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Epidemiological Features and Prognosis of Retinoblastoma in Fars southern Iran, 2010-2018

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Abstract

Background: Retinoblastoma (RB) is the most common intraocular malignancy in childhood. The aim of this study was to investigate the epidemiological features and survival rates of patients with RB in southwestern Iran.

Materials and Methods: This retrospective study was conducted on patients with RB referred to the only referral center of southwestern Iran from 2010 to 2018. Demographic characteristics at first symptom presentation, the time interval between the symptom presenting and the treatment, educational level, socioeconomic status, type of ocular symptoms, extra-ocular involvement, types of treatments, outcomes and follow-up, the treatment interval until death and the survival rate of the patient, and pathology reports were recorded and analyzed.

Results: This study included 46 new patients with RB (25 boys and 21 girls) including 65.2% unilateral, 26.1% bilateral, and 8.7% trilateral involvements. The mean age at first symptom presentation was 18.98±16.16 months. The mean delay time was 2.48 (Interquartile range: 5.16) for boys and 3.02 (Interquartile range: 5.37) for girls (P = 0.265); death rate was significantly different for boys and girls (12.0 % versus 430%; P = 0.039). E-nucleation was done in 95.3% of cases. In 29% of patients the tumor was well-differentiated, and about 64.5% of the cases were pathologically graded at pathological tumor stages 3 or 4. At the time of the study, 54.3% of the patients were alive. The mean survival time was 44.0 months.

Conclusion: Almost all cases were diagnosed in the advanced stages of the disease in Southwestern Iran. The disease is not preventable but early diagnosis improves the prognosis so we recommend that an eye examination at birth and designing and implementing prevention programs through parenting and child care personnel be performed in order to pay attention to early symptoms of the condition and in the absence of symptoms, screening should be done every six months.

Keywords: Epidemiology; Prognosis; Retinoblastoma; Survival

Introduction

Retinoblastoma (RB) is the most common intraocular malignancy in childhood (1), accounting for about 3% of cancers in children and 11% of tumors in the first year of life (2). Globally, the incidence of RB is about 1 in 16,000-24,000 live births, equivalent to 9,000 new cases a year (3). Some studies have shown that this condition is rising in developing countries (2). About 40% of the RB is hereditary (2) being due to mutations in the RB-1 gene (1, 4), and more than 55% of the patients develop the condition because of non-hereditary factors. A few studies have shown that the incidence of RB is more in boys (1/1-1/4:1), especially over the age of 4 (3: 1) (5). In the case of early detection, RB is treatable. (6) However, many children with this malignancy die around the world, especially in developing countries (6). The survival rate of RB patients differs according to the availability of diagnostic and treatment facilities, with mortality rates varying from 40% to 70% in Asia and Africa but 3-5% in Europe, the United States, and Canada (7). Despite the high importance of the issue, few articles have been published on the prevalence and epidemiological findings of RB in developing countries (8) including Iran (9, 10).The aim of this study was to evaluate the epidemiological features of RB in patients admitted to the only referral

hospital in southern Iran from May 2010 to July 2018.

Materials and Methods

This retrospective study was conducted on all files of the children with RB referring to Khalili Ophthalmology Center, Shiraz University of Medical Sciences, from May 2010 to July 2018. Khalili Ophthalmology Center is the only ophthalmologic referral center in Fars Province and southwestern Iran. To find all available files, the authors searched the C6902 code in the hospital information system. The records with a definite diagnosis of RB, even with the least information, were selected for the next steps. During this period, 50 patients with RB were admitted to Khalili hospital. Four patients were excluded from the study due to incomplete files and 46 cases were investigated. Data on the patients' background and demographic variables including the age of the patient at the time of presenting the first symptom, the age at which the diagnosis was made by the ophthalmologist, the time interval between the symptom presenting and the treatment, the sex of the patient, the family history of the disease (sporadic versus hereditary form), the patient's place of residence (Fars province versus other provinces), parents' educational level and socioeconomic status (high versus low economic level), the refusal to start or complete treatment, the left or right eye, type of ocular symptoms (leukocoria, proptosis, strabismus, red-eye, and decreased vision), extra-ocular involvement, the care and types of treatment (E-nucleation, chemotherapy, cryotherapy, etc.),outcomes and follow-up (based on their refusal to refer to an ophthalmologist or oncologist), the treatment interval until death and the survival of the patient (in months), and pathology reports, in case of availability, were extracted from the records. To complete the data, the pathologic lamellas of 31 patients present in the Khalili Hospital's pathology laboratory archives were re-examined by an ophtalmopathologist, reporting histological, cellular, and tumor (T), nodes (N), and metastases (M) grading findings. The defects in the information were removed by referring to existing paper files or telephone contacts with the patients' families. Furthermore, due to patients' continuing treatment in other centers, all available medical records in those centers were used, as well. Access to the medical records and contacting patients and their families for further information were authorized after approval of the ethics committee of Shiraz University of Medical Sciences (Code: 122-49, 28.11.97). When contacting the patients' families, first authors explained the study and in case of willingness, families answered the questions.

