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Epidemiological and clinical aspects of retinoblastoma in developing country

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Abstract

Introduction: Retinoblastoma is the most common intraocular tumor in child. Treatment depends on stratification and classification of retinoblastoma. The aim of this study was to describe epidemiological and clinical aspects of retinoblastoma in Madagascar.

Method: We report in this retrospective study 44 cases found during 5 years, from January 2015 to December 2019. We have collected information about epidemiological and clinical aspect, delay of diagnosis. Classification of retinoblastoma was done with Reese Ellsworth classification and International Classification of Intra-ocular Retinoblastoma (ICRB). Data was collected with excel software and analysis was done with R-studio 4.2.2 software. The quantitative variables were expressed as an average and the qualitative variables as a proportion and percentage.

Result: We had collected 44 cases. The incidence was 8.8 cases per year. Sex ratio was 1.3. Mean age was 40 months. Exophthalmos was found in 35% (n=12) of cases. Leukocoria was found in 24% (n=11) children. The delay time before diagnosis was 13 months. In 97.7% of cases, the retinoblastoma was unilateral. Intraocular form was found in 23 patients (52.3%). Among intraocular form 13 patients (57%) presented with grade E, including one patient with meningeal extension 9 patients (39%) with grade D, 1 patient (4%) in grade B. Extra ocular form was found in 21 patients (47.7%) : 17 (77%) had orbital invasion (stage III), 4 (23%) were metastatic (stage IV).

Conclusion: Diagnosis of retinoblastoma was made in advanced stage. Most of patients had extraocular form. Prognosis was worse in Madagascar. Making diagnosis early is necessary to prevent loss of life.

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Introduction

Retinoblastoma is the most common malignant intraocular tumor in children [1,2]. It can be uni or bilateral. It is due to a mutation of the RB1 gene located on the long arm of chromosome 13. The diagnosis is clinical by indirect ophthalmoscopy [1]. It affects 1/15,000 to 1/20,000 births per year in industrialized countries [2, 3]. However, this pathology constitutes a major public health problem in developing countries. Indeed, in Mali, it is the second most common cancer in children with an incidence of 24.6% [4]. In Madagascar, it represents 10% of pediatric cancers [5]. This pathology is responsible of 69.69% visual impairments among tumoral origin in children, seen at Ophthalmology department [6]. It is important for the clinician to recognize signs of retinoblastoma and appropriate management. Treatment depends on the stage of discovery and the clinical evolution of the disease. However, the diagnosis is made late, thus involving not only the visual prognosis but also the vital prognosis of the child. The reasons for this delay could be explained by: socio-economic difficulties and accessibility of eye care center [7]. Thus, the aim of our study is to describe the epidemio clinical aspects of retinoblastomas in order to better manage cases of retinoblastomas in developing countries.

Method

This was a retrospective, descriptive, and monocentric study based on the study of patient records seen at the Ophthalmology, Pediatric Oncology, Anatomo-pathology,

Pharmacy and Medical Imaging departments of Center Joseph Ravoahangy Andrianavalona University Hospital (CHUJRA). The study period was from January 2015 to June 2019. The study population was represented by patients who had retinoblastoma during this period. Each child had an interrogation in search of the circumstances of discovery, the notion of retinoblastoma in the family, in particular among first-degree relatives, the notion of other known sarcomas in the family, the age of the child, knowing that retinoblastoma appears most often in children under 5 years of age, the laterality of the lesions, the warning signs noticed by the parents or those around them. Each child who presented suspicious signs of retinoblastoma had a bilateral and comparative fundus examination under general anesthesia. During this examination were evaluated: the anterior segment, examination of the fundus by indirect ophthalmoscopy (with an indirect Schepens ophthalmoscope and a 20D lens) which will confirm the presence of an intraocular tumour: characteristics, number, diameter, laterality, their uni or multifocal presentation, the presence of vitreous swarming which will appear in the form of whitish deposits floating in the vitreous, the possible presence of a subretinal detachment. To define the stage of retinoblastoma we have used the Reese-Ellsworth classification. We used two classification for this study;

Reese Ellsworth classification (Table I).

ABC classification or International Classification of Intra-ocular Retinoblastoma (ICRB). (Table II)

The physical examination must be supplemented by a general examination in search of possible metastases. The most frequently used imaging techniques were B-mode ocular ultrasound, orbito-cerebral computed tomography and MRI of the orbital and cerebral region.

