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Retinoblastoma in Taiwan: Survival and Clinical Characteristics 1978–2000

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Purpose: Few estimates of the survival rates ofwas retinoblastoma have been reported from the Asia region. In this study, we aim to describe the survival and clinical characteristics of 96 retinoblastoma cases treated at Chang Gung Medical Center, Taipei, between 1978 and 2000.

Methods: We retrospectively analyzed the clinical records of 96 children (116 eyes) diagnosed with retinoblastoma and treated between 1978 and 2000. Information on sex, laterality, age at diagnosis, presenting signs, spread of tumor, treatment modality, survival rate, and family history were collected.

Results: Seventy-six (79.2%) cases were unilateral and 20 (20.8%) were bilateral. The mean age overall at the time of diagnosis was 24.7 months; in unilateral cases, 27.1 months; and in bilateral cases, 15.6 months. The most common presenting signs were leukocoria (75 cases, 78.1.0%), buphthalmos (34 cases, 35.4%), proptosis (16 cases, 16.7%), and strabismus (12 cases, 12.5%). Forty-two eyes had orbital extension, 27 patients had central nervous system invasion, 16 cases exhibited bone marrow involvement, and 3 cases had liver metastasis. Three (3.1%) patients had a family history of retinoblastoma. None of the cases developed a secondary neoplasm. The 3-year cumulative survival rate of the 96 patients was 64.41% (unilateral, 71.97%; bilateral 40.01%).

Conclusions: The mortality was much higher than that in reports on Western and Japanese patients. Delayed diagnosis with frequent extraocular spread at the time of diagnosis caused the low survival rate. Fewer familial cases were encountered in our study than in other studies. **Jpn J Ophthalmol 2002;46:577–580**

Key Words: Extraocular invasion, retinoblastoma, survival rate.

Introduction

Retinoblastoma is the most common intraocular malignant tumor in childhood. Early diagnosis and prompt treatment increase the likelihood of survival. A combination of new diagnostic methods, modern radiological techniques, effective chemotherapy, and local treatment have been advocated to save not only the life of the patient, but also to preserve useful vision in the affected eyes. However, the mortality rate still varies greatly in different parts of the world.[1–7]

There are very few estimates of the survival rates of retinoblastoma patients in Asia.[2,4,8] This study documented our experience with retinoblastoma in a single medical center of Taipei over a 22-year period.

Materials and Methods

The medical records of 96 consecutive patients with retinoblastoma diagnosed and treated at the Department of Ophthalmology, Chang Gung Medical Center Taipei, between 1978 and 2000 were reviewed. The data included sex, laterality, age at diagnosis, presenting signs, mode of treatment, family history, extraocular spread, and survival rates.

The cumulative survival rate was calculated by the Kaplan-Meier method.

The follow-up period ranged from 1 month to 257 months (mean = 45.9 months). Seventy patients re-

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mained alive, and 25 patients died prior to the cut-off date (August 31, 2000). One patient was lost to follow-up and, because of his debilitated condition at the last visit, was thought to have died.

Results

Of the 96 retinoblastoma patients treated between 1978 and 2000, 75 cases were diagnosed histologically, while 21 were diagnosed clinically. All patients were Chinese.

Sex and Laterality

There were 56 (58.3%) boys and 40 (41.7%) girls. Seventy-six (79.2%) had unilateral involvement and 20 (20.8%) had bilateral. Altogether there were 116 involved eyes (Table 1).

Age at Diagnosis

Age at diagnosis ranged from 40 days to 10 years and averaged 24.7 months. The age at diagnosis for unilateral and bilateral cases averaged 27.1 and 15.6 months, respectively.

Only 79.2% of patients were diagnosed before the age of 3, and 91.7% diagnosed before the age of 4. For unilateral cases, 75% were diagnosed before 3 years of age, and 90.8% before age 4. For bilateral cases, 95% were diagnosed before 3 years of age (Table 2).

Presenting Signs

The most frequent presenting sign in this study was leukocoria (75 cases, 78.1%), with glaucoma-related buphthalmos second (34 cases, 35.4%), followed by proptosis (16 cases, 16.7%) and strabismus (12 cases, 12.5%). Hyphema, uveitis, or hypopyon, and orbital cellulitis-like orbital swelling were other presenting signs (Table 3).

