare childhood eye cancer with a promising outcome upon early detection and treatment. The survival rate in developed countries is more than 99%. In Ethiopia, our previous published studies showed that 47% of them died from cancer.

Retinoblastoma is one of the focus areas of the WHO under Global Initiatives for Childhood Cancer. To catch up with the global initiatives in May 2018, we conducted the first retinoblastoma symposium in Ethiopia by hosting various ophthalmologists, paediatric oncologists, pathologists, parents, and support groups. Leaders and experts (focal eye care and disease control) from the Federal Ministry of Health led the symposium. World-known retinoblastoma experts from Canada, the USA, and Kenya participated in this symposium and shared knowledge on developing retinoblastoma guidelines.

At the end of the two-day meeting, a technical group comprising ophthalmologists, paediatric oncologists, pathologists, public health experts, parents with retinoblastoma, and organizations supporting children with cancer was established to develop a national retinoblastoma guidelines.

This team has worked on this guidelines to promote early cancer detection, smooth referral systems between institutions, standardize clinical care among health facilities, and support families and children with retinoblastoma. This guideline was reviewed, commented and enriched by experts in retinoblastoma from

Canada, Kenya, Israel, DRC, and France. This guideline will be the second for the sub-Saharan African region. It is also endorsed by the Federal Ministry of Health and to be implemented among all sectors and stakeholders.

INTRODUCTION

Retinoblastoma (RB) is the most common intraocular malignancy of childhood, but a relatively rare disease, occurring in approximately 1: 16,000–18,000 live births[1]. The tumor(s) arises from embryonic retinal cells, so most cases occur under the age of 4 years. This aggressive tumor proliferates, metastasizes early, and can be fatal; however, it is also curable if treated early. The most common presentation is leukocoria, a whitening of the ordinarily red reflex in the eye. Still, if this early sign does not prompt the family to seek care, the tumor can continue to grow and spread relatively undetected until it may be too late for a cure, which can happen within months[2]. Mortality from retinoblastoma in Africa and Asia is 40-70%, much higher than 3-5% in Europe, Canada, and the USA[2]. Likewise, the disease burden is much more significant in Low and Middle-Income Countries (LMICs), with an estimated 84% of all children with cancer in the world residing in LMICs[3]. Survival and visual outcome in retinoblastoma are dependent on the severity of the disease at the time of presentation, so early detection is paramount to survival; however, children in East Africa present an average of 9 to 11 months later than their counterparts in the US and Canada, one leading to poor survival rates[4].

Ethiopia has one of the highest incidences of retinoblastoma in sub-Saharan Africa, claiming 19% of all cases in a recent study of select sub-Saharan African countries. The number of cases is likely underreported[4]. In a recently published Ethiopian study, 40.1% of patients had extraocular retinoblastoma at presentation, with a median delay of 12 months between the onset of symptoms of retinoblastoma and presentation to Menelik II Hospital (the leading RB center in Ethiopia)[5]. Unpublished research from the same center indicated a low survival rate (49.5%). The patient's delayed presentation caused significant mortality at the center for retinoblastoma treatment[6]. In the US and Canada, early screening and treatment contribute to 95-97% survival, while survival in Africa and Asia ranges from 30-60%[2].

Ophthalmologists, oncologists, paediatric nurses, imaging specialists, pathologists, pharmacists, child-life specialists, and social workers are just a few of the members of a multidisciplinary team that is most suited to treating retinoblastoma[7]. Late referral and delayed diagnosis result in difficult-to-treat large tumors, blindness, extraocular disease, and mortality. There is evidence that earlier diagnosis improves treatment outcomes[8].

The purpose of this protocol is to improve the quality of care for retinoblastoma patients by standardizing the care across health institutions and providing a guide to Ethiopian health workers and policymakers on early detection and proper management and follow-ups of RB patients.

MATERIALS AND METHODS

The Ethiopian National Retinoblastoma Guideline technical group was established in 2018 to increase survival and decrease mortality from retinoblastoma in Ethiopia through;

(i) Ensuring early diagnosis of retinoblastoma by increasing awareness among the health care workers as well as the general public.
(ii) Ensuring early detection and immediate referral of children suspected of retinoblastoma.
(iii) Improving the quality of medical treatment of children with retinoblastoma through standard treatment and quality pathologic reports.
(iv) Ensuring psychosocial support for families with retinoblastoma.
(v) Influence national strategic planning for cancer care to include retinoblastoma diagnosis and treatment in Ethiopia

The core and expert committee were selected from the first Ethiopian Retinoblastoma symposium, which was conducted in May 2018. This committee comprises local and global retinoblastoma experts, a retinoblastoma support group, and a Federal Ministry of Health representative from Ethiopia.

Guideline development

This document aims to improve the quality of care for retinoblastoma patients by standardizing the care across health institutions and providing a guide to Ethiopian health workers and policymakers on early detection and proper management and follow up of RB patients.

As seen from the committee list, the Expert Committee that prepared this document comprised individuals from the medical field, researchers, representatives from the government, family support organizations, and public health experts in screening, diagnosis, genetics, and treatment.

In order to develop recommendations in each aspect of RB care, we identified the clinical problems in RB care and conducted an extensive literature review.

The criteria for evaluating the references used to support the recommendations were taken from previously published standards (Table 1)[9].

