Clinical-Epidemiological Profile and Survival of the Cases of Retinoblastoma in a Reference Hospital in Oncology in the State of Goiás

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Perfil Clínico-Epidemiológico e Sobrevida dos Casos de Retinoblastoma em um Hospital Referência em Oncologia do Estado de Goiás

Perfil Clínico-Epidemiológico y Sobrevida de los Casos de Retinoblastoma en un Hospital de Referencia en Oncología del Estado de Goiás

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ABSTRACT

Introduction: Retinoblastoma is the most common intraocular primary malignancy in childhood, it is rare and accounts for 2% to 4% of pediatric malignant tumors. **Objective:** To describe the clinical-epidemiological profile and survival of cases of retinoblastoma in a reference hospital in oncology in the state of Goiás, between 2008 and 2014. **Method:** Cross-sectional analytical observational study built from the analysis of medical records of patients diagnosed with retinoblastoma between 2008 and 2014. Analyzes were performed using descriptive statistics and chi-square association test. A significance level of 5% was adopted. Survival was assessed using the Kaplan-Meier method. **Results:** 55 patients with retinoblastoma were treated, with predominance of females (54.5%), in the age group of 1 to 4 years (27.3%) and of brown ethnicity (50.9%). The most prevalent clinical characteristics were intraocular involvement (74.5%), unilateral (65.5%), with no family history (56.4%) and with clinical signs of leukocoria (80%). Most of them did not present metastases at diagnosis (87.3%), the main treatment being unilateral enucleation (72.7%). Association between the clinical evolution of the patient and extraocular location (p = 0.001) was found, presence of metastasis (p = 0.001), and stage IV classified by Chantada et al. (p = 0.001). Patients classified as E were submitted to higher volume of enucleation (right eye – p = 0.05 and left eye – p = 0.001). The 5-year overall survival was 72.7%. **Conclusion:** These findings are relevant for planning preventive actions, as early diagnosis is one of the main allies in determining the cure and preserving vision.

Key words: retinoblastoma; child; blindness; epidemiology.

RESUMO

Introdução: O retinoblastoma é a malignidade primária intraocular mais comum na infância, é raro e corresponde de 2% a 4% dos tumores malignos pediátricos. **Objetivo:** Descrever o perfil clínico-epidemiológico e a sobrevida dos casos de retinoblastoma em um hospital de referência em oncologia do Estado de Goiás, entre 2008 a 2014. **Método:** Estudo observacional analítico do tipo transversal, construído com base na análise de prontuários de pacientes diagnosticados com retinoblastoma entre 2008 e 2014. Realizaram-se análises por estatística descritiva e teste de associação qui-quadrado. Adotou-se o nível de significância de 5%. A sobrevida foi avaliada por meio do método de Kaplan-Meier. **Resultados:** Foram atendidos 55 pacientes com retinoblastoma, permitindo identificar o predomínio do sexo feminino (54,5%); na faixa etária de 1 a 4 anos (27,3%); com etnia parda (50,9%). As características clínicas mais prevalentes foram: acometimento intraocular (74,5%); unilateral (65,5%); sem histórico familiar (56,4%); e com sinal clínico de leucocoria (80%). A maioria não apresentou metástases ao diagnóstico (87,3%), sendo o principal tratamento a enucleação unilateral (72,7%). Verificou-se associação quanto à evolução clínica do paciente em relação à localização extraocular (p = 0,001), presença de metástase (p = 0,001) e estádio IV de Chantada et al. (p = 0,001). Pacientes classificados como E foram submetidos a maior número de enucleações (olho direito – p = 0,05 e olho esquerdo – p = 0,001). A sobrevida global em cinco anos foi de 72,7%. **Conclusão:** Tais achados são relevantes para o planejamento de ações de prevenção, pois o diagnóstico precoce é um dos principais aliados na determinação da cura e na preservação da visão.

