Clinical Presentation and Outcomes of Stage III or Stage IV Retinoblastoma in 80 Asian Indian Patients

Swathi Kaliki, MD; Anamika Patel, MD; Sadiya Iram, DO; Vijay Anand Reddy Palkonda, MD

ABSTRACT

Purpose: To describe the clinical features and outcomes of patients with stage III or IV retinoblastoma.

Methods: This was a retrospective study of 80 patients.

Results: Based on the International Retinoblastoma Staging System (IRSS), the tumors (n = 81) belonged to stage IIIa (n = 38, 47%), IIIb (n = 1, 1%), IVa2 (n = 10, 12%), IVb1 (n = 14, 17%), and IVb3 (n = 18, 22%). Of 80 patients, 42 (53%) were compliant to treatment and 38 (47%) were non-compliant. All 38 patients who were non-compliant to treatment died of the disease at a mean duration of 13 months from diagnosis. Of the 42 patients compliant to treatment, 22 (52%) died before completion of treatment. Twenty patients with stage III disease (25%) could complete the multimodal treatment and 17 (71%) were alive and well at a median follow-up duration of 77 months.

Conclusions: Compliant multimodality treatment is beneficial in patients with IRSS stage III disease. IRSS stage IV retinoblastoma has poor prognosis despite treatment.

[*J Pediatr Ophthalmol Strabismus*. 2017;54(3):177-184.]

INTRODUCTION

Primary orbital extension of retinoblastoma is rare in developed countries and is more commonly seen in developing countries. It occurs most often due to delayed diagnosis. In a review of 1,160 patients with retinoblastoma in the United States from 1925 to 1974, orbital retinoblastoma was seen in 110 (9%) patients.[1] With increased awareness of retinoblastoma in the developed countries, the incidence of orbital retinoblastoma has shown a decreasing trend. In a review of 1,265 cases of retinoblastoma diagnosed in the United States from 1960 to 1990, proptosis was noted in only 6 (< 1%) patients.[2] However, it continues to be of concern in some of the developing countries, with an incidence of 52% to 85%.[3-6] A study from China showed that the frequency of extraocular disease decreased from 50% in 1956 to 1961 to 2% in 2002 to 2006, suggesting a decreasing trend in its occurence.[7]

Orbital retinoblastoma is a poor prognostic factor resulting in a high mortality rate, with death occurring in 91% patients within 2 years of diagnosis.[8] There is a 10 to 27 times higher risk of metastasis to the central nervous system, cerebrospinal fluid, bone

From The Operation Eyesight Universal Institute for Eye Cancer, L.V. Prasad Eye Institute, Hyderabad, India.
Submitted: June 19, 2016; Accepted: September 28, 2016
Supported by The Operation Eyesight Universal Institute for Eye Cancer (SK) and Hyderabad Eye Research Foundation (SK), Hyderabad, India.
The authors have no financial or proprietary interest in the materials presented herein.
Correspondence: Swathi Kaliki, MD, The Operation Eyesight Universal Institute for Eye Cancer, L.V. Prasad Eye Institute, Hyderabad-500034, India. E-mail: kalikiswathi@yahoo.com
doi:10.3928/01913913-20161019-01

marrow, bone, and lymph nodes in patients with orbital retinoblastoma compared to those without orbital extension.[8-11] Although the survival rate of patients with orbital retinoblastoma has improved over the years with multimodal management, the overall prognosis is still poor. In this study, we report our experience with orbital retinoblastoma with or without metastasis and discuss the treatment strategies and outcomes in Asian Indian patients.

PATIENTS AND METHODS

Institutional review board approval was obtained for the study. A computerized database search was conducted for the diagnosis "Retinoblastoma" from January 1995 to December 2014 at The Operation Eyesight Universal Institute for Eye Cancer, L.V. Prasad Eye Institute. The medical records of all patients with retinoblastoma were reviewed. The cases with primary orbital extension of retinoblastoma at presentation were noted. The contact details of these patients were recorded from the medical records. A telephone interview was conducted with all parents of patients with primary orbital extension of retinoblastoma. Those patients who had a minimum follow-up of 2 years and those in whom an outcome (alive or dead) could be recorded, either from the medical record or by telephone interview, were included in the study. The patients with incomplete data, those lost to follow-up with unknown outcome, and those with secondary orbital tumor status following enucleation or other surgical procedures were excluded from the study.