Table 1: Criteria for assigning a level of evidence to recommendations

Level of evidence	Criteria
1	Randomized Controlled Trials (RCTs) (or meta-analyses) without important limitations
2	RCTs (or meta-analyses) with important limitations Observational studies (non-RCTs or cohort studies) with overwhelming evidence
3	Other observational studies (prospective cohort studies, case-control studies, case series)
Consensus	Inadequate or no data in population of interest Anecdotal evidence or clinical experience 100% agreement of Steering & Expert Committee members

SCREENING

Early detection, when tumors are still small, maximizes survival and vision outcomes and reduces the need for radiation, chemotherapy, and enucleation. In addition, serial examinations help detect tumors early and protect vision because retinoblastoma tumors can grow gradually during early childhood[10,11].

Screening close relatives at risk of the disease are invaluable in early detection and treatment. In addition, early detection and immediate referral of children with retinoblastoma increase the possibility of saving lives and eyes and preserving functional vision. Hence, the ultimate goals of screening children at risk for retinoblastoma are the early diagnosis of the tumor followed by appropriate treatment when they are minimal and manageable with local therapies. Screening is based on risk stratification, including genetic testing and counseling.

Vision screening guidelines: In preschool, all children should undergo eye exams for conditions like RB and cataracts, as well as amblyopia or conditions that increase their chance of developing it. The child's general practitioner /paediatrician makes sure that these examinations are carried out. Regular children's vision screening may help to detect RB earlier. The Canadian Paediatric Society (CPS) suggested checking for RB symptoms during routine eye exams[12].

Table 2: Vision screening guidelines from the Canadian Paediatrics Society[12]

Age	Screening guideline
Newborn to 3 months	A complete examination of the external eye structures including the conjunctiva, cornea, iris, and pupils
	Red reflex inspection of the red reflex to rule out lenticular opacities or RB.
	Failure of visualization or abnormalities of the reflex are indications for an urgent referral to an ophthalmologist
	High-risk newborns (at risk of retinopathy of prematurity and family histories of hereditary ocular diseases) should be examined by an ophthalmologist
6 to 12 months	Conduct examination as above
	Ocular alignment should again be observed to detect strabismus. The corneal light reflex should be central and the cover-uncover test for strabismus normal
3 to 5 years	Conduct examination as above
	Visual acuity testing should be completed with an age appropriate tool
6 to 18 years	Screen as above whenever routine health examinations are conducted
	Examine whenever complaints occur

SCREENING - RECOMMENDATIONS

(i) We recommend that all infants and children in whom someone has observed a white pupil (either in person or in a photograph) have a full dilated-eye examination, including a red reflex test within 72 hours by an ophthalmologist or medical practitioner who is fully aware of the importance of leukocoria as a sign of RB[7,13].

(ii) We recommend that health workers look for a white pupil or strabismus during routine immunization visits [Consensus].

(iii) We recommend that any child aged less than five years of age with strabismus or suspected strabismus be seen by their primary care provider (General Practitioner (GP) /paediatrician:

(a) We recommend that the oblique viewing red reflex test be applied to any child with

strabismus or suspected strabismus after pupillary dilation[14].

(b) We recommend urgent referral (within 72 hours) to an ophthalmologist of any child with strabismus or suspected strabismus and an abnormal red reflex[7].

(c) We recommend that secondary or tertiary RB centers see the child in (b) above within 72 hours for the above signs or abnormalities, which constitutes an emergency (see "Referral and Diagnosis" section) [Consensus].

(iv) We support the Canadian Paediatric Society (CPS) recommendations concerning the suggested timing of vision screening for the general population[12].

(v) We recommend incorporating information related to retinoblastoma screening in the national immunization information booklet [Consensus].

(vi) We recommend that primary doctors and paediatricians do a routine red reflex test for all sick children under five years visiting their outpatient clinics [Consensus].

FEATURES AND CLASSIFICATION OF RETINOBLASTOMA CENTRES IN ETHIOPIA

According to a recent study, 19% of retinoblastoma patients in sub-Saharan Africa were from Ethiopia. The number of cases is likely underreported[4]. The need for RB centers and human resources is challenging in caring for retinoblastoma patients. This guideline section discusses the mandatory resources that should be allocated for primary, secondary, or tertiary-level retinoblastoma centers. For appropriate resource and expertise allocation, we recommend that the retinoblastoma service-providing centers be classified as primary, secondary, and tertiary (Table 2).

*Primary centers***:** These centers aim to make a preliminary disguise of retinoblastoma by first contact level health providers (nurses, health officers, general practice doctors, and paediatricians). Based on the referral system of Ethiopia, health posts, health centers, district-level hospitals, and privately owned clinics will be considered Primary RB Centers.

Secondary level RB centers: These centers should be able to make a clinical diagnosis of retinoblastoma, treat it by enucleation, and send the eye for pathological examination by a qualified pathologist. Regional referral hospitals, private or public comprehensive hospitals, and specialized eye centers will be labeled secondary RB Centers.

Tertiary level RB centers: The tertiary retinoblastoma centers should be able to confirm the diagnosis with B-Scan ultrasound and/or MRI and treat retinoblastoma by focal treatment, chemotherapy, and enucleation. In addition, these centers can manage complex cases with advanced treatment modalities and conduct various research. University teaching hospitals with training, service and research capacities in the eye cancers field are considered tertiary centers.

Retinoblastoma specialist: A paediatric ophthalmologist, retinal specialist, ocular oncologist, oculoplastic surgeon or a general ophthalmologist with specialized training on RB (and sometimes more than one, working as a team) will manage the ongoing care of children with RB. The primary treatment for unilateral RB is the removal (enucleation) of the affected eye. A surgeon specializing in RB will know how to harvest tumors for genetic studies after eye removal. Specific training in the overall management of RB will include knowledge about and experience with focal therapy.