Palavras-chave: retinoblastoma; criança; cegueira; epidemiologia.

RESUMEN

Introducción: El retinoblastoma es la neoplasia maligna primaria intraocular más frecuente en la infancia, es raro y corresponde del 2% al 4% de los tumores malignos pediátricos. **Objetivo:** Describir el perfil clínico-epidemiológico y la sobrevida de los casos de retinoblastoma en un hospital de referencia en oncología en el Estado de Goiás, entre 2008 y 2014. **Método:** Estudio observacional analítico transversal, construido a partir del análisis de las historias clínicas de los pacientes diagnosticados con retinoblastoma entre 2008 y 2014. Los análisis se realizaron mediante estadística descriptiva y prueba de asociación ji cuadrada. Se adoptó un nivel de significancia del 5%. La sobrevida se evaluó mediante el método de Kaplan-Meier. **Resultados:** Fueron tratados 55 pacientes con retinoblastoma, lo que permitió identificar un predominio femenino (54,5%); en el grupo de edad de 1 a 4 años (27,3%); con etnia parda (50,9%). Las características clínicas más prevalentes fueron: afectación intraocular (74,5%); unilateral (65,5%); y sin antecedentes familiares (56,4%) y con signos clínicos de leucocoria (80%). La mayoría no presentaba metástasis al diagnóstico (87,3%); siendo el principal tratamiento la enucleación unilateral (72,7%). Hubo asociación entre la evolución clínica del paciente y la localización extraocular (p = 0,001), presencia de metástasis (p = 0,001) y estadio IV de Chantada et al. (p = 0,001). Los pacientes clasificados como E tenían más ojos enucleados (ojo derecho – p = 0,05 y ojo izquierdo – p = 0,001). La sobrevida global a los 5 años fue del 72,7%. **Conclusión:** Estos hallazgos son relevantes para la planificación de acciones preventivas, ya que el diagnóstico precoz es uno de los principales aliados para determinar la cura y preservar la visión.

Palabras clave: retinoblastoma; niño; ceguera; epidemiología.

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INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular cancer in childhood, is rare, embryonic in nature, with onset in the retina, and originates from the neuroectoderm, being highly curable when diagnosed early[1]. It mainly affects children in early childhood (up to 5 years), occurring in 1/20 thousand live births and two thirds of cases in the first two years of life[2].

Regarding the genetic nature of this tumor, Rb may have a congenital (6%) and familial (10% of cases) origin, in which the gene is located on chromosome 13q14. Nonhereditary or sporadic cases total 70% to 80%[3]. It has a rapid evolution and, in most cases, leads to death, if left untreated. Worldwide, it is estimated that its incidence ranges from one case to between 14,000 and 34,000 live births per year[4].

The most common clinical sign is leukocoria (white pupil)[5], in approximately 60% of cases, with strabismus being the second most common symptom (around 20%)[6]. Other less common clinical signs are glaucoma, decreased visual acuity, hemorrhage, and color and iris size abnormalities[7].

Rb can be unilateral (affects one eye) or bilateral (affects two eyes). Unilateral cases are the most frequent, and the diagnosis is made, on average, at 23 months, unlike bilateral cases, whose diagnosis is made on average from 12 to 15 months. This is because in the first case it is common for patients to arrive at the consultation with advanced disease, without the possibility of preserving vision[1,8,9].

The presence of an intracranial tumor in the region of the pineal gland associated with Rb is known as the trilateral form of the disease, which affects only children with the hereditary form of this pathology[10]. This type of Rb has an occurrence percentage around 2% to 3%, is more common in children under 5 years of age and is usually fatal[11].

Importantly, the healing process and the sequelae caused by the disease depend on an early diagnosis. Therefore, it is estimated that 90% of patients whose tumor is detected at an early stage will evolve with cure, and most will have their vision preserved[12]. However, after systemic dissemination, the patient has a worse prognosis and survival[13,14].