Diagnosis of RB in Khalili Eye Center

During the study, for all referred patients to Khalili ophthalmology center in Shiraz, indirect ophthalmoscopy (12500, Welch Allyn, New York, USA) and fundoscopy were done by an ophthalmologist. According to the presence of a yellow-white mass in fundoscopy, the disease was diagnosed. Then, for the majority of patients, an ultrasound eye examination was performed by an experienced radiologist. The diagnosis was confirmed by filling-defect and mass detection. In some patients, computed tomography scan of orbit or magnetic resonance imaging was performed to confirm the presence of calcification. Also, post-operation pathological specimens were examined by the pathologist of the ophthalmology center and the final diagnosis of RB was established.

Statistical analysis

The data were collected using both visual evaluation and the software "Cleansing and preparation of data for statistical analysis" techniques (11). Frequency, relative frequency, mean, median, and standard deviation were used to describe the collected data. The mean survival time and 95% confidence intervals were calculated

and categorized according to the Kaplan-Meier analysis by subgroups of patients. The log-rank test was used to compare survival in different groups of patients. Also, the Chi-square test was used to compare quantitative variables and the Mann-Whitney U test to compare qualitative variables. For the first type error, $P < 0.05$ was considered with the two-tailed tests.

Results

Of the 50 patients admitted to Khalili Ophthalmology Center, 46 patients entered the study.The number of cases admitted between 2010 and 2018 showed an upward trend (Figure1). The sex ratio was 1.19: 1 (25 boys versus 21 girls). At the time of the study, 54.3% of the patients (n = 25) were alive. This ratio showed a significant difference in girls and boys (P = 0.039). The mean survival time was 44.0 months with a confidence interval of 32.8 to 55.2 (Table I). The median survival time for boys and girls was respectively 43.0 (95% CI: 21.75, 64.25) and 45.0 (95.1% CI: 36.81, 53.19) months. Comparing the survival curve of girls and boys did not show a statistically significant difference (Figure 2). At diagnosis, 65.2% of patients (n = 30) had unilateral tumors. This ratio was not significant in girls and boys (P = 0.208). Left eye involvement was 24% in girls and boys (P = 0.352). The most common symptom was leukocoria among boys and girls (P = 0.869). The prevalence of this symptom was 54.3% (n= 25) in patients (Table II). Of the 46 patients, treatment information of 43 patients was available and extractable. E-nucleation was performed in at least one eye in 95.3% of patients (n = 41). Results showed that 11.6% of the patients (n = 5) refused to start or complete treatment (Table III). In 29% of the cases (n = 9), the tumor was well differentiated. About 64.5% of the cases were pathologically graded at pathological tumor stages 3 or 4 stage (Table IV).

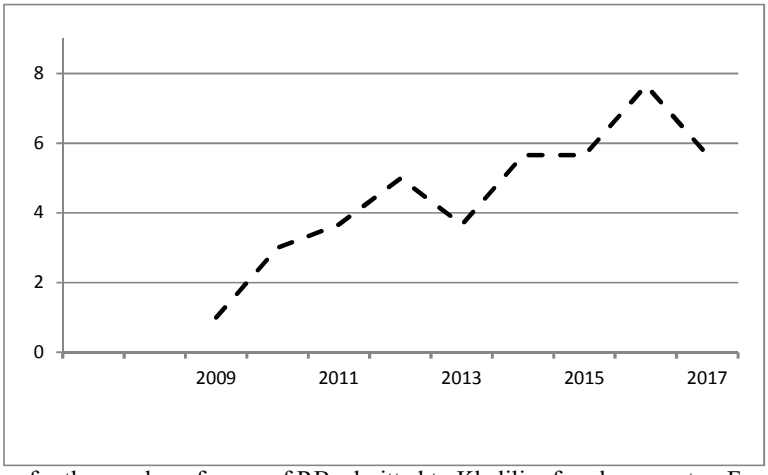

Figure1. Timeline for the number of cases of RB admitted to Khalili referral eye center, Fars Province, Iran.