Paediatric oncologists and radiotherapists: A paediatric oncologist(s) dedicated to treating RB patients will participate in the care and lead management when chemotherapy is required. They will evaluate Cerebrospinal Fluid (CSF) and bone marrow when the child is at risk for metastatic disease. In addition, the oncologist actively recruits patients who need chemotherapy to suitable multicenter clinical trials, as available.

Social worker/Psychosocial support: A specifically dedicated social worker helps RB families cope with the emotional and financial implications of a new cancer diagnosis, providing counseling to facilitate coping with the crisis, adjustments, support and resource management, and education about RB and the treatment process. In addition, psychosocial support includes palliative care and bereavement support for end-of-life patients and their families.

Table 3: Minimum mandatory staffing and resources requirements for secondary and tertiary RB centers in Ethiopia

Facility	Secondary level RB centers	Tertiary level RB centers
Personnel	Ophthalmologist	Ophthalmologist
	Pathologist	RB specialist
	Anaesthetist	Paediatric oncologist
		Radiologist
		Pathologist with RB expertise
		Anaesthesiologist
		Social worker/psychosocial support
		Genetic councilor
		Ocularist
Surgical capacity	Examination under anaesthesia	Examination under anaesthesia
	Capacity to perform enucleation	Capacity to perform enucleation
Treatment		Laser therapy (Transpupillary thermotherapy by diodd laser)
		Cryotherapy
		Chemotherapy
	B-Scan ultrasound	B-Scan ultrasound
	MRI	MRI
	CT Scan	CT Scan
		Genetics – Ocular screening of Proband's family
Research	Basic research	Basic research
		Clinical trials

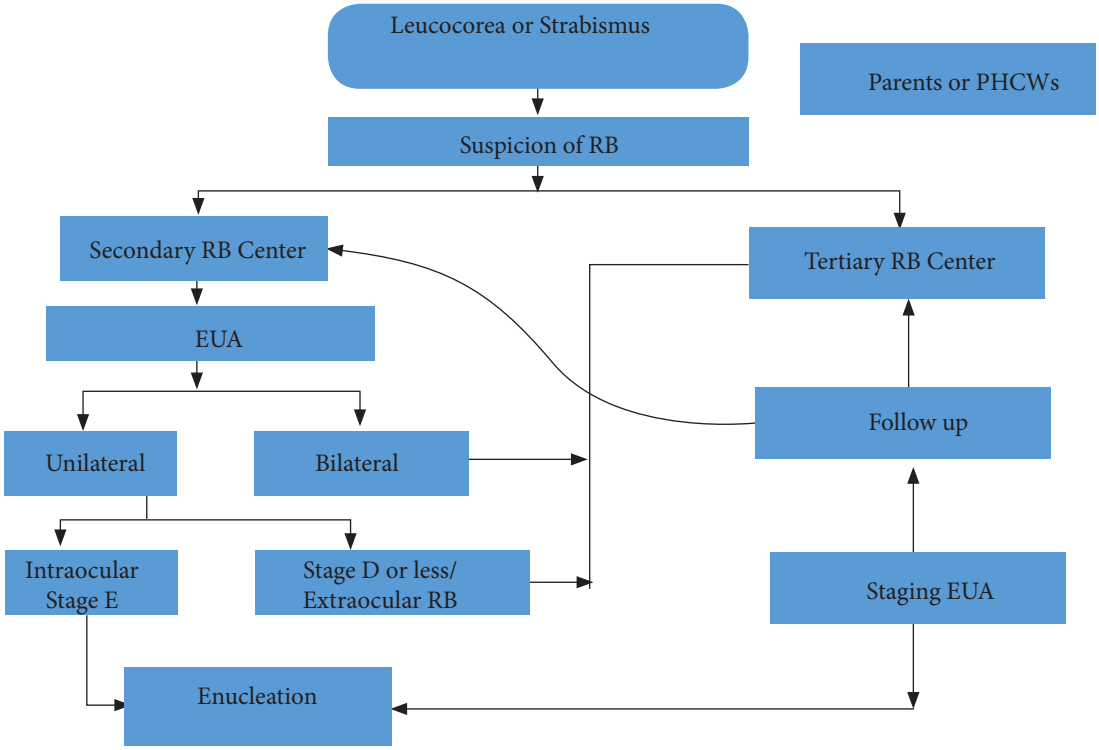
REFERRAL AND DIAGNOSIS

Early referral to the appropriate retinoblastoma centers is essential for timely diagnosis and good treatment outcomes in the care of retinoblastoma families. The primary care physician plays a critical role in the referral process. Secondary and tertiary RB centers further establish the diagnosis and develop the initial treatment plan.

The delay in referral lag (time between the initial visit with a primary healthcare professional and appointment with an ophthalmologist) had serious consequences for some patients with RB[15].

A retrospective study in Ethiopia showed that 28 (74.5%) patients delayed seeing a healthcare provider for three months after the onset of symptoms. The delay in presentation was due to a lack of knowledge and cost. Cost and distance are significant barriers to seeing referred RB centers and receiving appropriate treatment[16].

Figure 1: Referral algorithm for retinoblastoma cases in Ethiopia



REFERRAL AND DIAGNOSIS-RECOMMENDATIONS

(i) We recommend that any child with signs consistent with RB be referred to an ophthalmologist to receive a full retinal examination with dilated pupil and have a detailed history taken to confirm or rule out a diagnosis of RB [Consensus].