The diagnosis of Rb is most often clinical and can be made by indirect binocular ophthalmoscopy. In addition, tests such as ultrasound and tomography may be useful in its differential diagnosis[11]. Computed tomography of the skull is important in confirming calcification and in evaluating the extent of the tumor by the optic nerve and the brain, the aspect seen in more than 90% of cases is a hyperdense intraocular area containing nodular or punctate calcifications[15].

Therefore, success in managing Rb depends on the ability of parents and pediatricians to detect the disease while it is still intraocular; the advanced stage of the disease correlates with delayed diagnosis. Thus, it is of fundamental importance that the ocular evaluation is performed in all newborns and in all subsequent visits[14].

In this perspective, the red reflex test (RRT), also known as the "eye test", which is offered free of charge by the Unified Health System (SUS), incorporated into the routine care of the newborn, allows the early detection of ocular pathologies, being an important screening test, indicated for children at any age, and can be performed still in the nursery, before hospital discharge. The classification of the extent of cancer in its presentation is fundamental to recognize the prognosis, predict the outcome and improve treatment[16].

The strategy of Rb treatment is to save life and preserve vision whenever possible and, therefore, it has to be individualized. Factors that need to be considered include the laterality of the disease, the potential for vision preservation, and staging (intraocular and extraocular)[17].

Staging is used by clinicians to predict prognosis as well as define which treatment options may be most effective, based on the results of eye exams, imaging tests, and any biopsies performed. Thus, it is important to emphasize that treatment protocols will focus on the association of local and/or systemic therapies[18]. The treatment of Rb basically combines ophthalmic therapies, such as cryotherapy and laser therapy, with chemotherapy. Chemotherapy can be used both to attack the tumor and to shrink it, making laser therapy or cryotherapy more efficient, however, its use alone rarely leads to cure. Radiotherapy is also effective in the treatment of Rb, including a small plate with radioactive seeds placed outside the eye (near the tumor); on the other hand, surgery to extract the eyeball (called enucleation) is usually only indicated in cases of more advanced tumors, when they do not respond toother forms of treatment 2, that is, the purpose of treatment is to reduce morbidity, maintain visual function and allow excellent survival[12].

In this context, epidemiological studies are extremely important, since they help guidelines in public policies and, mainly, for the planning of cancer prevention actions, with early diagnosis being one of the main allies in determining the cure and preserving vision. Therefore, the present study aims to describe the clinical and epidemiological profile and survival of cases of Rb between 2008 and 2014 in a reference hospital in oncology in Goiania, GO.

METHOD

Analytical observational cross-sectional study, prepared through the analysis of medical records of the pediatric oncology service of Hospital Araújo Jorge (HAJ), in Goiânia, GO, from 2008 to 2014.

HAJ was founded in 1967, being the first unit of the Association to Combat Cancer in Goiás (ACCG), where about 60,000 patients are treated every year, of which 89% are by SUS. In Goiás, HAJ is the only High Complexity Oncology Assistance Center (Cacon) recognized by the Ministry of Health, and the only one qualified with a pediatric oncology service[19].

This institution is located in the city of Goiânia, capital of the State of Goiás, with a distance of 209 km from Brasília, the national capital. In 2021, Goiânia, GO had a population of 1,555,626 inhabitants, according to data from the Brazilian Institute of Geography and Statistics (IBGE)[20].

Rb cases were identified using the tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[21] and coded from C69.0 to C69.9 (malignant neoplasms of the eye), or more specifically C69.2 (malignant neoplasms of the retina). The treatment of Rb used in HAJJ is allocated to different procedures, such as chemotherapy, focal therapy and surgical methods, and must be adapted to each individual case.

Data collection took place from October to December 2020. The clinical evolution of the patients was monitored over a period of five years. Data related to follow-up were obtained directly from periodic consultations, reported in the medical records themselves, and via telephone contact, in cases where the patient did not return, made by the institution with patients. Death cases were verified in the Mortality Information System (SIM) with Rb as the cause of death of patients.

