Postenucleation Adjuvant Chemotherapy With Vincristine, Etoposide, and Carboplatin for the Treatment of High-Risk Retinoblastoma

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Background: Analysis of 52 eyes with high-risk retinoblastoma managed with postenucleation adjuvant chemotherapy using vincristine sulfate, etoposide phosphate, and carboplatin showed no evidence of systemic metastasis in any case during a mean (range) follow-up of 66 (12-202) months.

Purpose: To determine the efficacy of postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin in the prevention of metastasis for patients with high-risk retinoblastoma.

Methods: Retrospective, nonrandomized, interventional case series of 52 eyes in 51 patients with high-risk retinoblastoma consisting of tumor invasion into the anterior segment, posterior uvea 3 mm or greater, postlaminar optic nerve, or any combination of posterior uvea and optic nerve involvement.

Results: Of 51 consecutive patients with high-risk retinoblastoma, there were 30 males (59%) and 21 females (41%), with a median age of 28 months at diagnosis. All 52 eyes were classified as group E. The main histopathologic risk factors included anterior segment invasion (7 [13%]), isolated massive posterior uveal invasion of 3 mm or greater (6 [12%]), isolated postlaminar optic nerve invasion (15 [29%]), or any posterior uveal invasion with any optic nerve involvement (24 [46%]). There was additional invasion into the sclera (3 [6%]) and extrascleral structures, including the orbit (1 [2%]). A single histopathologic high-risk factor was present in 32 eyes (62%), whereas 20 eyes (38%) manifested 2 or more high-risk characteristics. Based on previously published series, untreated high-risk retinoblastoma carries at least a 24% risk for metastatic disease. In the present series, using vincristine, etoposide, and carboplatin in all cases, there was no metastasis during a mean follow-up of 66 months (median [range], 55 [12-202] months).

Conclusions: Retinoblastoma with invasion into the postlaminar optic nerve and/or posterior uvea is at high risk for metastasis and death. In this study, postenucleation chemotherapy using vincristine, etoposide, and carboplatin was effective in preventing metastasis in every case (100%).

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RETINOBLASTOMA (RB) IS THE most common primary malignant intraocular tumor in the world, and the second most common primary intraocular malignancy in the Western Hemisphere, after uveal melanoma. It is estimated that 7202 to 8102 new cases of RB are diagnosed worldwide each year.[1] The mean age-adjusted incidence of RB in children aged birth to 4 years is 11.8 cases per million, with a 5-year survival of 96.5% in the United States.[2,3] On the basis of the mortality data and birth rates in corresponding continents, it is estimated that 3001 to 3376 children die of RB annually, with most deaths occurring in less developed areas, such as parts of Africa (death rate of 70%) and Asia (death rate of 42%).[1] Poor survival in these regions is due to late diagnosis, leading to advanced malignant neoplasms showing invasive features that are prone to micrometastatic disease.[1,4,5]

In RB, there are histopathologic factors that have been identified from enucleated eyes predictive of the development of metastatic disease and related mortality.[6-9] Patients demonstrating such risk factors are often given postenucleation adjuvant chemotherapy for protection from metastasis and improvement in survival.[10]

There is some controversy regarding the exact definition of high-risk histopathologic features[11,12] and further debate regarding the most effective chemotherapeutic protocol for treatment of such patients.[13,14] In this retrospective, noncomparative study, we investigated the role of a single chemotherapeutic protocol using vincristine sulfate, etoposide phos-