(ii) We recommend that secondary and tertiary centers accept direct referrals with suspicion of RB from primary healthcare providers, such as general practitioners and paediatricians [Consensus].

(iii) We recommend that primary healthcare providers obtain and record a complete contact address, including telephone contacts, and immediately refer all RB cases to a secondary or tertiary RB center [Consensus].

(iv) We recommend that all children referred with any possibility of RB be seen within 72 hours, or as soon as possible, at the secondary or tertiary RB center for a thorough ocular and systemic examination to confirm or rule out a diagnosis of RB. The referring physician has a responsibility to communicate with the nearby secondary or tertiary center about the referral[7,13].

(v) We recommend that difficult unilateral cases (e.g., a very young child, potential to save the eye; unilateral multifocal and (or) germline RB1 mutation), or risk for extraocular disease and bilateral cases be referred from a secondary center to a tertiary center[7,13].

(vi) We recommend that any child with high-risk pathological features (see "Follow-up" chapter) be referred to a tertiary center[7,13].

(vii) We recommend that the RB center promptly inform the referring physician of the diagnosis, management, and outcome of the referral and invite the referring physician to remain involved with the non-RB care and follow-up of the child, as appropriate [Consensus].

(viii) We recommend that in order to reduce risks associated with radiation exposure, all children with RB have an MRI of the head and orbits at diagnosis rather than a CT scan, if possible, to check for evidence of intracranial cancer and the extent of the disease[7,13].

(ix) We recommend developing RB programs at Tertiary Eye Care Units (TECUs) because they will likely have a paediatric oncology service and palliative care support [Consensus].

(x) In secondary label RB centers, if the patient's socio-economic conditions don't allow him/her to travel to third-level RB centers, we recommend that unilaterally affected eyes be enucleated unless that unilateral eye is group A or B [Consensus].

(xi) We recommend that all bilateral RB patients be referred to tertiary RB Centers for treatment and follow-up [Consensus].

(xii) We recommend the establishment of RB centers per the country's strategy for childhood cancer [Consensus].

GENETIC COUNSELLING

Retinoblastoma was first cancer for which a causal genetic mutation was discovered[17]. Any other family members may be at risk if retinoblastoma is diagnosed in one member of the family. When molecular genetic testing is available, genetic counseling can provide families with more precise information about their cancer risks[7]. Effective genetic information translation enables individuals who are at-risk to adhere to routine cancer surveillance for both themselves and their at-risk springs. Additionally, it encourages people to adopt a healthy lifestyle and make informed reproductive choices in order to reduce their risk of developing second cancer[18]. Due to the lack of genetic counseling in Ethiopia, the medical team is responsible for counseling the parents /guardians of RB. Patients with a family history of retinoblastoma should undergo genetic testing to determine their risk level[19].

When retinoblastoma is diagnosed, clinicians and parents communicate in an emotionally charged manner that includes explaining the disease's malignant nature to them, telling many of them that the removal of their child's eye(s) is necessary to save their life, and starting palliative care as needed. This is when genetic counseling takes place[18]. Ethiopian healthcare providers do not yet have access to a genetic counseling discipline.

GENETIC COUNSELLING- RECOMMENDATIONS

(i) We recommend antenatal history, including a detailed family history of eye disease, and referral to an ophthalmologist when this history is positive. For all individuals with RB and/or a family history of RB, except those excluded by genetic testing[7,13].

(ii) We recommend that expectant couples undergo early prenatal counseling and their infants undergo perinatal management to facilitate the earliest possible treatment[20,21].

(iii) We recommend standardized counseling in the absence of genetic testing for patients, parents, and other relatives to discuss RB, the risk and hereditary pattern of RB, pregnancy options, post–delivery surveillance screening protocols to diagnose tumors early in infants at risk, and treatment options[22,23].

(iv) We recommend that family members at risk be screened as soon as possible after birth, frequently until age seven years, according to the empiric risk of developing RB[20,21,23].

(v) We recommend awareness counseling about the risk of other cancers in adult survivors and relatives[21,24,25].

(vi) We recommend that children with RB be offered repeated genetic counseling as they grow up so that they completely understand their options and appropriate care for themselves and their children [Consensus].

(vii) We recommend RB1 gene mutation identification testing for the first affected person (proband) in each RB family[20,26].

(viii) When the RB1 gene mutation in a proband /family becomes known, we recommend genetic testing for all at-risk relatives[26,27].

(ix) We recommend that surveillance be discontinued for relatives determined to be NOT at risk by genetic testing [22,23,28].

PUBLIC AWARENESS AND EDUCATION

Lack of awareness about the symptoms of retinoblastoma among the public and health professionals is the main reason for the late presentation of patients. Hence, increasing knowledge and educating healthcare workers on Retinoblastoma (RB). In this guideline, we describe various successful public awareness campaigns on RB. Finally, we recommend increasing RB awareness and education in Ethiopia.

Public awareness campaigns: Awareness campaigns to educate the public on the signs and symptoms of leukocoria are likely to increase the rates of early detection of RB. In Ethiopia, a study was conducted to assess the referral pattern of patients with RB in 2018. Among the 73% (30/41) patients who presented ≥3 months after to the RB Center in Addis, 97% (29/30) of them did not think the white pupillary reflex was a problem. Hence, the lack of awareness among the public was the cause of the late presentation.