Analysis of cerebrospinal fluid and bone puncture were the most useful laboratory tests in evaluating the clinical stage of retinoblastoma. Metastatic extension was searched. Records of patients diagnosed with retinoblastoma were taken. The medical record of all patients with retinoblastoma in the Ophthalmology and Pediatric Oncology departments of the CHUJRA were collected. Then to select the patients in our study, inclusion criteria and exclusion criteria were applied. The inclusion criteria was: diagnosis of retinoblastoma made at Ophthalmology and at Paediatric Oncology Department. The exclusion criteria was: any cause of leukocoria or white pupil in children should raise suspicion of retinoblastoma. However, other pathologies may be the cause of leukocoria. The most frequent was: the persistence of the primitive vitreous, cataract, Coats disease, retinopathy of prematurity.

The data collected of this study come from patients' medical records. Concerning the epidemiological, clinical and therapeutic files, the data were collected in the different departments through which each patient passed. The data was entered and processed using R 4.2.2 software. Statistical test uses was comparison of average, percentage of classification.

We have studied:

Epidemiological status incidence, gender, age

Clinical status: familial history of retinoblastoma or other tumor, warning sign, reason of consultation, delay time of diagnosis, laterality, retinoblastoma form (intra ou extraocular),

Examination with tropicamide using Schepens and 20Dioptria lens can showed: laterality, retinoblastoma form (intraou extraocular), International Classification of Intraocular Retino blastomaor classification ABC for retinoblastoma intraocular (TableII).

Studies limits were :

Incompleted data in some patients

Character retrospective of study, we can't evaluate evolution of disease

Monocentric study

Ethical consideration: data for each patient was anonymous. We have respected the accord of parents for study.

Result

During 5 years 44 patients were includied. Average incidence was 8.8 cases per years (Table III). Sex ratio was 1.3. Mean age at time of diagnosis was 40 months. The earliest age found was 12 months. The latest age of 11 years (132 months), found in two patients in 2015, and 2018. During the study, no family history of retinoblastoma or any other known cancer had been mentioned. Exophthalmos is the most common reason for consultation, found in 35% of cases (12 patients). Leukocoria and ocular redness follow in frequency, found in 11 and 6 patients respectively (Figure 1). On average, the delay time of diagnosis was 13 months. The minimum delay was two weeks. The maximum time to diagnosis was found at 37 months. In 97.7% of cases, the retinoblastoma was unilateral. Among these, the right eye was the most affected (24 patients). The bilateral form was found in only one patient. Initially, retinoblastomas were classified according to their intra or extra ocular clinical form. The intraocular form was the most observed. It was found in 23 patients (52.3%). Among 23 patients with the endocular form (figure 2):

- 13 patients (57%) presented with grade E, including one patient with meningeal extension
- 9 patients (39%) presented with grade D
- 1 patient (4%) had been diagnosed early at grade B in 2018.

The extra ocular form was found in 21 patients (47.7%). Among the 21 cases with extra ocular retinoblastoma:

- 17 (77%) had uncomplicated orbital invasion (stage III).
- 4 (23%) were metastatic (stage IV) in particular to the parotid lymph nodes, bone marrow, cerebrospinal fluid, meninges and brain. Two patients had more than 2 sites of metastases (medullary and bone, bone and brain). Two cases (9.5%) of retinoblastoma complicated by orbital cellulitis were also recorded.

Discussion

Epidemiological status

In Madagascar, retinoblastoma accounts for 10% of pediatric cancers. It was the third pediatric cancer before lymphomas and leukemias [5]. In France, retinoblastoma ranks 9th among pediatric cancers and represents 29% [8]. Retinoblastoma affects 1/15,000 to 1/20,000 births per year in developed countries [1,3]. In the United States, it represents 11.8 per million births in children aged 0 to 4 years [3]. In England, its