Table 1. Characteristics of 96 Patients with Retinoblastoma (1978–2000, Taiwan)

	No. of Cases	%
Sex		
Male	56	58.3
Female	40	41.7
Laterality		
Unilateral	76	79.2
Bilateral	20	20.8
Family history		
Yes	3	3.1
No	93	96.9

Table 2. Cumulative Age at Diagnosis of 96 Patients with Retinoblastoma (1978–2000, Taiwan)

	Unilateral (n = 76)*	Bilateral (n = 20)	Overall
Age (y)	Cases (%)	Cases (%)	Cases (%)
0–4			
<1	17 (22.4)	9 (45%)	26 (27.1)
<2	38 (50.0)	16 (80%)	54 (56.3)
<3	57 (75.0)	19 (95%)	76 (79.2)
<4	69 (90.8)	19 (95%)	88 (91.7)
>4			
<5	73 (96.1)	20 (100%)	93 (96.9)
<6	75 (98.7)		95 (99.0)

* One unilateral case diagnosed at 10 years of age.

Spread of Tumor

During the follow-up period, 63 cases presented with intraocular diseases. Thirty-three cases demonstrated orbital involvement, some with extrascleral and some with optic nerve extension; 25 cases died eventually. Twenty-seven cases had central nervous system (CNS) invasion, most with optic nerve involvement initially and with chiasm, suprasellar extension later; some cases showed multiple skull bone metastasis at a later stage; 20 cases died ultimately. Sixteen cases had bone marrow involvement; 14 of them died. Three patients developed liver metastasis at the terminal stage despite treatment (Table 4).

Secondary Neoplasms

None of our cases developed a secondary malignant neoplasm before the cut-off date.

Mode of Treatment

Enucleation was performed in 72 cases (75%), and orbital exenteration in 3 cases; all exenteration operations were done in the early years of this study. Forty-two unilateral cases received radiation therapy either after enucleation, when there was evidence of

Table 3. The Presenting Signs in 96 Retinoblastoma Cases

Presenting Signs	No. of Cases*	%
Leukocoria	75	78.1
Buphthalmos	34	35.4
Proptosis	16	16.7
Strabismus	12	12.5
Hyphema	8	8.3
Uveitis/hypopyon	7	7.3
Orbital cellulitis	1	1.0

* Some cases had more than one presenting sign.

Table 4. Spread of Tumor and Outcomes in 96 Retinoblastoma Cases

Spread of Tumor	No. of Cases*	Dead	Alive
Orbit	33	25	8
CNS†	27	20	7
Bone marrow	16	14	2
Liver	3	3	0

* Some patients had multiple spread of tumor.
CNS: central nervous system.

tumor invasion beyond the section line, or simply as a palliative treatment for severely disfiguring orbital involvement. Thirteen patients with bilateral tumors received external beam radiation therapy as a primary treatment. Some received enucleation after the appearance of new growth or tumor recurrence, and local treatment was not possible. Chemotherapy was used in 32 patients with orbital, CNS, and bone marrow involvement. Three patients received local treatment, 2 received laser photocoagulation, and 1 underwent cryotherapy. In the 3 cases treated with local adjuvant therapy, treatment was carried out in the less involved eyes of bilateral cases (Table 5).

Survival Rate

The cumulative survival rate of the 96 cases calculated by the Kaplan-Meier method was 64.41% (unilateral, 71.97%; bilateral, 40.01%) (Figures 1 and 2). Survival rate in the unilateral cases was significantly higher than in the bilateral cases ($P = .0086$, $P < .05$).

Family History

In our study, only 3 patients had a positive family history of retinoblastoma, and all of them had unilateral involvement.

Discussion

The mortality of retinoblastoma varies in different regions of the world. In America, Europe, and some developed countries, survival has exceeded 90% recently.[1,7] In underdeveloped countries, retinoblastoma is still associated with high mortality, with wide variations in Asia. In Japan, the cumulative survival rate of 1,147 patients from 1975 to 1982 was 93.0% at 5 years and 90.3% at 10 years.[2] However, on some Philippine Islands, the mortality rate was reported to be 95%.[8] In a series of 68 cases in Singapore from 1968 to 1995, the 3-year survival rate was 83%.[4] Our results from Taiwan demonstrated that the 3-year cumulative survival rate of 96 patients between 1978 and 2000 was 64.41%, much lower than for Western and Japanese patients.

Early diagnosis and prompt treatment are important factors in achieving high survival rates. In developing countries, late referral has been implicated as

Table 5. Treatment Modalities in 96 Retinoblastoma Cases

Mode of Treatment	No. of Cases*	Eyes
Enucleation	72	72
Exenteration	3	3
Radiotherapy	42	55
Chemotherapy	32	–
Laser photocoagulation	2	2
Cryotherapy	1	1

* Some patients received multiple treatment modalities.