The demographic data (age, gender, laterality) were recorded. Family history of retinoblastoma was noted. The presenting complaints and duration of symptoms were recorded. Examination under anesthesia, bone marrow aspiration, cerebrospinal fluid analysis, computed tomography (CT) of the orbit and brain, and photographic documentation were performed in all cases. The tumor extent (extrascleral extension, optic nerve extension, intracranial extension) based on examination under anesthesia and CT was recorded. All tumors were classified based on International Retinoblastoma Staging System (IRSS)[12] and American Joint Cancer Committee classification (AJCC) (7th edition).[13]

All cases underwent a thorough systemic examination by the medical oncologist. Multimodality treatment with chemotherapy, surgery, and radiotherapy was planned in all cases. Neoadjuvant high-dose systemic chemotherapy with vincristine (0.025 mg/kg, day 1), etoposide (12 mg/kg, days 1 and 2), and carboplatin (28 mg/kg, day 1) every 3 weeks was given as primary treatment. Chemotherapy was continued until the orbital component regressed (3 to 9 cycles were planned). Regression of the orbital component was confirmed by repeat CT of the orbit and brain. Secondary enucleation with polymethylmethacrylate implant was performed in eyes that became phthisical with no evidence of orbital tumor component. Orbital exenteration was performed if there was inadequate response to systemic chemotherapy with persistence of orbital tumor component. External beam radiotherapy (45 to 50 Gy) was given to the orbit. Adjuvant high-dose systemic chemotherapy (3 to 9 cycles to achieve a total of 12 cycles) was subsequently given. In patients with tumor cells in cerebrospinal fluid, additional intrathecal chemotherapy (either single drug methotrexate or triple drug combination of methotrexate, cytarabine, and hydrocortisone twice a week) was given until cerebrospinal fluid was negative for tumor cells.

The treatment details, histopathology details of the enucleated/exenterated specimen, and outcome (alive or dead) were recorded. If death of the patient was recorded by telephone interview, it was presumed to be due to retinoblastoma if there was no other contributory diagnosis. Autopsy reports were not available in any patient.

Statistical analysis was done with the two-tailed Fisher's exact test for non-parametric data to identify the factors predictive of poor prognosis and to assess the difference in outcome based on the IRSS. Statistical significance was defined as a P value of less than .05.

RESULTS

Of 1,592 cases of retinoblastoma, 142 (9%) had primary orbital extension of retinoblastoma with or without intracranial extension and local/systemic metastasis at presentation. Based on our inclusion criteria, 80 patients were included in the study. The demographic details are listed in **Table 1**. The mean age at presentation was 47 months (median: 38 months; range: 2 to 276 months). Family history of retinoblastoma was present in 3 (4%) patients.

The clinical details are listed in **Table 2**. Based on the IRSS, stage IIIa (n = 37, 46%) was most common. Based on the AJCC, T4b (n = 41, 51%) was most common. Multimodality treatment with che-

TABLE 1

Demographics of Patients With Orbital Extension of Retinoblastoma

Variable	No. (80 Patients, 81 Eyes)
Age at presentation (mo)	
Mean	47
Median	38
Range	2 to 276
Gender	
Male	45 (56%)
Female	35 (44%)
Laterality of tumor	
Unilateral	51 (64%)
Bilateral	29 (36%)
Orbital extension of retinoblastoma	
Unilateral	79 (99%)
Bilateral	1 (1%)

TABLE 2

Clinical Features of Patients With Orbital Extension of Retinoblastoma

Variable	No. (All Cases, 81 Eyes)
Tumor extension at presentation	
Extrascleral extension	47 (58%)
Optic nerve extension	63 (78%)
Intracranial extension	27 (33%)
RLN involvement	5 (6%)
Tumor cells in BM	16 (20%)
Tumor cells in CSF	18 (23%)
IRSS classification	
Stage III	39 (48%)
Stage IIIa	38 (47%)
Stage IIIb	1 (1%)
Stage IV	42 (52%)
Stage IVa1	0 (0%)
Stage IVa2	10 (12%)
Stage IVb1	14 (17%)
Stage IVb2	0 (0%)
Stage IVb3	18 (22%)
AJCC classification	
T4	81 (100%)
T4a	14 (17%)
T4b	41 (51%)
T4c	24 (30%)
T4d	2 (2%)