incidence is 1 in 23,000 births [2]. In Thailand, an incidence of 2.8 to 5.8 per million inhabitants was found, in a study conducted in three centers [9]. These results confirm our study which found an incidence of retinoblastoma of 8.8 cases per year. In a study conducted in Pakistan, over the same period, 101 cases were found [10]. This gives an average of 20 cases per year. A study conducted by Kagmani and Alen from January 2000 to December 2005 in Cameroon found 57 cases of retinoblastoma [11]. At Gabriel Touré Teaching Hospital, Mali, an incidence of 26 cases per year had been estimated [4]. In Sudan, during a retrospective study conducted from 1999 to 2009, an average of 2.5 cases had been reported [12]. In Madagascar, a study conducted in 2010, 12.5 cases per year was found [13]. In 2015, a study reported an incidence equal to ours: 10.4 cases per year [14]. The incidence rate in 2013 was 8 new cases per year [15]. Our results are lower than those found in the literature in general with an incidence of 8.8 cases per year. Reason was: some patient was excluded in this study because the patients had presented only once for an ophthalmological or pediatric oncology consultation. Another reason was, another ophthalmology and oncology centers take care of retinoblastoma and not including in our study. In developing country, number of patient don't go to the hospital and received traditional medical treatment.

Our study found apredominance of male at 57% with a ratio of 1.3. According to the literature, retinoblastoma affects boys and girls indistinctly [3,16]. In France, the ratio between the two genders is 0.9 [8]. In Ghana, in 2010, a sex ratio of 1.1 was found [17]. Results in Thailand also corroborate to these results by showing that retinoblastoma affects boys as much as girls [9]. Studies in Bamako[4] show results similar to ours. In China, a male predominance of children with retinoblastoma, i.e. 56% of patients, had been found [18]. In India, results similar to ours were found with 57.5% of patients with retinoblastoma being male [19]. In this Indian study in 2015, Chwala et al. hypothesized that this male predominance was due to a lack of attention to female children, particularly in rural areas.

The average age of diagnosis of patients in our study was 40 months. The extremes range from 12 to 132 months (11 years). The only case of bilateral retinoblastoma among our patients was 24 months old. Retinoblastoma is diagnosed before the age of 5 on average. The unilateral forms are discovered at the age of 2 years, and the bilateral forms earlier at 1 year [1,20]. Our results are consistent with the average age of diagnosis in Sudan[12] (36 months), Mali (50 months) [4], and Cameroon (40 months)[11]. In India, during 4-year study from 2009 to 2013, they found an average age of diagnosis of 36 months for unilateral forms[19]. Compared to industrialized countries, the age of diagnosis is high in Madagascar. For all clinical forms of retinoblastoma, the diagnosis is made before the age of 4 years in Europe [21]. In the USA, according to a study by Broaddus, the incidence of the average age of diagnosis is 11.8 cases per million in children aged 0 to 4 years [3]. In Thailand, according to a study conducted on three cancer registries, research had shown that most retinoblastomas were diagnosed before the age of two [9]. This study showed that most of children in developing country was take care late.

Clinical status

The literature shows that 90% of retinoblastomas are sporadic [1,20]. Of these sporadic forms, 60% are unilateral, and there is no constitutional abnormality of the RB1 gene [16]. In 40% of cases, the tumor is bilateral and always hereditary [1]. That's why history is important in the clinical examination of a child with retinoblastoma. History of retinoblastoma in the family was important to establish the genealogical tree of the child. In our study, no family history of retinoblastoma was mentioned. The bilateral retinoblastoma case studied had no family history of retinoblastoma. This assumes that 100% of retinoblastoma cases in our study are sporadic. Our results do not agree with the Malagasy studies carried out in 2013 [15] in which hereditary retinoblastomas and/or a family history of sarcomas were found in 12% of patients. The sporadic retinoblastomas accounted for 88% of cases in this study. In 2005, Rasolofojaona showed that sporadic forms accounted for 80% of cases compared to 20% for familial forms [7].

In the literature, in Great Britain, 12% of patients diagnosed with retinoblastoma had at least one relative with the same disease [2]. This same study found that in patients with the bilateral form of retinoblastoma, 26% had a family history of retinoblastoma [2]. In Alexandria, a family history of retinoblastoma was found in 6% of patients [22]. These results are thus consistent with national studies, showing that the sporadic forms of retinoblastoma are the most frequent. Our study was limited by incomplete information recorded in the medical records of patients. Genetic research was not possible because analysis of mutation of RB1 gene was expensive for all patient.