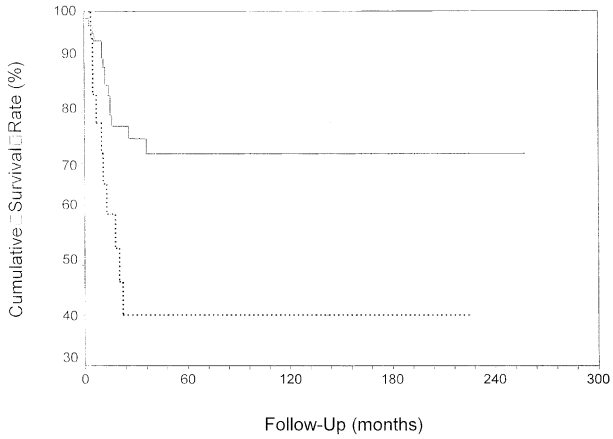

Figure 1. The survival plots of unilateral (n = 76), and bilateral retinoblastoma (n = 20) patients in Taiwan (Kaplan-Meier method, $P = .0086$, $P < .05$). Solid line: unilateral cases, dotted line: bilateral cases, +: cases censored.

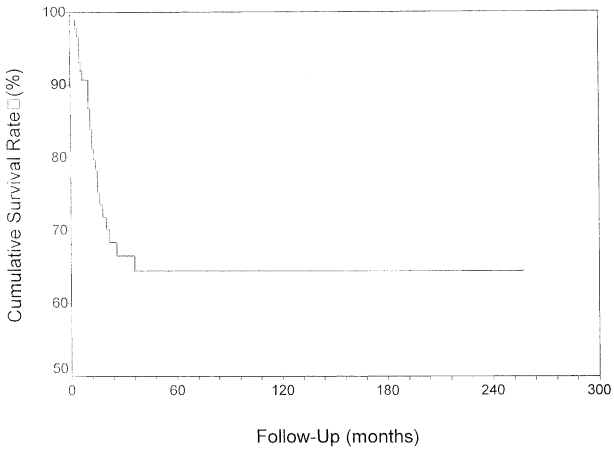

Figure 2. The survival plot of 96 cases of retinoblastoma in Taiwan. +: cases censored.

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the prime reason for the poor survival rate of some pediatric tumor patients. In our series, only 79.2% of patients were diagnosed before 3 years of age. The average age at diagnosis was 27.1 months, exceeding the corresponding age of 16–21.5 months among Western children.

In our series, presenting signs of leukocoria, buphthalmia, and strabismus were seen in 78.1%, 35.4%, and 12.5% of our patients. By the time the children came to the clinic, enucleation was urgently needed. Many parents are still reluctant to permit enucleation in their children and turn to Chinese herbal drugs or traditional therapy. Invariably, they wait until the condition is much worse before returning for treatment. By that time, orbital involvement is frequently found, which leads to a poor outcome. Because of the delayed diagnosis, many of our patients presented initially with buphthalmos (35.4%) or proptosis (16.7%). In a 1992 Japanese report, only 1.9% of patients presented with hazy cornea and 0.5% with exophthalmos.[2] In an extensive study of the presenting signs of retinoblastoma in New York, proptosis and buphthalmia were seen in only 0.5% and 0.7% of 1265 cases of retinoblastoma, while leukocoria and strabismus indicating an intraocular disease were the most commonly encountered signs.[10] In a study in Brazil, 50% of patients had extraocular disease when first admitted to an institution, and 26% of these sought medical attention more than 1 year after the onset of symptoms. It was concluded that the older age at diagnosis and lateness of referral were strong determinants for the outcome of extraocular retinoblastoma, a disease often indicating a mortality of more than 50%.[11] Delayed diagnosis and treatment frequently result in orbital, CNS, bone marrow, and liver involvement, often leading to fatal outcomes.

A positive family history had been reported in 5–10% of retinoblastoma patients.[10,12,13] However, only 3 of our patients (3.0%) had a positive family history. This could probably be attributed to the high mortality rate of retinoblastoma in children in past years. In earlier times, few affected children survived to reproductive age. Therefore, no "gene pools" have been established yet. In recent years, young educated parents are more willing to accept modern treatment promptly, and not rely on traditional therapy as previous generations did. Government-sponsored medical insurance was instituted in Taiwan since 1995, eliminating costly medical expenses for families. Parents now seldom hesitate to have sick children treated. Hopefully this will increase the survival rate of retinoblastoma patients in the future.

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