The sociodemographic variables analyzed were gender, age group at diagnosis, ethnicity, and city of origin. The clinical-epidemiological variables were affected eye, tumor location (intraocular and extraocular), tumor laterality (unilateral, bilateral and trilateral), family history of the neoplasm, metastasis in diagnosis, metastases during treatment, clinical evolution, treatment and the main signs and symptoms present in the diagnosis of Rb. The cases were analyzed in relation to location, laterality, relapse, and the International Classification for Intraocular Retinoblastoma (ABCDE)[22], considering the clinical evolution (live and death).

The inclusion criteria established for patients were having a diagnosis of Rb in the period from 2008 to 2014. Cases of patients who did not continue treatment in the HAJJ were excluded, totaling seven exclusions. A total of 55 patients remained.

The Microsoft Excel 2007 program was used for data tabulation, and statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 20.0[23]. Categorical variables were described by absolute (n) and relative (%) frequencies. For associations, the chi-square test was used and, when necessary, the *likelihood* ratio correction was performed. A significance level of $p < 0.05$ was used for all analyses. Survival was estimated by the Kaplan-Meier method, and statistical significance by the Mantel-Cox test ($p < 0.05$).

This study was approved by the Research Ethics Committee (CEP) of the Evangelical University of Goiás (UniEVANGÉLICA) under opinion number 3738509 (CAAE: 25176619.5.0000.5076) and by the CEP of the ACCG of HAJ, opinion 3749383 (CAAE: 25176619.5.3001.0031). All ethical requirements related to studies involving human beings, necessary for their success and protection related to the confidentiality of information, were followed, as evidenced in Resolution nº. 466/12 of the National Health Council[24].

RESULTS

55 cases of Rb were selected from the HAJ pediatric oncology service, from 2008 to 2014. The study population consisted mostly of females (54.5%), in the age group referring to the diagnosis from 1 to 4 years (27.3%), followed by the age group from 0 to 29 days (20.0%) with a mean of 18 months (standard deviation = 13.5 months), with brown ethnicity being the most prevalent (50.9%). Most cases came from the State of Goiás (67.3%) (Table 1).

Regarding the clinical characteristics evaluated, the left eye was the most affected (40.0%); followed by both eyes (32.7%), with the majority having intraocular tumor development (74.5%); unilateral involvement (65.5%); and no family history of Rb (56.4%). Most did not relapse (87.3%) but developed it during treatment (29.9%). The main metastatic sites were brain parenchyma, cerebrospinal fluid and bone marrow. Regarding clinical evolution, most remained alive (72.7%); and the main treatment was unilateral enucleation (72.7%) (Table 2).

Regarding the signs and symptoms at diagnosis, it was possible to observe that most cases presented leukocoria (80.0%), followed by strabismus (41.8%) and conjunctival hyperemia (18.0%). It is important to emphasize that the signs and symptoms, in some individuals, were repeated two or three times, for example: strabismus and leukocoria, or conjunctival hyperemia, strabismus and leukocoria (Figure 1).

Table 1. Sociodemographic characteristics of retinoblastoma cases treated in Goiânia, GO, 2008-2014 (n=55)

Variables	n	%
Gender		
Female	30	54.5
Male	25	45.5
Ethnicity		
White	27	49,1
Non-white	28	50.9
Age group at diagnosis		
0 to 29 days (at birth)	11	20.0
1 to 3 months	6	10.9
4 months to 6 months	5	9.1
7 months to 1 year	8	14.5
1 to 4 years	15	27.3
5 to 8 years	10	18.2
State of origin		
Goiás	37	67.3
Tocantins	10	18.2
Federal District	4	7.3
Pará	2	3.6
Maranhao	2	3.6

The overall survival curve calculated at the five-year follow-up was 72.7%, illustrated in the Kaplan-Meier curve (Figure 2).