RLN = regional lymph nodes; BM = bone marrow; CSF = cerebrospinal fluid; IRSS = International Retinoblastoma Staging System; AJCC = American Joint Cancer Committee

motherapy (systemic and intrathecal), enucleation/exenteration, and external beam radiotherapy was planned in all cases (**Table 3**). Of these 80 patients, only 42 (53%) were compliant with treatment. All patients who were non-compliant with treatment died due to the disease at a median duration of 8 months (mean: 13 months; range: < 1 to 43 months) from diagnosis. Of 42 patients compliant with treatment, 22 (52%) died before completion of treatment. All patients with intracranial tumor extension, cerebrospinal fluid metastasis, and bone marrow metastasis on presentation died despite initiation of treatment. Factors predictive of poor life prognosis despite compliance with multimodal treatment included intracranial tumor extension at presentation (P = .001), tumor cells in cerebrospinal fluid (P = .001), IRSS stage IV disease (P = .0001), AJCC T4a disease (P = .009), or AJCC T4c disease (P = .009) (**Table 4**).

Of 24 patients with IRSS stage III disease who were compliant with treatment, 20 patients (25%) completed the multimodal treatment (12 cycles of high-dose systemic chemotherapy, enucleation/orbital exenteration, and external beam radiotherapy), whereas 4 (17%) died due to disease progression while receiving treatment. Of these 24 patients, 17 (71%) were alive and well at a median follow-up duration of 77 months (mean: 64 months; range: 24 to 133 months). In the group of 20 patients with stage III disease who completed treatment, 19 (95%) eyes became phthisical after a median of 6 cycles of neoadjuvant chemotherapy with no evidence of orbital component by clinical examination and repeat CT of the orbit (**Figure 1**). These phthisical eyes were enucleated and one eye had residual orbital component necessitating orbital exenteration. Histopathology features of these 20 cases included viable intraocular tumor (n = 8, 40%) with viable tumor in the optic nerve (n = 4, 20%), optic nerve cut end (n = 2, 10%), choroid (n = 4, 20%), ciliary body (n = 3, 15%), and scleral and extrascleral tissue (n = 3, 15%). Overall, 17 (71%) of 24 patients with IRSS stage III disease survived the disease (P = .0001) (**Table 5**).

TABLE 3

Treatment and Outcome of Patients With Orbital Extension of Retinoblastoma

Variable	No. (80 Patients, 81 Eyes)
Treatment	
Primary treatment with systemic chemotherapy	77 (95%)
Mean	6
Median	6
Range	3 to 10
Secondary enucleation	46 (57%)
Secondary orbital exenteration	4 (5%)
Adjuvant external beam radiotherapy	31 (38%)
Adjuvant systemic chemotherapy	33 (41%)
Mean	6
Median	6
Range	2 to 9
Compliant with treatment	
Yes	42 (53%)
No	38 (47%)
Outcome (n = 80 patients)	
Alive and well after completion of treatment[a]	17 (85%)
Death due to the disease despite completion of treatment[a]	3 (15%)
Death due to the disease in the midst of treatment[b]	22 (52%)
Death due to the disease due to non-compliance with treatment[c]	38 (100%)

[a]20 patients completed treatment as planned.
[b]Of 42 patients undergoing treatment, 22 died.
[c]38 patients were non-compliant with treatment.