In Honduras, an RB awareness campaign was initiated to promote early diagnosis. Information about RB was disseminated, using posters and flyers, to parents via government health clinics during the annual vaccination campaigns beginning in 2003. Following the public awareness campaigns, extraocular RB decreased from 73% to 35%. The median age at diagnosis and the median time between the first sign or symptom and diagnosis was 3.8 and 1.7 months[29]. In Brazil, 20 new RB cases were diagnosed due to a national campaign for early diagnosis of RB. This program was initiated in September 2002, with a public service announcement highlighting leukocoria as a symptom of cancer (www.tucca.org.br) which was broadcasted on several television stations throughout the country. In addition, a toll-free telephone number was offered to the public so that anyone could call to get more information. In addition to the television advertisement, educational materials were provided to the general public, primary healthcare workers, and ophthalmologists[30]. Ethiopian RB patients' mean parental lag time was 7.97 months[16].

Health workers awareness: According to recommendations from the American Paediatric Association, every child in their first year of life should undergo the red reflex test at least once as part of a regular checkup[31].

A study among paediatricians in southern Ethiopia found that their awareness of the ranges of presentation and available treatment for RB needed to be improved[32].

Medical students' understanding of RB was increased in Jordan by modifying the teaching curriculum for the ophthalmology rotation and placing a stronger emphasis on red flags of RB[33]. Teaching retinoblastoma awareness could be added to training programs for undergraduate medical and nursing students, and refresher courses could be held for those currently working.

PUBLIC AWARENESS AND EDUCATION – RECOMMENDATIONS

(i) We recommend that RB be included in children's vaccination cards [Consensus].
(ii) We recommend that information on RB be included in under five clinic patient education sessions [Consensus].
(iii) We recommend that basic information on signs and symptoms of RB be given to local and religious leaders [Consensus].
(iv) We recommend the dissemination of information about RB using flyers and posters in the local language[29].
(v) We recommend disseminating information about RB through professional talks and articles in printing, electronic and social media[30].
(vi) We recommend public transport to spread awareness about RB[13].
(vii) We recommend organizing public awareness campaigns at the national level once per year in line with the RB week globally [Consensus].
(viii) We recommend working closely with the NGOs (Like local religious authorities and doctors without borders) to raise awareness of RB care and patient follow-up [Consensus].

EDUCATION FOR HEALTH WORKERS – RECOMMENDATIONS

(i) We recommend that major paediatric and vision screening associations provide information on signs and symptoms of RB in their print, mass media, and online public information materials [Consensus].
(ii) We recommend that information about the proper performance of the red reflex test be provided to all those with a responsibility to perform this screening (paediatricians, GPs, nurses, public health officers) (see "Screening" section) [Consensus].
(iii) We recommend that information on signs and symptoms of RB be provided to healthcare professionals who see young children and pregnant women in their clinics [Consensus].
(iv) We recommend that RB education be included in the healthcare curricula [Consensus].
(v) We recommend incorporating RB into existing paediatric cancer and eye disease programs [Consensus].
(vi) We recommend that basic signs and symptoms of "white Pupillary reflex " in addition to RB are taught to health extension workers [Consensus].
(vii) We recommend that professional societies working on eye and children (Ophthalmological Society of Ethiopia, Ethiopian Paediatric Society, etc.) include RB as part of their continued education [Consensus].
(viii) We recommend establishing a national RB center focusing on increasing awareness, conducting and disseminating research, and advocating for better RB Care in Ethiopia [Consensus].
(ix) We recommend establishing and strengthening family support groups on RB to enhance awareness and care towards RB [Consensus].

TREATMENT

Retinoblastoma treatment options can range between different centers worldwide and are constantly evolving. Nevertheless, all retinoblastoma experts generally have the same fundamental objectives: protecting life and preventing metastatic disease, preserving the globe, and eventually optimizing vision[34]. The extent of the retinoblastoma at the time of diagnosis (the intraocular disease classification and the stage of systemic disease), the condition of the contralateral eye, the child's general health, their socioeconomic situation[35], and their access to specialized care are all factors in how the disease will be managed[2,36].

Systemic Intravenous Chemotherapy (IVC) typically entails the monthly administration of 2, 3, or 4 chemotherapeutic drugs using a central or peripheral catheter for 6–9 consecutive cycles[37]. Three medications, including vincristine, etoposide, and carboplatin, make up the most popular treatment protocol (VEC)[37,36]. In addition, patients with bilateral illness, known germline mutations, retinoblastoma in the family history, or probable occurrences of the optic nerve or choroidal invasion are currently considered criteria for IVC[37].

Intra-Arterial Chemotherapy (IAC) is a complex and frequently expensive procedure that is best carried out in an angiography suit[34]. In addition, IAC delivers a chemotherapeutic dose to the eye that is ten times more than IVC[39]. Therefore, it is essential to the current management of retinoblastoma, particularly in unilateral

tumors[40]. However, IAC might not be possible in developing nations due to the cost, and specialist training needed[39].

In addition to IVC or IAC, focal therapy is frequently employed to consolidate tumors. Cryotherapy and transpupillary thermotherapy are the two most often used focal therapies nowadays (TTT)[34]. Cryotherapy is indicated in treating small tumors and foci of sub-retinal or pre-retinal seeds[34]. Chemo-cryotherapy increases intraocular medication concentration[37]. Transpupillary Thermotherapy (TTT) with a diode laser is used with chemotherapy as the primary treatment for tiny cancers smaller than 3mm in diameter and 2mm in thickness[41].

External Beam Radiation (EBRT) is mostly of historical significance in developed nations due to the numerous side effects. With orbital recurrence, extraocular tumor expansion, and a positive optic nerve margin after enucleation, EBRT still has a place in treatment; it has a role in developing countries[45]. It has been reported that 71% of patients receiving EBRT and IVC for orbital retinoblastoma achieve tumor control[41].