As for the clinical evolution of the patient, it was correlated with tumor location, laterality, metastasis, and the stage of Chantada et al 1. Most patients with intraocular localization survived (87.5%), as opposed to most patients with extraocular localization who died (60.0%), showing a statistically significant difference (p = 0.001). Regarding laterality, there was no statistically significant difference between clinical outcomes (p = 0.300). Most patients who did not present metastasis remained alive (97.1%), as opposed to all patients who presented metastases, who died (100%), showing a statistically significant difference (p = 0.001). Regarding the classification according to the stage of Chantada et al., there was a predominance of live patients with stage I (93.8%), as opposed to all patients who died in stage IV (100%), showing a statistically significant difference (p = 0.001) (Table 3).

The Rb followed the ABCDE22 by which it was possible to observe that in the right eye, in classification A – less advanced stage –, there was a higher percentage of preserved eyes (75.0%) than enucleated eyes (25.0%) and, when analyzing classification E, representing a more advanced stage,

Table 2. Distribution of clinical variables of patients with retinoblastoma in the study. Goiânia, GO, 2008-2014 (n=55)

Variables	Categories	n	%
Eye involved	Right eye only	14	25.5
	Left eye only	22	40.0
	Both	18	32.7
	Both + pineal	1	1.8
Tumor location	Intraocular	41	74,5
	Extraocular	14	25.5
Laterality	Unilateral	36	65.5
	Bilateral	18	32.7
	Trilateral	1	1.8
Family history of neoplasia	Has no history	31	56.4
	History of another cancer	22	40.0
	History of retinoblastoma	2	3.6
Metastases at diagnosis	Present	7	12.7
	Absent	48	87.3
Relapse	Present	16	29.9
	Absent	39	70.1
Clinical evolution	Alive	40	72.7
	Death	15	27.3
Treatment	Unilateral enucleation	40	72.7
	Bilateral enucleation	7	12.7
	Preserved both	8	14.6

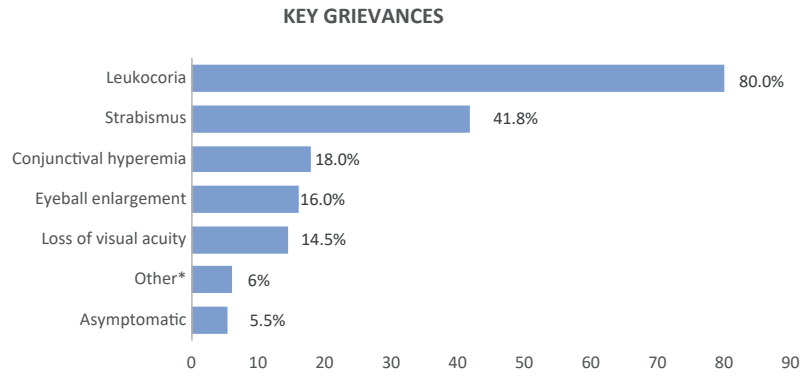

Figure 1. Main signs and symptoms present in the diagnosis of retinoblastoma
(*) ptosis, iris color change, nystagmus, blindness, eye pain, eyelid edema.

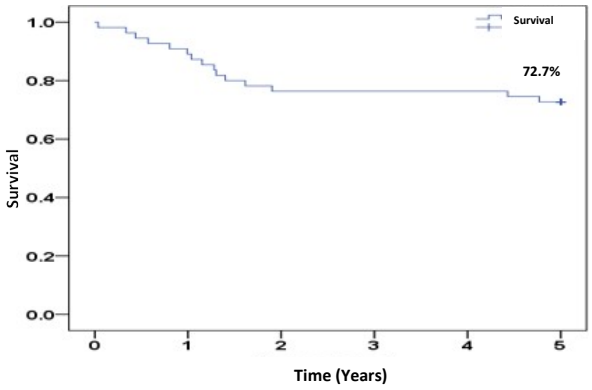

Figure 2. Kaplan-Meier curves illustrating five-year overall survival of retinoblastoma patients

there was superiority of enucleated eyes (84.2%) in relation to preserved ones (15.8%), showing a statistically significant difference between the groups ($p = 0.05$). Regarding the left eye, in classification B, all had their eyes preserved (75.0%); on the other hand, when analyzing classification E, most had enucleated eyes (93.3%) in relation to the preserved ones (6.7%), showing a statistically significant difference between the groups ($p = 0.001$) (Table 3).