Three (15%) patients with IRSS stage III disease died despite completion of treatment. The mean interval between completion of treatment and death was 2 months (median: 2 months; range: 1 to 3 months). All patients had optic nerve tumor extension and one case had additional extrascleral tumor extension at presentation. Two patients had undergone secondary enucleation and one patient needed orbital exenteration due to minimal response to neoadjuvant chemotherapy. On histopathology, one patient had no optic nerve/choroidal/scleral/extrascleral tumor extension, whereas others had massive choroidal invasion (n = 1) and extraocular extension and involvement of optic nerve transection (n = 1). Four (17%) patients with IRSS stage III disease died while receiving treatment. Two patients completed 6 cycles of neoadjuvant chemotherapy, underwent enucleation, and developed central nervous system disease within 1 month and died. A third patient showed minimal response to neoadjuvant chemotherapy, developed bone metastasis while receiving treatment, and died. A fourth patient received 10 cycles of neoadjuvant chemotherapy with minimal response, developed lymph node and bone metastasis while receiving treatment, and eventually died. Despite compliance with treatment, all patients with IRSS stage IV disease (n = 18) died before completion of treatment.

DISCUSSION

In the developing world, the frequency of orbital retinoblastoma ranges from 8% to 85%.[3-7,14-18] In our series, the frequency of orbital retinoblastoma with or without intracranial extension was 9%, and was less frequent compared to other parts of the developing world.[3-6,15-18] Most classification systems of retinoblastoma, including the Reese–Ellsworth classification and International Classification of Retinoblastoma, assess probability of globe preservation in intraocular disease and do not include extraocular disease in their classification system.[19-21] Various

TABLE 4

Details of Patients Compliant to Treatment[a]

Variable	Incomplete Treatment[b] (n = 22)	Complete Treatment (n = 20)	*P*
Tumor extension			
Extrascleral extension	13 (59%)	10 (50%)	.76
Optic nerve extension	19 (86%)	15 (75%)	.44
Intracranial extension	9 (41%)	0 (0%)	.001
Regional lymph nodes involvement	2 (9%)	1 (5%)	1.0
Tumor cells in bone marrow	6 (27%)	0 (0%)	.02
Tumor cells in cerebrospinal fluid	9 (41%)	0 (0%)	.001
IRSS classification			
Stage III	4 (18%)	20 (100%)	.0001
Stage IIIa	4 (18%)	19 (95%)	.0001
Stage IIIb	0 (0%)	1 (5%)	.49
Stage IV	18 (82%)	0 (0%)	.0001
Stage IVa1	0 (0%)	0 (0%)	1.0
Stage IVa2	6 (27%)	0 (0%)	.02
Stage IVb1	3 (14%)	0 (0%)	.23
Stage IVb2	0 (0%)	0 (0%)	1.0
Stage IVb3	9 (41%)	0 (0%)	.001
AJCC classification (7th edition)			
T4	22 (100%)	20 (100%)	1.0
T4a	2 (9%)	10 (50%)	.005
T4b	12 (55%)	10 (50%)	1.0
T4c	7 (32%)	0 (0%)	.009
T4d	1 (5%)	0 (0%)	1.0
Outcome			
Alive and well	0 (0%)	17 (85%)	.0001
Death due to the disease	22 (100%)	3 (15%)	

IRSS = International Retinoblastoma Staging System; AJCC = American Joint Cancer Committee

[a]Multimodal treatment with 12 cycles of high-dose systemic chemotherapy, enucleation or orbital extenteration, and external beam radiotherapy was advised in all patients. Additional intrathecal chemotherapy was done for patients with tumor cells in cerebrospinal fluid.

[b]Patients were compliant with treatment but died in the midst of treatment.

staging systems have been proposed to include extraocular retinoblastoma in the classification system.[22-24] The most widely accepted staging system is the IRSS proposed by Chantada et al., which classifies retinoblastoma based on clinically apparent disease.[12] In our series, the tumors belonged to stage III in 48% of cases and stage IV in 52%. Based on sub-classification, stage IIIa (47%) was the most common type.

In a study of patient outcome based on the IRSS in 533 patients, the probability of disease-free survival at 3 years was 0.97 for stage 0, 0.96 for stage I, 0.86 for stage II, 0.70 for stage III, and 0.05 for stage IV disease; thus, higher stages correlated with poorer prognosis.[25] In our study, only patients with orbital retinoblastoma with or without metastasis (stage III and IV) were included, and the survival rate of stage III patients who were compliant with treatment was 71% at a median follow-up period of 77 months. All patients with stage IV disease died despite multimodal treatment. The IRSS was predictive of the outcome of the disease ($P < .0001$).