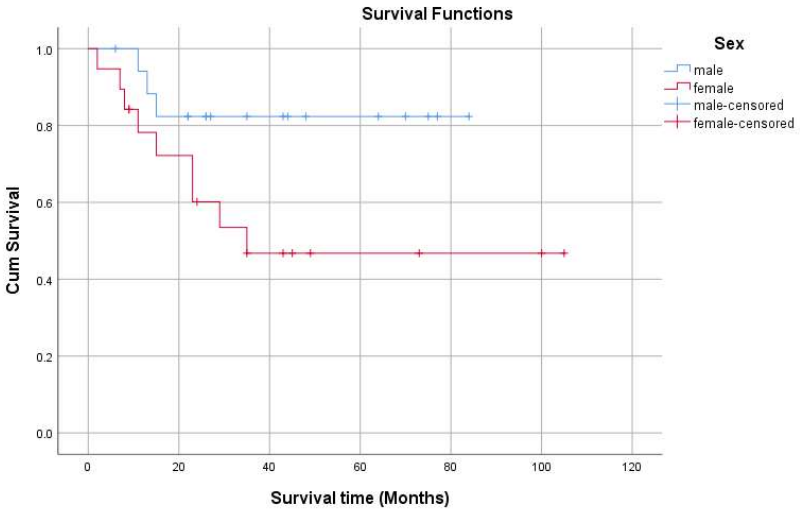

Figure 2. Comparison of survival curve of girls and boys with RB.

Table I: Characteristics of patients with RB

Variable	Overall (%)	boys	girls	P-Value (m v/s f)
Overall	46(100.0)	25 (54.3)	21 (45.7)	0.41
Age at first symptom (Months)				
Mean ± SD	18.98(16.16)	20.64(18.54)	17(12.94)	0.716
Median (Interquartile range)	16.0(5.0, 28.3)	18.0(4.0, 32.0)	12.0(6.0, 24.0)	-
Age at Diagnosis± SD	21(18.019)	23.04(21.2)	18.57(13.39)	0.667
Delay time(Interquartile range)	2.73(IQR: 5.211)	2.48(IQR: 5.16)	3.02(IQR: 5.37)	0.265
Survival Time (Months)				
Mean (95% confidence interval)	49.0 (38.6, 59.5)	45.1 (33.1, 57.0)	54.3 (34.6, 74.1)	0.072
Residence				
Fars	22(47.8)	10(40.0)	12(57.0)	0.246
Other Provinces	34(52.2)	15(60.0)	9(43.0)	
Socioeconomic status				0.247
High	14(30.4)	10(40.0)	4(19.0)	
Moderate	19(41.3)	8(32.0)	11(52.4)	
Low	13(28.3)	7(28.0)	6(28.6)	
Family history)				NS
Yes	1(2.2)	1(4.0)	0(0.0)	
No	45(97.8)	24(96.0)	21(100.0)	
Survival				0.039
Alive	25(54.3)	15(60.0)	10(47.6)	
Dead	12(26.1)	3(12.0)	9(42.9)	
Censored	9(19.6)	7(28.0)	2(9.5)	

Table II: Disease's characteristics of patients with RB.

Variable	Overall (%)	boys	girls	P-value
Overall	46(100.0)	25(54.3)	21(45.7)	
Types of eye involvement				**0.208**
Unilateral	30(65.2)	19(76.0)	11(52.4)	
Bilateral	12 (26.1)	5(20.0)	7(33.3)	
Trilateral	4(8.7)	1(4.0)	3(14.3)	
Eye				**0.352**
Right	22(47.8)	14(56)	8(38.1)	
Left	11(23.9)	6(24.0)	5(23.8)	
Both	13(28.3)	5(20.0)	8(38.1)	
Extra-ocular involvement				**0.293**
Yes	11(26.0)	5(20.0)	7(33.3)	
No	34(74.0)	20(80.0)	14(66.7)	
Main symptom				**0.869**
Leukocoria	25(54.3)	14(56.0)	11(52.4)	
Strabismus	5(10.9)	2(8.0)	3(14.3)	
Redness	5(10.9)	3(12.0)	2(9.5)	
Decreased vision	3(6.5)	1(4.0)	2(9.5)	
Proptosis	8(17.4)	5(20.0)	3(14.3)	
Secondary involvement				**0.216**
Yes	11(23.9)	4(16.0)	7(33.3)	
No	35(66.1)	21(84.0)	14(66.7)	