Brachytherapy is typically used as a secondary treatment for medium-sized (≤16mm in largest basal diameter and > 3 to ≤ 9mm in thickness) chemo-resistant tumors with or without localized vitreous or subretinal seeding, following recurrence after IVC or IAC. It can also be used to manage diffuse anterior segment retinoblastoma with or without IVC in the absence of choroidal or retinal tumors[42].

Enucleation is the fastest and least costly treatment. It is reserved for massive group E tumors, poor tumor visualization (e.g., due to vitreous hemorrhage), presence of extraocular extension, suspected invasion of the optic nerve or choroid, or recalcitrant tumors that have failed previous globe salvage therapies[44,45]. Children with extraocular RB usually present with severe pain caused by an orbital mass[46]. Retinoblastoma symptoms in Ethiopia revealed that extraocular tumors were found in 40.1% of cases[5].

Enucleation remains the primary therapy option for patients in advanced stages in Ethiopia. According to a prospective study conducted in Ethiopia, 114 (45.4%) of the 251 eyes were subjected to primary enucleation (87/114, or 76.5%) or exenteration (27/114, or 23.5%)[5].

Table 4: AJCC Clinical Staging1 8th edition, 2017[46]

cT1		Intra-retinal tumour(s) with subretinal fluid ≤5mm from base of any tumour
	cT1a	Tumours ≤3mm and further than 1.5mm from disc and fovea
	cT1b	Tumours >3mm or closer than 1.5mm from disc or fovea
cT2		Intraocular tumour(s) with retinal detachment, vitreous seeding, or subretinal seeding
	cT2a	Subretinal fluid >5mm from the base of any tumour
	cT2b	Vitreous seeding and/or subretinal seeding
cT3		Advanced intraocular tumour(s)
	cT3a	Phthisis or pre-phthisis bulbi
	cT3b	Tumour invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber
	cT3c	Raised intraocular pressure with neovascularization and/or buphthalmos
	cT3d	Hyphaema and/or massive vitreous haemorrhage
	cT3e	Aseptic orbital cellulitis
cT4		Extraocular tumour(s) involving orbit, including optic nerve
	cT4a	Radiologic evidence of retrobulbar optic nerve involvement or thickening of optic nerve or involvement of orbital tissues
	cT4b	Extraocular tumour clinically evident with proptosis and/or an orbital mass
N1		Evidence of preauricular, submandibular, and cervical lymph node involvement
cM1		Clinical signs of distant metastasis
	cM1a	Tumour(s) involving any distant site (e.g., bone marrow, liver) on clinical or radiologic tests
	cM1b	Tumour involving the CNS on radiologic imaging (not including trilateral retinoblastoma)
H		Hereditary trait

	HX	Unknown or insufficient evidence of a constitutional RB1 gene mutation
	H0	Normal RB1 alleles in blood tested with demonstrated high-sensitivity assays
	H1	Bilateral retinoblastoma, retinoblastoma with an intracranial primitive neuroectodermal tumour (i.e., trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of a constitutional RB1 gene mutation
pT1		Intraocular tumour(s) without any local invasion, or with focal choroidal invasion, or preor intralaminar involvement of the optic nerve head
pT2		Intraocular tumour(s) with local invasion
	pT2a	Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head
	pT2b	Tumour invasion of stroma of iris and/or trabecular meshwork and/or Schlemm's canal
pT3		Intraocular tumour(s) with significant local invasion
	pT3b	Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve
	pT3c	Any partial-thickness involvement of the sclera within the inner two thirds
	cT3d	Full-thickness invasion into the outer third of the sclera and/or invasion into or around emissary channels
cT4		Extraocular tumour(s) involving orbit, including optic nerve
	cT4a,	Evidence of extraocular tumour: tumour at the transected end of the optic nerve, tumour in the meningeal spaces around the optic nerve, full thickness invasion of the sclera with invasion of the episcleral adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids.

Table 5: International Intraocular RB Classification (IIRC)[47]

Group A: Very low risk (T1a)	**Small discrete tumours not threatening vision** **All tumours are 3mm or smaller, confined to the retina** • Located at least 3mm from the foveola and 1.5mm from the optic nerve • No vitreous or subretinal seeding
Group B: Low risk (T1b)	**No vitreous or subretinal seeding** **Tumours any size or location not in Group A** • No vitreous or subretinal seeding • Subretinal fluid no more than 5 mm from tumour base
Group C: Moderate risk (T2)	**Focal vitreous or subretinal seeding and discrete retinal tumours of any size and location** • Local, fine, and limited seeding (T3) • Discrete intraretinal tumours of any size and location (T2b) • Up to one quadrant of subretinal fluid (T2a)
Group D: High risk (T3b)	**Diffuse vitreous or subretinal seeding** • Diffuse intraocular disseminated disease Extensive or "greasy" vitreous seeding • Subretinal seeding may be plaque-like • More than one quadrant retinal detachment

Group E: Very high risk (T4a)	**Very high risk with one or more of the following:** • Irreversible neovascular glaucoma • Massive intraocular hemorrhage • Aseptic orbital cellulitis • Tumour anterior to anterior vitreous face • Tumour touching the lens • Diffuse infiltrating Rb • Phthisis or prephthisis

TREATMENT –RECOMMENDATIONS

(i) We recommend that children with RB be cared for by a multidisciplinary team that provides coordinated and collaborative care in and shared between specialized centers, with expertise and up-to-date protocols and equipment for optimal management of RB [Consensus].