Multimodal management with chemotherapy, surgery, and radiotherapy is recommended for orbit-

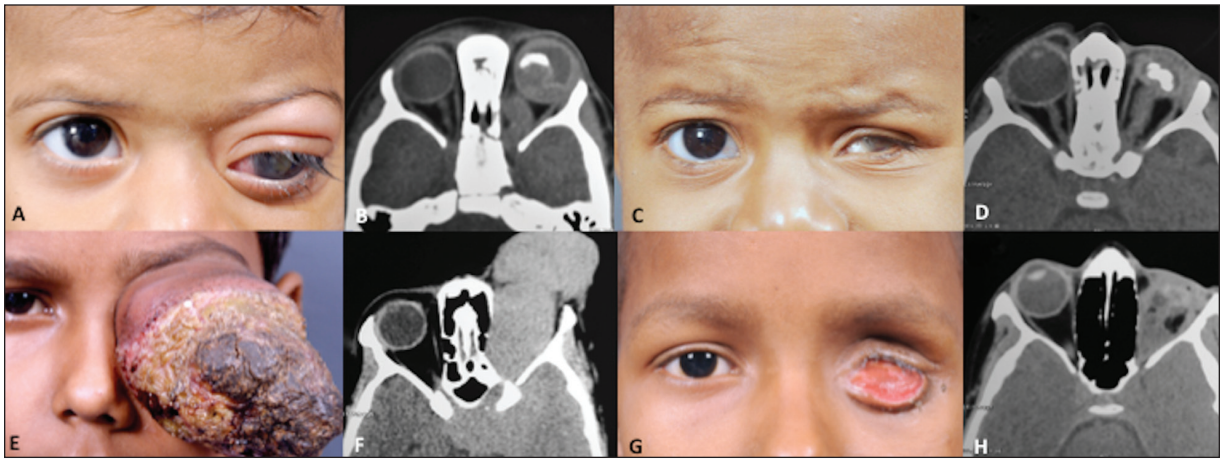

Figure 1. Patient with optic nerve extension of retinoblastoma. (A) A 12-month-old girl presented with leukocoria and proptosis. (B) On computed tomography (CT) of the orbit, there was retinoblastoma with optic nerve extension. (C) The globe became phthisical after 9 cycles of systemic chemotherapy. (D) CT orbit showed decrease in optic nerve thickening. The child underwent enucleation, external beam radiotherapy, and 3 more cycles of systemic chemotherapy and is doing well at 36 months of follow-up. (E) A 9-year-old boy with massive extraocular extension of retinoblastoma. (F) On CT of the orbit and brain, there was retinoblastoma with massive extrascleral extension, optic nerve extension, and intracranial extension. (G) The child showed dramatic response to 6 cycles of systemic chemotherapy with phthisis bulbi. (H) CT of the orbit and brain revealed minimal residual component of orbital lesion. The intracranial portion of the tumor had regressed. The child underwent orbital exenteration but died of the disease before completion of adjuvant systemic chemotherapy and radiotherapy.

TABLE 5

Outcome of Treatment Based on International Staging of Retinoblastoma System in Patients Compliant With Treatment

Variable	Stage III (n = 24)	Stage IV (n = 18)	*P*
Treatment[a]			
Complete	20 (83%)	0 (0%)	.0001
Incomplete[b]	4 (17%)	18 (100%)	
Outcome			
Alive and well	17 (71%)	0 (0%)	.0001
Death due to the disease	7 (29%)	18 (100%)	

[a]Multimodal treatment with systemic chemotherapy, surgery, and radiotherapy. Additional intrathecal chemotherapy in patients with tumor cells in cerebrospinal fluid.
[b]Patients died due to progressive disease while receiving treatment.

al retinoblastoma. Retinoblastoma is a chemosensitive tumor and various chemotherapy strategies have been tried in the management of orbital retinoblastoma. Carboplatin is specifically beneficial in orbital retinoblastoma because of increased penetration into brain and bone marrow, which are the two potential metastatic sites for retinoblastoma, and etoposide has a synergistic effect with platinum-based drugs.[26-28] Various combinations including etoposide, ifosfamide, cyclophosphamide, vincristine, doxorubicin, idarubicin, cisplatin, teniposide, and thiotepa have been studied, achieving a 3- to 5-year event-free survival rate of 53% to 84% in stage III disease.[26-31]