Table III:. Disease management of patients with RB.

Variable	Overall (%)	boys	girls	P-value
Overall	43(100.0)	24(55.8)	19(44.2)	
Other treatments				**0.440**
Yes	9(21.0)	4(16.7)	5(26.3)	
No	34(79.0)	20(83.3)	14(73.7)	
Systemic Chemotherapy				**0.685**
Yes	36(83.7)	19(79.0)	17(89.5)	
No	7(16.3)	5(21.0)	2(10.5)	
E-nucleation				**0.305**
Yes				
Right	23(53.5)	14(58.3)	9(53.0)	
Left	17(39.5)	9(37.5)	8(47.0)	
Both	1(2.3)	1(4.2)	0(0.0)	
No	2(4.7)	0(0.0)	2(10.5)	
Exenteration				**-**
Yes	2(4.7)	0(0.0)	2(10.5)	
No	41(95.3)	24(100)	17(89.5)	
Refused Treatment				**0.496**
Yes	5(11.6)	2(8.3)	3(15.8)	
No	38(88.4)	22(91.7)	16(84.2)	

Table VI: Pathological features of retinoblastoma patients admitted 2010-2018, Khalili referral eye center, Fars Province, Iran, 2010-2018

Variable	Overall (%)	boys	girls	P-value
Overall	31(100.0)	17(54.8)	14(45.2)	
Optic Nerve Involvement				**0.805**
Yes	6(19.3)	3(17.6)	3(21.4)	
No	25(80.7)	14(82.4)	11(78.6)	
Vitreous Involvement				**0.290**
Yes	9(29.0)	6(35.3)	3(21.4)	
No	22(71.0)	11(64.7)	11(78.6)	
Orbit Involvement				**0.039**
Yes	3(9.7)	0(0.0)	3(21.4)	
No	28(90.3)	17(100.0)	11(78.6)	
Choroid Involvement				**0.788**
Yes	4(12.9)	2(11.8)	2(14.3)	
No	27(87.0)	15(88.2)	12(85.7)	
Angel Involvement				**0.370**
Yes	1(3.2)	1(5.9)	0(0.0)	
No	30(96.8)	16(94.1)	14(100.0)	
Cellular Pathology				**0.617**
Highly differentiated	9(29.0)	4(23.5)	5(35.7)	
Partialy differentiated	7(22.6)	5(29.4)	2(14.3)	
Undifferentiated	12(38.7)	7(41.2)	5(35.7)	
Others	3(9.7)	1(5.9)	2(14.3)	
Pathologic Grading				**0.599**
pathological tumor stage 1	3(9.7)	3(17.6)	0(0.0)	
pathological tumor stage 2a	2(6.5)	1(5.9)	1(7.1)	
pathological tumor stage 2b	5(16.1)	2(11.8)	3(21.4)	
pathological tumor stages 3 or 4	20(64.5)	10(59.0)	10(71.0)	

Discussion

This study aimed to investigate the epidemiology of RB in southwestern Iran and followed the investigators' previous study (9). The mean age of the patients was estimated to be about 19 months at the time of diagnosis and the delay time for treatment was about 3 months. The results of this study indicated that most of the patients were boys. The higher incidence of disease in boys compared with girls in this study was consistent with the previous report (9). Of course, in a study in Oman by 2004, the incidence of the disease in girls was higher than boys. The same result was reported from India in 2002 but in the recent study published in 2018, the disease incidence was higher in boys (12). The percentage of unilateral and bilateral eye involvement in the present study was almost the same as that reported in Nigeria (13). However, compared with the reported data of the cases in India, the proportion of unilateral involvement was greater in the present study (14). In this study, the ratio of bilateral/trilateral involvement was equal in girls and boys. This finding was in compliance with the results of a study from Brazil (2); in which in spite of no statistically significant difference, the proportions were significant in boys and girls. Therefore, the equal ratio in this study may be due to the inadequate number of patients. The mean age of symptom