(ii) We recommend that tertiary RB centers work together to ensure optimal care for each child. This might include cross-referrals and cross-consultations to access specific technical or human resources [Consensus].

Ocular treatment

Enucleation

(iii) Immediate enucleation is indicated for all Group cT3/ group E[7].
We recommend that upfront enucleation without pre-enucleation chemotherapy be performed for any cT3 /IIRC Group E eyes, which impose risk for difficult-to-treat systemic metastases. Pre-enucleation chemotherapy is dangerous since it may mask features of extraocular extension, causing under staging and under treating of systemic disease[48].

(iv) We recommend that enucleation be performed for Group cT2/group D eyes when the other eye is normal or Group A/cT1a[7].

(v) We recommend enucleation for recurrent tumors when all other treatment modalities (including EBR) have failed to prevent tumor spread outside the eye or when complications prevent evaluation and treatment of progressive disease[7].

(vi) We recommend enucleating a unilateral RB, except if there is sufficient experience and accessibility (geographic and financial) for eye salvage [Consensus].

Cryotherapy

(vii) We recommend cryotherapy for the treatment of small peripheral RB and (or) laser therapy for small posterior RB, primarily in Groups A/cT1a, B/cT1b, and C/ cT2a, or recurrences after other therapy[7].

(viii) We recommend that cryotherapy through a conjunctival incision may be used for posterior RB refractory to laser focal therapy[7].

(ix) We recommend using pre-chemotherapy cryotherapy 24–72 hours before chemotherapy to increase drug penetration into the eye, particularly for vitreous seeding, but not in the presence of retinal detachment[7].

Chemotherapy

(x) We recommend that chemotherapy consolidated by focal therapy replace primary EBRT[49].

(xi) We recommend systemic chemotherapy for the primary treatment of bilateral Group B/cT1b, C/ cT2a, or D/cT2b eyes and limited therapy for unilateral IIRC Group B /cT1b or C/cT2a eyes with good visual potential[7].

(xii) We recommend pre– enucleation chemotherapy to reduce the tumoral volume in severely buphthalmic eyes[50].

Radiotherapy

(xiii) We recommend that radiotherapy be used only as salvage therapy for the remaining eye after chemotherapy and focal therapy have failed to control the tumor[7].

Laser

(xiiii) We recommend laser coagulation for small tumors (Groups A/cT1a and B/cT1b eyes), residual tumors after chemotherapy, or recurrences following chemotherapy, particularly for lesions posterior to the equator[51].

Extraocular disease

For decision-making for treatment:

(xv) We recommend that patients with extraocular disease be categorized as having the intention to cure or to palliate.

Intention to cure = Patients with high-risk features on histology, or patients who present with proptosis without evidence of systemic metastasis.

Palliation = Those with evidence of metastasis clinically or investigations [Consensus].

(xvi) We recommend that ophthalmologists involved in the child's case review the pathological features of every enucleated eye for high-risk features, including invasion of the optic nerve, sclera, choroid, or anterior segment, that could predispose to extraocular disease or metastasis[52].

(xvii) We recommend treatment with prophylactic chemotherapy when high-risk features are observed, including invasion of the optic nerve, sclera, choroid, or anterior segment[52].

(xviii) We recommend adjuvant chemotherapy for children with post-laminar optic nerve involvement[53,54], with or without a tumor in the resection margin, or any degree of scleral involvement[55].

(xix) We recommend that metastatic disease be treated in palliative, using doses of doxorubicin or spot radiotherapy for symptom relief. We recommend avoiding three drug chemotherapy. These patients should be kept as close to their families as possible [Consensus].

(xx) We recommend that for extraocular RB (in the absence of systemic metastasis), treatment protocols generally include, but are not limited to: orbital radiation for orbital recurrence post-enucleation and systemic chemotherapy [Consensus].

(xxi) We do not recommend exenteration of the orbit for RB since chemotherapy will provide more effective palliation, even for massive proptosis[56,57].

(xxii) We recommend that extraocular RB treatment protocols generally include, but not be limited to, orbital radiation for orbital recurrence post-enucleation, systemic chemotherapy, stem cell/bone marrow transplant after an excellent response to systemic chemotherapy, and intrathecal chemotherapy for CNS disease with meningeal spread[58].

(xxiii) If RB metastasis is present in bone marrow, bone, or other organs or tissues, we recommend enucleation of the eye, adjunctive chemotherapy, and hematopoietic stem cell transplant if there is a chemotherapy response[58].

(xxiv) If RB extends into the orbit, to the cut end of the optic nerve, optic chiasm, or brain, we recommend enucleation of the eye, adjunctive chemotherapy, extended doses of intrathecal chemotherapy, irradiation of the involved tissues, followed by hematopoietic stem cell transplant if there is a chemotherapy response[58].

(xxv) If the RB tumor involves the meninges of the brain and spinal cord, we recommend palliative treatment [Consensus].

FOLLOW UP

Retinoblastoma is a cancer that most often affects very young children. Children with RB are particularly vulnerable to the long-term implications that the illness and the treatments given to them may have impact on organ development and function[59]. The need for lifelong follow up arises from the possibility of secondary tumors arising in heritable retinoblastoma survivors[60]. In a prospective investigation of around half of all new instances of retinoblastoma that were identified in treatment facilities around the world in 2017, the 3-year survival rate ranged from 57.3% in low-income countries to 99.5% in high-income countries[61]. Retinoblastoma is still a fatal illness in less affluent settings, and East African nations have reported survival rates as low as 30%[62]. In addition, descriptive research conducted in two sub-Saharan African nations revealed that two-thirds of the patients were lost at follow-up[63]. Delay with advanced disease, the stage at presentation and high rates of patient care default contribute to poor survival outcomes in developing countries[64]. Our earlier research revealed that Ethiopia's 40.9% of retinoblastoma cases were lost to follow-up[5]. A lack of resources may hinder long-term follow-up, patient awareness, and adult care system ignorance about the needs of childhood cancer survivors, particularly those with particular needs, like RB survivors[7]. Financial limitations were the leading cause of follow-up failure in the Ethiopian RB referral study[16].