DISCUSSION

Knowing the clinical-epidemiological profile of Rb is of great value for the planning and expansion of effective actions to combat the neoplasm, in order to diagnose it early, avoiding metastatic diseases with the objective of preserving vision. Thus, it was observed that female and mixed-race children were the most affected in the present study; however, there was little difference between sex and ethnicity in relation to Rb in the studied population, showing, according to studies, that the disease does not present a predilection for gender and ethnicity[11,25].

Regarding the age group, there was a higher prevalence between the range of 1 to 4 years, followed by the age group of 0 to 29 days (at birth). Generally, Rb is diagnosed in children with an average of 18 to 20 months of life, with 95% of these diagnoses made up to 5 years of age[26,27]. The number of cases discovered at birth is related to the screening exam offered free of charge by the SUS, indirect ophthalmoscopy (TRV or "eye test"), which performs the ophthalmological evaluation in this age group, and subsequent future evaluations at 1 year, 3 years and during the preschool period (between 5 and 6 years)[17]. In this context, late diagnosis, in addition to worsening prognosis, represents a challenge in both developing and developed countries[8].

When the tumor location was analyzed, there was a predominance of patients with intraocular Rb, showing, in the present study, a good evolution in early diagnosis, since intraocular tumors have a good cure rate and preservation of vision[28]. In contrast to this question, extraocular dissemination is often related to late diagnosis, compromising prognosis and survival[29].

Regarding the laterality of the tumor, it was observed that most were diagnosed with unilateral tumor. Studies in Brazil show that the unilateral form is the most prevalent, as evidenced by Souza Filho et.al.[12], with a prevalence of 51.85%, and by Costa[11], with 67.4%.

Regarding family history, most reported no family history of Rb, which is evidenced by studies in which non-hereditary or sporadic cases make up a total of 65% to 70%[3,11]. It is noteworthy that, in children with a family history of the disease, a control plan is applied that allows a more intense and attentive evaluation, suggesting an observation every four months until the child completes 6 years of life[17].

Another point analyzed was in relation to the presence of metastases at diagnosis, there was a higher percentage of patients who did not present them, because, as already demonstrated, most cases did not present a very late diagnosis. However, when the development of metastasis

Table 3. Distribution of cases according to clinical evolution in relation to location, laterality, presence of metastases and the stage of Chantada et al.

Variables	Vivo n (%)	Death n (%)	*p*
Tumor location			
Intraocular	35 (87.5)	6 (40.0)	0.001
Extraocular	5 – 12.5	9 (60.0)	
Laterality			
Unilateral	24 (60.0)	12 (80.0)	
Bilateral	15(37.5)	3 (20.0)	0.300
Trilateral	1 (2.5)	-	
Metastasize			
Present	1 (2.5)	15 (100)	0.001
Absent	39 (97.5)	-	
Estádio de Chantada et al.*			
0	2 (100)	-	
I	30 (93.8)	2 (6.2)	
II	7 (58.3)	5 (41,7)	0.001
III	1 (25.0)	3 (75.0)	
IV	-	5 (100)	
Total	40 (72.7)	15 (27.3)	
ABCDE**	**Right eye preserved n (%)**	**Enucleated right eye n (%)**	
A	3 (75.0)	1 (25.0)	
B	3 (75.0)	1 (25.0)	
C	1 (50.0)	1 (50.0)	0.05
D	2 (50.0)	2 (50.0)	
E	3 (15.8)	16 (84.2)	
Total	12 (36.4)	21 (63.6)	
ABCDE**	**Left eye preserved n (%)**	**Enucleated left eye n (%)**	
A	-	-	
B	4 (100)	-	
C	2 (50.0)	2 (50.0)	0.001
D	-	3 (100)	
E	2 (6.7)	28 (93.3)	
Total	8 (17.1)	33 (82.9)	