Sequential combination of high-dose chemotherapy, surgery, radiotherapy, and extended high-dose chemotherapy is beneficial in patients with orbital retinoblastoma. In a preliminary clinical trial of 6 patients with unilateral non-metastatic orbital retinoblastoma (IRSS IIIa), an event-free survival rate of 100% was achieved at a mean follow-up period of 32 months, using high-dose chemotherapy with vincristine, etoposide, and carboplatin (3 to 6 cycles) followed by sequential enucleation, orbital radiotherapy, and additional adjuvant chemotherapy (total: 12 cycles).[32] Orbital exenteration could be avoided in 100% of cases, and histopathology features included

viable intraocular tumor (n = 6, 100%) and scleral and extrascleral tumor extension (n = 4, 67%).[32] In another study, a similar treatment protocol was used in 28 patients with IRSS stage III disease and 19 patients were compliant with treatment, with a survival rate of 58% (n = 11) at a median follow-up period of 15 months.[33] Orbital exenteration could be avoided in 100% of cases, and histopathology features (n = 22) included viable tumor in the optic nerve (n = 8, 36%), cut end of optic nerve (n = 3, 14%), and extrascleral tumor extension (n = 5, 23%).[33] In our study, a uniform protocol of high-dose chemotherapy with vincristine, etoposide, and carboplatin followed by enucleation/orbital exenteration, external beam radiotherapy, and extended high-dose chemotherapy (total: 12 cycles) was used in all stage III patients. Twenty-four patients were compliant with treatment and 20 patients could complete the treatment, achieving an event-free survival rate of 71% (n = 17) at a median follow-up period of 77 months. Following chemotherapy, 19 (95%) eyes became phthisical and were enucleated, and one eye had residual orbital component necessitating orbital exenteration. Histopathology features included viable intraocular tumor (n = 8, 40%) with viable tumor in the optic nerve (n = 4, 20%), optic nerve cut end (n = 2, 10%), choroid (n = 4, 20%), ciliary body (n = 3, 15%), and scleral and extrascleral tissue (n = 3, 15%).

The survival of patients with stage IV disease is dismal, with a 5-year survival rate of 0% to 59%.[26-31,34-38] Patients with no central nervous system or cerebrospinal fluid metastasis have a better 5-year survival rate of 20% to 59% compared to patients with central nervous system or cerebrospinal fluid metastasis (0% to 14%), despite aggressive treatment with systemic chemotherapy, intrathecal chemotherapy, and cranial-spinal radiotherapy.[26-31,34-38] Additional autologous hematopoietic stem cell rescue has been shown to be beneficial in some patients with stage IV disease.[29,35,36] Leal-Leal et al. analyzed the effectiveness of five different chemotherapy regimens for metastatic orbital retinoblastoma in 81 patients and concluded that metastatic orbital retinoblastoma has a high mortality rate despite the use of different chemotherapy regimens, with a disease-free survival rate of 5% at 144 months of follow-up.[38] The median disease-free survival time was 6 months.[38] In our study, high-dose chemotherapy with vincristine, etoposide, and carboplatin was given in all patients with IRSS stage IV disease, with additional intrathecal chemotherapy in those with tumor cells in cerebrospinal fluid. The mortality rate was 100%, despite compliance with treatment. Cerebrospinal fluid became negative for tumor cells with intrathecal chemotherapy in 4 (44%) of 9 patients; however, they eventually succumbed to the disease.

Based on our results, the multimodal treatment regimen of high-dose chemotherapy with vincristine, etoposide, and carboplatin followed by enucleation or orbital exenteration, external beam radiotherapy, and extended high-dose chemotherapy (total: 12 cycles) was beneficial in patients with IRSS stage III disease, achieving an event-free survival rate of 71% at a median follow-up of 77 months. However, this treatment regimen was not beneficial in patients with IRSS stage IV disease. Although the search for an ideal treatment protocol for patients with metastatic orbital retinoblastoma continues, this study underscores the importance of early detection and compliance with the treatment to improve survival in these patients.

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