Retinoblastoma: A Report from A Referral Center in Iran: 1979-2007

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Abstract

***Purpose*:** Retinoblastoma (RB) is a relatively common childhood tumor. In this report we discuss the clinical characteristics, treatments and outcome of the treated RB patients from a referral center in Iran in order to understand this medical problem in our society.

***Methods*:** A retrospective study was carried out on RB cases treated in Farabi Eye Hospital since 1979 to 2007. The variables analyzed were age, sex, affected eyes, time of the diagnosis, treatment modalities, pathological findings and the survival rate.

***Results*:** We analyzed 557 cases with a mean age of 32.2 months [standard Deviation (SD)= 22]. There was a male predominance (60%). There were 380 unilateral cases (68.6%). Enucleation was performed in 65.6% of the patients. Nearly 82% of the eyes were in group Va and Vb Reese-Ellsworth or in a very advanced condition. Of the enucleated cases, 43.2% of the eyes have had undifferentiated types of tumors. Disease free survival was 68.5% in this study (by a mean follow-up of 61.9 months).

***Conclusion*:** Considering the advanced stages of disease in the majority of patients at the time of diagnosis, the enucleation ratio of our RB patients was higher than other countries.

***Keywords*:** Childhood Tumors, Epidemiology of Retinoblastoma, Retinoblastoma

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Introduction

Retinoblastoma (RB) is the most common embryonal tumor of the retina in children occurring at an incidence of approximately 1/15,000-1/30,000 in western countries.[1] Two third of the cases are unilateral.[2] It occurs in both sporadic and inherited forms, the latter including 40% of all the cases. The survival rate for RB has been improved since 1970s.[3] The cure rate of these patients in developed countries is more than 90%. Advanced intraocular tumors and metastatic diseases occur more frequently in developing countries, accounting the poorer outcomes of the disease in these countries.[2-4]

In the past, external beam radiotherapy or enucleation was the main treatment modality for RB. However, some complications as cataract, facial growth disturbance, optic neuropathy, facial asymmetry and secondary tumors can occur following radiotherapy.[5] The primary chemotherapy has been reported to reduce the overall activity and size of tumor, thus making the local treatment possible and lowering the frequency of enucleation.[6]

The aim of this report is to describe the clinical characteristics, treatments and outcome of patients with RB in our pediatric ocular oncology unit as a developing country profile in the past years to define where we are and to determine the future goals in the management of RB patients in our country.

Methods

This study comprised a retrospective, non-comparative case series of 557 consecutive RB patients diagnosed at Farabi Eye Hospital (a university hospital of Tehran University of Medical Sciences) as the main referral center of the country for the ocular diseases, between 1979 and 2007. It is estimated that more than 80% of all RB cases occurring in Iran during this study period have been ascertained. There was no registry in Iran for RB. The retrieved information were from the medical records and including age at first visit, duration of symptoms before the first visit, symptoms, gender, laterality of RB, disease stage, family history, treatment, pathologic findings and outcome for RB patients. Tumor stage was determined and recorded (Reese-Ellsworth classification system) by an experienced ophthalmologist (H.Ch.) at the initial examination under general anesthesia.[7]

Improving the survival of RB cases and saving the eye were the main aims during the time of treatment planning in our institution. Bone marrow aspirate and cerebrospinal fluid (CSF) evaluation performed in all cases. Before mid nineties the main treatment for RB cases were enucleation (for group IV and V), photocoagulation (for localized small tumors), cryotherapy and external beam radiotherapy (for I to III, some group IV and V patients and recurrent cases). Since late 1990, systemic chemotherapy and /or other adjunctive treatments (subtenon carboplatin, rare intravitreal injections, cryotherapy) were given to the patients by the published protocols and the staging of the disease in the first visit.[6-8] Exenteration was performed in patients with optic nerve or orbital involvement in the CT-scan imaging or pathology report, monocular patients with an end stage tumor and some bilateral advanced or recurrent cases. Chemotherapy included VC (Vincristine, Carboplatin), VEC (Vincristine, Etoposide, Carboplatin) or OPEC (Oncovorin, Cyclophosphamide, Etoposide, Carboplatin) protocols during this time.[8] The children were followed up frequently for the first five years and yearly thereafter.