Exophthalmos and leukocoria were the most frequent reasons for consultation in the Ophthalmology and Paediatric Oncology departments, thirty five percent and 24% respectively. Andriamiarimanjaka's study from 2005 to 2009 reported exophtalmos and proptosis as the main reasons for consultation [13]. A study carried out from 2010 to 2015 in Madagascar reported that proptosis represented 41.7% of the reasons for consultation [14]. As a result, there is an improvement in the reasons for consultation since leukocoria is becoming more frequent. Formation of retinoblastoma'sign were conducted to liberal doctors during the period from 2017 to 2019. This could explain the increase in the rate of children with leukocoria seen in consultation. Sudan result are consistent with ours [12]. Those in Bamako from 2005 to 2007 found 54.5% exophthalmos as the reason for consultation [23]. In developed countries, retinoblastoma is seen at an early stage. The most common reason for consultation is leukocoria [24,25]. In Taiwan, a clinical study conducted in 2006 demonstrated that leukocoria represents 71.4% of the reasons for consultation against 2.1% for exophthalmos [26]. Nowadays, developed countries are discussing early detection. In contrast, in the country the early diagnosis of retinoblastoma is still a challenge.

Delay time of diagnosis was defined as tme between the appearance of presenting sign and the first consultation whom diagnosis of retinoblastoma could be made. On average it was 13 months varying from 2 weeks to 37 months. The warning signs had been noticed from birth in 3 patients. We observed during our study that the first sign vary. Exophthalmos

represents only 4%. Leukocoria dominated within 35%. The diagnostic delay is important because the parents do not come to consult a doctor as soon as the leukocoria appears. Most of medical doctor and parents don't know the first sign of retinoblastoma and diagnosis was made late. In Rabat, the average time to diagnosis was 6.5 months in a study conducted from 2003 to 2008 [27]. In Niger, 66.7% of patients had consulted more than 12 months after the onset of symptoms [28]. In Alexandria in 2017, Soliman and al. found an average diagnostic time of 6 weeks for unilateral forms and 3 weeks for bilateral forms [29]. This last study had determined that the main causes of delayed diagnosis were, an error of diagnosis during the first consultation with the ophthalmologist (25% of cases), and an error of judgment of the complaints of the sick child (11% cases).

During our study, 98% of the cases of retinoblastoma that we found were unilateral. In Madagascar, the results are similar to ours with a clear predominance of unilateral forms. In 2017, unilateral retinoblastoma accounted for 84.6% of cases [14]. In 2013, among 48 eyes studied, 34 or 83% had unilateral retinoblastoma [15]. In Niger, unilateral retinoblastoma accounted for 75% of cases [28]. In Casablanca, 60 to 70% of retinoblastoma cases were unilateral [30]. In Cameroon, results similar to ours found 87.7% of unilateral cases [11]. In the USA, during a study conducted from 1974 to 2004, the unilateral form represented 72.8% of cases [3]. In Europe, unilateral retinoblastoma accounts for 65.6% of cases [21]. Our results are consistent with those of the literature. Cases of unilateral retinoblastoma are more frequent than bilateral retinoblastoma. However, during our study, only one patient presented with bilateral retinoblastoma, 2% of cases. In previous national studies, bilateral forms of retinoblastoma accounted for 15.4% in 2017[14] and 17% in 2013[15]. In 2010, 10% of retinoblastoma cases identified out of a total of 50 files were cases of bilateral retinoblastoma [13]. In the United States, bilateral retinoblastoma has a lower incidence than unilateral retinoblastoma [3]. However, bilateral retinoblastoma is diagnosed there at an earlier age. Thus, 89% of cases of bilateral retinoblastoma are diagnosed at the age of 1 year compared to 57.8% for unilateral retinoblastoma [25]. Our results are discordant concerning the incidence of bilateral retinoblastoma. It can be explained by formation of warning sign to medical doctor to identify leukocoria very early and dectect more unilateral retinoblasoma than bilateral.