FOLLOW UP –RECOMMENDATIONS

(i) We recommend that all survivors of RB receive individualized, lifelong follow-up and surveillance, counseling, and interventions for late effects of disease and treatment, delivered by a multidisciplinary team.

Ophthalmology follow-up

(ii) We recommend that following completion of treatment, EUAs for children at risk of developing new RB tumors continue as often as every three weeks or at longer intervals as tumor activity decreases until the risk of new tumors and recurrences is low. The child can cooperate in a clinic at about three years of age. The frequency of examinations will be highest when the child has a proven RB1 germline mutation[20,26,65].

(iii) We recommend that following the end of EUAs, clinic visits for the retinal exam should continue

every six months to age 9, annually to age 15, and every 2–3 years after that for life[7].

(iv) We recommend that children shown to not carry the RB1 mutant allele of their family through a blood test do not require EUA or intense surveillance[7].

(v) We recommend the examination of an enucleated socket for infection, a fit of prosthesis, and implant exposure or extrusion at every EUA and clinic visit[7].

(vi) We recommend prescribing and monitoring protective eyewear for functionally uniocular children[7].

(vii) We recommend that RB survivors of school age with significantly reduced visual fields or visual acuity less than 6/12 undergo visual assessment and referral to a low vision clinic[7].

Oncology follow-up

(viii) We recommend that RB survivors treated with chemotherapy or EBR undergo oncology clinic follow-up at 3- to 6-monthly intervals for five years after finishing chemotherapy, and then every 1–2 years until age 18 years, and then lifelong follow-up every two years in an adult oncology facility[7].

(ix) We recommend that persons carrying an RB1 germline mutation, or nongermline RB survivors treated with chemotherapy or EBR, be seen in an oncology clinic for counseling about the risk of secondary non-RB cancers annually for life by an oncologist[7].

(x) We recommend MRI, if possible, in patients with RB1 germline mutations since diagnostic radiation may increase their already significant risk of secondary non-RB malignancies[66].

(xi) When there is clinical or pathological evidence of risk of extraocular RB (TNM staging), we recommend bone marrow aspirate and (or) lumbar puncture every three months for three years after the last chemotherapy[58].

(xii) We recommend that persons at risk for systemic metastases based on pathological examination of the enucleated eye be monitored for five years with periodic bone marrow aspirates, MRI of the head and orbits, and whole-body MRI, if available[7].

(xiii) We recommend that patients at risk for CNS metastases be monitored every 3 to 8 months for five years, with lumbar punctures, MRI of the head, orbits, and spine, and whole-body MRI, if available, followed by lifelong annual surveillance via an alternative follow-up program as locally available[7].

(xiv) We do not recommend oncology clinic follow-up for children with unilateral RB, treated only by enucleation [Consensus].

PSYCHOSOCIAL CARE AND ACCESS TO SERVICES

The psychosocial burden of caregiving directly or indirectly affects the outcome of cancer patients[67]. Previous studies have found a correlation between coping among parents of RB patients and the disease's progression[60,68-70]. Parental coping with paediatric RB is correlated with the progression of the illness, including suspicion, initial discovery, the final diagnosis of the disease, surgery, hospital discharge, recovery from surgery (1–3 months), and recovery over the years following the diagnosis of the illness. Additionally, it appears that anxiety, insecurity, and uncertainty serve as common coping mechanisms for each of these stages[68,70].

Parents of children with retinoblastoma are expected to adjust to fear of the death of their child, their inability to control their child's future, a new way of caring for their child, and dependence on healthcare services[71].

Our prior work showed that 40% of Ethiopian retinoblastoma cases present with an extraocular disease with almost no chance of cure[5]. These contributed to more aggressive and multiple modes of treatment that may add more burden to caregivers. In addition, intense mental distress was reported by the Ethiopian RB caregivers who participated in our study, suggesting the need for psychosocial support and care for RB caregivers[72]. This corroborates previous research that has shown that parents of children with RB have poor psychological health and require professional assistance or counseling [68,70].

PSYCHOSOCIAL CARE AND ACCESS TO SERVICES-RECOMMENDATIONS

(i) We recommend ongoing psychosocial support and timely and equal access to care for all RB children and their families[7].

(ii) We recommend that RB families have easy and equitable access to:

- A social worker or clinical psychologist with RB or childhood cancer expertise from the time of diagnosis onwards.
- Structured psychosocial assessments at diagnosis and key points during treatment.
- Accurate, understandable, as-needed information in a variety of formats.
- Risk/informed consent information meeting parent language/age/education criteria.
- Advocacy services by professionals or community agencies for parents requiring additional support to access appropriate services.
- A centralized referral source providing links to hospital and community support groups.

- Long-term psychosocial support from diagnosis through adulthood.
- High-level genetic testing at a certified laboratory and genetic counseling for all affected family members.
- Financial support for out-of-pocket costs related to treatment.
- Visual rehabilitation services.
- Aids for low vision.
- Prosthetic eye service.
- Paediatric palliative care and bereavement services[7].

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