(*) International Classification for Retinoblastoma according to Chantada et a[l.1].
(**) International Classification for Intraocular Retinoblastoma proposed by Murphree[22].

during treatment was evaluated, there was an increase of nine cases. One study shows that the risk period for metastases is one to two years after treatment or enucleation. After two years without relapse, the child is considered cured. Even so, ophthalmological follow-up for the rest of life is necessary, due to the risk of late complications (cataracts, neuropathy, retinopathy), especially in patients who have been treated with radiotherapy[30].

Regarding the clinical evolution, most survived, and there were 15 deaths in the study. This failure is attributed to social, economic, and cultural factors, which justified the late search for treatment[13].

With regard to treatment, unilateral enucleation was the most prevalent. The treatments are premised on promoting additional improvements in the preservation of the eyeball, in order to obtain better visual acuity

results, but when the patient does not respond to eye-sparing therapies, with low vision potential or secondary glaucoma, he undergoes enucleation[31], a fact that occurred in the present study.

Regarding signs and symptoms, it was possible to observe that most cases presented leukocoria, a symptom that was predominant in several studies[4-6]. It is worth noting that leukocoria can be found in other pediatric ocular pathologies, being the same as that of Rb. In addition, this characteristic is not present in all patients as a first sign, especially in older patients, so more caution and care should be taken with patients older than 5 years[32]. The second most prevalent sign in the study was strabismus, which is usually present in the initial phase, and is also evidenced as the second most common finding after leukocoria[15,32,33].

The five-year survival of patients diagnosed with Rb in this study was 72.7%. A study published in 2013 shows that, in Sergipe, survival by Rb was 47.2%[5], highlighting the importance of early diagnosis to reduce the mortality of the disease.

As for the clinical evolution of the patient, a significance was shown regarding tumor location, metastasis, and stage of Chantada et al.[1]. It was possible to observe that patients who had extraocular localization, presence of metastasis and stage IV died more, corroborating studies that mention extraocular localization, the presence of metastases and the stage with worse prognosis determinant factors in predicting patient survival[2,8,9,13].

Regarding ABCDE[22], it was possible to observe a significance in relation to patients who had their right eye affected with E classification, representing a more advanced stage. There was superiority in enucleated as opposed to preserved eyes, and the same happened in the left eye, as evidenced in studies[12,14] in which the predominance of patients in classification E is correlated with delayed diagnosis and, therefore, early detection of the tumor would increase the chances of preserving the patient's vision[6].

As limitations inherent to the study, difficulties arising from the use of secondary data, cross-sectional design – impossibility of establishing a causal relationship, incompleteness of the data caused by lack of awareness or adequate professional training – stand out, in addition to the distancing of the researcher from the study participants.

CONCLUSION

These findings are relevant for the planning of prevention actions, since early diagnosis is one of the main allies in determining the cure and in preserving vision; that is, for the patient with Rb, it is the fundamental factor for the success of therapy and survival.

Therefore, it is extremely important to promote educational campaigns for the population, as well as the continuing education of health professionals, especially primary care clinicians, about the first signs and symptoms of Rb, and the recommendation of periodic evaluations in the first years of the child's life, in order to provide opportunities to reduce mortality rates and increase eye preservation rates, in addition to minimizing the late effects of treatment.

CONTRIBUTIONS

All authors contributed substantially to the design and/or planning of the study; in the analysis and/or interpretation of the data; in the writing and/or critical review; and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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