development in patients in this study was 6 months less than that in Turkey and the United Kingdom (13). Given that the active health services in the UK are delivered with much quality than in Iran, this finding may indicate a lower age of onset of the disease in southwestern Iran. Since almost all patients had sporadic forms of the disease, genetic and environmental factors of the parents may be involved in the early onset of illness, or the existence of other genetic disorders in the patient facilitates the RB gene mutation and caused its occurrence at earlier ages. On the other hand, like early-onset leukemia, which is due to a gene mutation in the early stages of fertilization or fertility, this mutagenesis perhaps led to early-onset RB with a more advanced stage of pathology. In most childhood diseases, early diagnosis of the disease may depend on the pattern of behavior search and parental care, and the parents' sensitivity to the symptoms, and their access to the specialized centers. However, the results of this study showed that there was no statistically significant relationship between the socioeconomic status of parents and the survival rate of patients.

The mean delay time for treatment in this study was 2.7 months, which was slightly lower than that in the previous study, 3.3 months in the same region (9). This reduction in the delay time may indicate improvement in the search pattern and treatment of patients in the southwestern Iran. The mean delay time for treatment was 9.4 months in the northwestern Iran, 10.5 months in Brazil, 1.87 months in England, and 3.8 months in Switzerland (2, 13). Accordingly, the duration of post-diagnosis treatment delay in southwestern Iran was reasonable in comparison with other regions of Iran as well as other countries. In the present study, the most common symptom was leukocoria followed by strabismus. Proptosis was at the bottom of the list, while in Nepal, Nigeria, and Ethiopia, proptosis had the highest rate of occurrence (15, 16). This difference can be due to the lack of awareness among health professionals or lack of appropriate diagnostic standards and delayed diagnosis in these countries.

The mean age of disease presentation in the present study was lower than that in other countries (17, 18, 19). In addition, almost all of the patients underwent E-nucleation after diagnosis, and postoperative pathological findings showed an advanced stage of the disease, which affected the prognosis and survival of the patients. Such parameters suggested a significant delay in the diagnosis of eye symptoms by the parents and the referral for screening and examination by the ophthalmologist. The most common routes of metastasis were direct infiltration via the vitreous and optic nerve to the central nervous system. This finding was in concordance with a study from Ethiopia(15). Standard therapeutic options including E-nucleation, Exenteration, and systemic chemotherapy were done for patients depending on their visual prognosis. In developed countries, chemotherapy is the most common treatment approach (20). The difference may be due to the higher stage of RB in these patients which may partly be due to delayed diagnosis or delayed treatment. If serious attention is paid to parents' training to diagnose the symptoms of the disease, and screening is performed by at least one red-reflex examination in children under two months and then every six months in children under three years of age, the E-nucleation rate decreases up to 50%. However, if the diagnosis is made after the development of symptoms and the parents notice them, the E-nucleation rate is often higher than 90%. Accordingly, increasing the level of parental awareness of the disease can help improve patients' prognosis. Although almost all patients with RB admitted to Khalili Ophthalmology Center entered this study, the sample size was still inadequate to identify factors associated with the incidence or prognosis of the disease. Considering that Khalili hospital is the only referral eye center in the region, it is

estimated that almost all cases in this area are included in this study. At the same time, multi-center studies are proposed to increase sample size and increase the statistical power of the results. Moreover, failure to routine follow-up of the patients and the disease consequences, as well as the impossibility of follow-up by the investigators affected the results of the study about the disease consequences.

Conclusion

Almost all cases were diagnosed in the advanced stages of the disease in Southwestern Iran and nearly all patients underwent surgery and lost at least one eye. Given that the disease is not preventable but early diagnosis improves the prognosis, it is recommended that an eye examination at birth and designing and implementing prevention programs through parenting and child care personnel be performed in order to pay attention to early symptoms of the condition and then consult with an ophthalmologist, and in the absence of symptoms, screening should be done by at least one red-reflex examination in children less than two months and then every six months in children under three years of age.

Conflict of interest

The authors declare no conflict of interest.

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