Classification

In this classification, retinoblastoma has been categorized according to its intraocular development alone or the presence of an extraocular extension. Intraocular retinoblastoma is a tumor that grows inside the eyeball. It can then be subdivided into endophytic or exophytic intraocular retinoblastoma [16]. Extraocular retinoblastoma is defined as retinoblastoma that has evolved beyond the eyeball [31]. Extraocular localization is a natural evolution of untreated retinoblastoma. In our study, 52.3% of the cases collected were intraocular retinoblastomas, against 47.7% extraocular. A previous study at CHUJRA presents results similar to ours with 52% of intraocular retinoblastoma cases and 48% of extraocular cases in 2017 [14]. Thus, the intraocular forms are more frequently found during the diagnosis of retinoblastoma at CHUJRA. However, the frequency of extraocular forms are still high. In developing countries, the extraocular form of retinoblastoma is still common. In India, a study conducted in 2015 showed that 24% of cases of retinoblastoma were intraocular compared to 37.5% of cases for the extraocular form [22]. In 2017, the proportion of cases of intraocular retinoblastoma was 27% compared to 44% for extraocular forms [32]. In Niger, a study carried out on the particularities of retinoblastoma in this country had found figures higher than ours with an extraocular presentation of retinoblastoma found in 94.78% of their patients [28]. Thus, our results are consistent with findings in the literature from developing countries.In developed countries, the extra ocular form is rare. Indeed, in the United States, extraocular retinoblastoma accounted for 12% of cases in 1987 [33]. In a more recent study, conducted in 2012, extraocular retinoblastoma represents 1% of cases [34]. As a result, we note that our results are discordant compared to the results in developed countries. It can be explained by the precocity of diagosis. During our study, 21 patients, or 47.7%, presented with the extraocular form of retinoblastoma. The most common presentation was orbital invasion (stage III) according to the International Retinoblastoma Staging System, present in 77% of patients with extraocular retinoblastoma. Five of the 21 patients (23%) had a metastatic form, corresponding to stage IV of the International Retinoblastoma Staging System. Sites of metastases were bone marrow, cerebrospinal fluid, meninges, and brain. However, the search for metastasis sites was limited according to our observations during the study. Most of the patients did not systematically perform the extension assessments. Compared to the total number of patients we collected, stage III represents 38.6% of all patients and stage IV represents 11.3%. Nationally, 5% of patients had presented the metastatic form from the outset in 2013 [15]. Stage III was found in 75% of patients during this same study. The sites of metastases most frequently found were lymph nodes, cerebral as well as visceral [15]. Thus, the frequency of patients with metastatic retinoblastoma is higher in our study compared to previous national studies. This could be explained by the limited number of patients having undergone extension assessments. However, the frequency of stage III extraocular retinoblastoma is much lower. Internationally, the results comparable to ours are those of developing countries. The extraocular form is a frequent presentation of retinoblastoma [35]. In India, stage III retinoblastoma according to the International Retinoblastoma Staging System was the most common presentation, found in 63.4% of patients with extraocular retinoblastoma [36]. In Mexico, advanced forms of retinoblastoma with involvement limited to the orbit represent 18% of cases and metastatic forms 11.4% [37]. In Malaysia, a study conducted in 2008 found 51% of cases of extraocular retinoblastoma out of 105 patients [38]. Of these cases, 20% were metastatic. The sites of metastases found were in the bones, the central nervous system and in the lymph nodes [38]. In Côte d'Ivoire, invasion of the optic nerve was the preferential localization of metastases with 43% of patients, followed by endocranial involvement present in 28% of patients and of the orbit in 25% of patients [39]. In developed

countries, the extraocular form of retinoblastoma is rare [40]. In France, extra ocular forms are rare, especially metastatic forms [41,42]. The most common site of dissemination is at the level of the optic nerve.

Among the cases of intraocular retinoblastoma, grade E and D of the ABC classification (figure 2) were predominant (57% and 39%). Cases of retinoblastoma who come for consultation at the CHUJRA are thus diagnosed at a high stage. Only one case was seen at an early stage (grade B).

Studies conducted in 2015 and 2013 at the same university hospital report results similar to this [14,15]. The diagnosis of intraocular retinoblastoma is made late in Madagascar. In Casablanca, 69.5% of cases were classified as grade D or E [30]. In Bamako, where Reese-Ellsworth staging was used, the majority of patients seen in the Gabriel Touré Teaching Hospital presented with an advanced stage of the disease (stage V) [23]. In India, in a study by Chawla andal, a predominance of grades D and E had also been found, but the frequency of early forms at the time of diagnosis is higher than our results [19]. In China, in a study initiated at the Beijing Tongren Hospital over a period of 3 years, grades D and E were also the most frequent [18]. The difference was the number of early cases of intraocular retinoblastoma that they diagnosed. Similarly, in France, retinoblastomas have been diagnosed at Reese-Ellsworth stage I or II [25].

Table I Reese-Ellsworth (RE) Classification Scheme.