The patients were divided into three groups. Group 1 defined as all patients with unilateral RB. Group 2 included all bilateral RB patients. The first eyes-showing the first symptoms of the disease- in bilateral cases were included in this group. Group 3 were all patients in the aforementioned two groups. In the analysis of staging, pathologic findings, and treatments, all eyes (including both eyes of bilateral cases) were included in the analysis. Treatments were divided in two categories: surgical and nonsurgical treatments.

SPSS software (version 16; SPSS, Chicago, IL) was used for statistical analyses (χ^2, t test).

Results

Five hundred and fifty-seven patients (332 boys and 225 girls), aged from 1/2 month to 168 months (mean: 32.2 months), were included in this study. The general characteristics, demographic findings,

symptoms, and outcomes are shown in Table 1. Unilateral cases had significantly more leukocoria compared to bilateral cases (P<0.001).

One hundred thirty five (24.2%) patients had known family history of RB at presentation. Twenty-seven (4.8%) cases had family history in their parents or the siblings, in 56 (10.1%) cases one or more cousins were involved and in 52 (9.3%) cases remote family history was present. The differences in family history and age at the time of diagnosis of RB between the two groups (1 and 2) were significant (P<0.001). Interestingly, the mean age at the time of the first diagnosis for those patients with near family history was even higher than bilateral cases (30.4 versus 24.7 months). However, there was no significant difference based on the duration of symptoms before the first oncology visit between the two groups. The mean follow-up time (F/U) was 61.9 months (range, 1-321 months). Due to unrecorded visits or lost to follow-up, we had around 28% (N=156) missing data on some variables.

The staging of the cases has been presented in Table 2. Most (82.4%, N=604) of the eyes were in group Va and Vb or in very advanced condition with extraocular extension in both groups, being more prominent in unilateral cases (P<0.001).

In our records, the positive results for tumoral cells in bone marrow aspiration was 11.6% in all group, 14.0% in unilateral cases (N=380) and 11.1% in bilateral cases (N=177). By CSF analysis the positive results were found in 5.5, 9.4, and 3.4 percent of the cases, respectively.

As shown in Table 3, in group 3, 65.4% of the cases needed enucleation during the course of treatment. In 57.1% of the cases enucleation was the first treatment.

Table 4 presents the pathology results of our patients. In 89% of these patients, the histology reports were in the charts. There was a mild preponderance of undifferentiated forms in bilateral cases compared to unilateral cases in this report (P<0.05).

Of the patients for whom survival data were available (N=402 and 61.9 months mean F/U time), 68.8% (N=271) were alive at the end of this study. The death ratio in unilateral (N=53 out of 277) cases and bilateral (N=71 out of 118) were 19% and 61.8% accordingly (P<0.001). We had no information about the related and unrelated causes of death and also any second primary neoplasm in these patients.

Table 1. Demographic findings and outcome in retinoblastoma patients

	Unilateral (380 cases)	Bilateral (177 cases)	All cases (557 cases)
Sex			
Male (%)	56.5	64.4	59.6
Mean age (mo)(%)	35.7	24.7	32.2
≤12	14.2	33.9	20.5
≤24	42.1	65.0	49.4
≤36	65.8	84.2	71.6
≤48	81.6	91.5	84.7
≤60	88.9	94.4	90.7
≤72	95.8	100	91.7
≤168	100		100.0
Laterality (%)			
OD	54.7	50.8	47.0
Family history (%)	21	31.0	24.2
Duration of symptoms before specialist visit (mo)	5.8	7.6	6.2
Signs and symptoms (%)			
Leukocoria	62.9	49.4	58.6
Strabismus	10.3	7.9	9.5
Buphthalmous (glaucoma)	9.7 (9.2)	7.9 (13.6)	9.2 (10.6)
Exophthalmos	8.7	14.7	10.6
Follow-up (mo)	63.5	41.3	61.9
Outcome (%)			
Dead	13.9	40.1	22.3
Alive	58.9	26.6	48.7
Unknown	27.1	33.3	29

Table 2. First oncology visit staging of retinoblastoma patients

Staging (group) (%)	Group 1: Unilateral (380 cases)	Group 2: Bilateral (177 cases)	All involved eyes in all cases (734 eyes)
Ia	0.3	0	1.1
Ib	0.3	0	1.6
IIa	0.5	0	0.5
IIb	0.5	0	3.1
IIIa	0	0	0.3
IIIb	1.3	1.1	6.5
IVa	0.5	1.1	4.4
IVb	0.3	0	0.1
Va	62.1	53.7	49.0
Vb	3.9	2.3	2.9
Not evaluable	6.3	7.3	6.1
Phthisis bulbi	0.8	3.4	3.7
Orbital involvement	23.2	31.1	20.7

The first eyes-showing the first symptoms of the disease- in bilateral cases were included in group 2 but both eyes of bilateral cases were included in group 3 of this table.

Table 3. Treatments in retinoblastoma patients

Treatment	Group 1: Unilateral (380 cases)	Group 2: Bilateral (177 cases)	All involved eyes in all cases (734 eyes)
Surgeries (%)			
Enucleation	80.8	71.8	65.4
Exenteration	9.5	14.7	10.2
Enucleation and then exenteration	5.5	5.6	4.4
None	4.2	7.9	20
Nonsurgical			
Chemotherapy	22.1	34.5	25.2
Laser	-	-	0.1
Cryotherapy	1.3	11.3	7.5
Radiotherapy	2.9	0.6	1.6
Chemotherapy+ Radiotherapy	8.9	13.0	9.0
None	64.7	40.7	56.4

The first eyes-showing the first symptoms of the disease- in bilateral cases were included in group 2 but both eyes of bilateral cases were included in group 3 of this table.

Table 4. Pathology in retinoblastoma patients

Pathology	Group 1: Unilateral (380 cases)	Group 2: Bilateral (177 cases)	All involved eyes in all cases (734 eyes)
Undifferentiated	57.4	49.6	43.2
Differentiated	25.0	24.5	22.2
Unspecified retinoblastoma	17.6	27.7	34.6
Choroid extension	18.07	26.0	17.0
Sclera	8.4	8.5	6.8
ON head	10.0	11.9	8.9
Surgical margin of ON	18.7	12.4	13.4
Iris	7.9	7.3	6.3
Ciliary body	11.8	11.3	10.4
Orbit	11.6	13.0	9.8

ON: Optic nerve
The first eyes-showing the first symptoms of the disease- in bilateral cases were included in group 2 but both eyes of bilateral cases were included in group 3 of this table.

Discussion

The management of children with RB has much improved in the developed countries in the recent years but in developing countries we have been faced with significant problems in the management of these patients. In this study, regarding to the higher stages of the RB at the time of the diagnosis, the enucleation ratio was higher than in developed countries. The number of death was much higher in bilateral cases.

RB is the most common intraocular malignancy seen in childhood and a common problem in pediatric oncology in underdeveloped and developing countries. Although the diagnostic methods have been improved in the recent years but in Iran as a developing country, at the time of this study, the mean age at diagnosis was still high.

Similar to some other studies, male predominance (60%) has been observed in our study population but the gender difference was not significant between unilateral and bilateral cases.[9] However, in other studies, no gender predilection has been reported in RB.[10,11]

The mean age of the patients at diagnosis in the developing countries is higher than developed countries.[2,4,9,12] Like the previous studies, we observed that the mean age at diagnosis for bilateral cases was lower than that observed in unilateral cases (35.7 vs. 24.7, P<0.001).[2,9] Recently published study by another referral center in Iran showed 32.7 months mean age for unilateral and 22.8 months for bilateral cases in 1991-2001.[13] Abramson reported a mean age at diagnosis of 25 months for unilateral and 13 months for bilateral cases.[14] In Great Britain, Lennox reported a mean age of 26 months for unilateral and 8 months for bilateral cases at the time of diagnosis.[15] In Turkey, median presentation age of patients with unilateral disease was 24 months versus 9.5 months in patients with bilateral disease.[9] In our report, only 71.6% of the patients were diagnosed before 3 years of age.