Reese-Ellsworth (RE) Classification For Intraocular Retinoblastoma	
GROUP I	***a.*** Solitary tumor, less than 4 disc diameters in size, at or behind the equator
	b. Multiple tumors, none over 4 disc diameters in size, all at or behind the equator
GROUP II	***a.*** Solitary tumor, less than 4 to 10 disc diameters in size, at or behind the equator
	b. Multiple tumors, none over 4 to 10 disc diameters in size, all at or behind the equator
GROUP III	***a.*** Any lesion anterior to the equator
	b. Solitary tumors larger than 10 disc diameters behind the equator
GROUP IV	***a.*** Multiple tumors, some larger than 10 disc diameters
	b. Any lesion extending anteriorly to the ora serrata
GROUP V	***a.*** Massive tumors involving over half the retina
	b. Vitreous seeding

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Table II International Classification for Retinoblastoma (ICRB) Scheme.

International Classification for Intraocular Retinoblastoma (ICRB)	
Group A	*Small intraretinal tumors away from foveola and disc*
	* All tumors are 3 mm or smaller in greatest dimension, confined to the retina **and** * All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc
Group B	*All remaining discrete tumors confined to the retina*
	* All other tumors confined to the retina not in Group A * Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding
Group C	*Discrete Local disease with minimal subretinal or vitreous seeding*
	* Tumor(s) are discrete * Subretinal fluid, present or past, without seeding involving up to ¼ retina * Local fine vitreous seeding may be present close to discrete tumor * Local subretinal seeding less than 3 mm (2DD) from the tumor
Group D	*Diffuse disease with significant vitreous or subretinal seeding*
	* Tumor(s) may be massive or diffuse * Subretinal fluid, present or past without seeding, involving up to total retinal detachment * Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses * Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E	*Presence of any one or more of these poor prognosis features*
	* Tumor touching the lens * Tumor anterior to anterior vitreous face involving ciliary body or anterior segment * Diffuse infiltrating retinoblastoma * Neovascular glaucoma * Opaque media from hemorrhage * Tumor necrosis with aseptic orbital cellulites * Phthisis bulbi

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Table III. Incidence of retinoblastoma from January 2015 to June 2019

Year	Case Number
2015	4
2016	9
2017	7
2018	18
2019	6
TOTAL	44

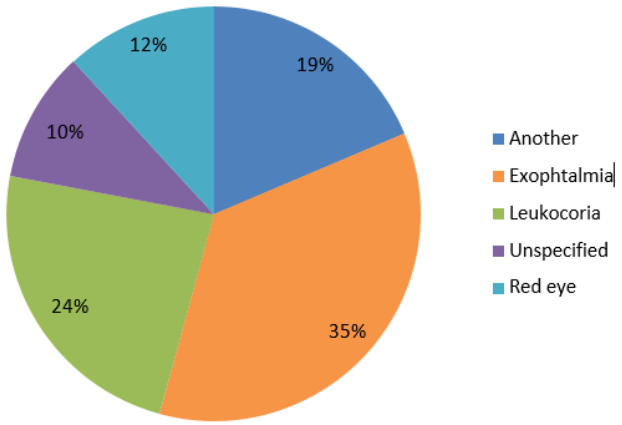

Figure 1: Frequency of reason for consultation

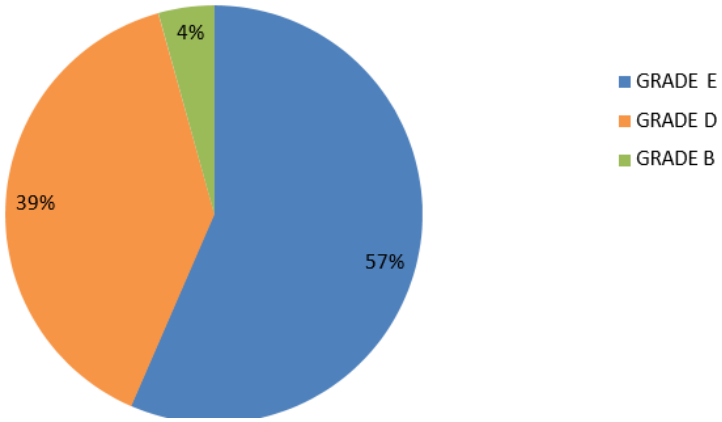

Figure 2: Classification of intraocular retinoblastoma

Conclusion

Retinoblastoma was diagnosed in advanced stage in developing country like Madagascar. Half of patients had extraocular form and quarter of patients have metastases. Prognosis was worse in Madagascar. Early diagnosis is still a challenge to prevent loss of vision and loss of life.

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