We found leukocoria as the most common initial symptom, followed by strabismus confirming the results of previous large studies.[2-5] Our results are consistent with those of other studies concerning the proportion of patients with unilateral (68.2%) and bilateral (31.8%) disease.[2-5,9]

Although orbital mass is very rare in developed countries,[16] but it is still a problem in developing countries, such as in Taiwan (16.7%), in Turkey (14.5%) and in our series (9.7% in pathology, 1.6% in imaging reports).[17]

According to RE classification, 82.4% of our patients had advanced intraocular disease and intraocular and extraocular extended neoplasm. In the United States, the percentage of patients with group V (advanced intraocular disease) varies between 48 and 83% of the cases.[18]

We found that the mean interval between the appearance of the first symptoms realized by the parents and specialist visit was 6.2 months in all patients. In few studies, specialists were responsible in the later diagnosis of the tumor in almost half of those cases.[9,19,20] Seventy-five percent of our patients had been diagnosed within 6 months from the recognition of the first symptoms. This is shorter than the mean overall lag time of 8.3 months reported by Erwenne.[21] The time limit of 6 months is an important factor, because diagnosis of bilateral RB beyond 4 months seems to correlate with greater risk of blindness and compromises salvage treatment.[19]

In spite of shorter diagnosis interval in the familial cases in the other studies,[20] the first specialist visit and delayed diagnosis in our familial cases was later than the nonfamilial ones. In a study by Wallach the mean age at diagnosis was only 3.6 months in familial cases, whereas in our cases the mean age at diagnosis was 23.5 months.[19] It is shown that advanced age and delayed diagnosis increase the risk of extraocular extension and diminish the perspective for cure.[4,21] It has been suggested that all physicians and medical staffs who are involved in the diagnosis and treatment of RB must be trained adequately in recognizing early presenting signs and symptoms of RB and their vital role in the detection of RB should be emphasized. By increasing parental awareness and immediate referral and workups by the responsible team in suspected cases; more children may have access to eye-sparing treatment modalities and avoid less optimal outcomes. It is better to organize systematic screening at least in patients who are born with the RB1 mutation.

Before 1980s, the enucleation ratio in patients with RB was 96%, and between 1980 and 1990, this ratio decreased to 70-85%.[22] Recently, early diagnosis and eye-sparing treatment modalities have improved the patient survival rate and have decreased the enucleation rate. Presently, enucleation is being performed in 53% of group V patients in developed countries.[18] In our study, 65.4% of the eyes were enucleated and 7.6% of the cases had bilateral enucleation. Our enucleations are higher than that in developed countries although the number of enucleation has been decreased from the early years of the study and will be reported in the next report from this center in the near future.[9]

RB is an eminently curable cancer and treatment is usually highly successful. The mortality rate of RB varies in different regions of the world. The survival of patients with RB has gradually improved over the years, in part because of the early diagnosis and multidisciplinary approach and management.[2] Of our followed cases, 68.5% were alive with the mean follow-up time of 61.9 months (range, 1-321 months) in group 3. Recently, in some developed countries, survival rate has exceeded 90%,[3,23] this rate is still associated with wide variations in underdeveloped or developing countries in different locations.[4,12,17,20,21] In our series with 557 cases, 37.2% of the bilateral and 80.9% of unilateral cases were alive at the end of this study (with more mean F/U time than other studies). We do not have any access to the cause of deaths data in these patients but mortality in the bilateral cases was much more than unilateral cases (P<0.001). Majority of deaths from RB occur within three years of diagnosis in developed countries.[2] The high survival rate reported in the known big centers for the treatment of RB is due to the strict policy of referral to specialist centers.

This retrospective review of clinical findings in RB patients, in a main referral center in Iran, was carried out on the RB cases population diagnosed over a long period of time. Different treatment protocols were used for the treatments during the time.

We can say that the enucleation ratio of our patients is still higher than what is observed in developed countries. This discrepancy is due to the high frequency of advanced cases at the presenting time. The prompt planning for increasing the pediatricians, ophthalmologists, and general population knowledge about this disease, team working and possible national screening program to decrease the delayed diagnosis is crucial. It is evident that creating a national registry is the necessary next step in the care of these patients.

Conclusion

In conclusion, in Farabi Eye Hospital, Tehran-Iran, RB cases were diagnosed in advanced stages of tumor in the 28 years of this study, thereby the enucleation ratio of our patients was still higher. Additionally, iris and orbital involvement were significantly associated with death in this study.

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