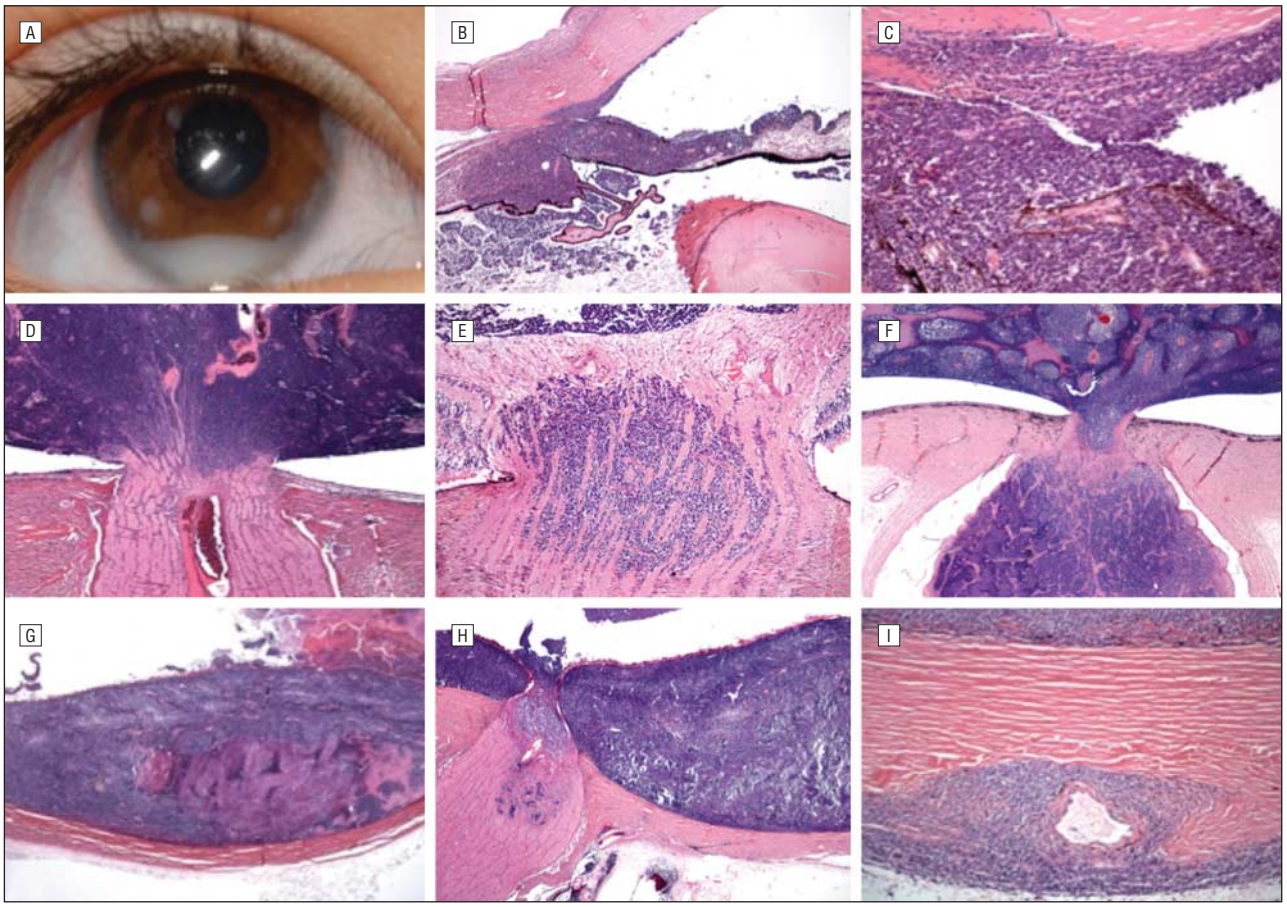

Figure. Successful management of high-risk retinoblastoma using vincristine, etoposide, and carboplatin, illustrating the various degrees of invasive malignancy. Anterior chamber invasion of retinoblastoma with pseudohypopyon (A) and iris, ciliary body, and trabecular meshwork invasion on ×10 magnification (B) and ×40 magnification (C). Tumor invasion into the optic nerve in the prelaminar (D), laminar (E), and postlaminar (F) regions. Solitary massive choroidal invasion of 16 mm (G), combined massive chorioidal and optic nerve invasion (H), and massive choroidal invasion with extrascleral extension (I).

phate, and carboplatin (VEC) in the prevention of RB metastasis in high-risk cases following enucleation.

METHODS

This study was a retrospective, nonrandomized, noncomparative, interventional case series. Institutional review board approval was obtained. The medical records of all patients with RB managed with enucleation on the Ocular Oncology Service at Wills Eye Institute in Philadelphia from January 1, 1994, through December 31, 2010, were reviewed. The histopathologic features of the enucleated specimen were reviewed. High-risk histopathologic features were defined as the presence of 1 or more of the following features: tumor invasion into the anterior segment, posterior uvea of 3 mm or greater, postlaminar optic nerve involvement, or any posterior uveal invasion with any optic nerve involvement (**Figure**). Optic nerve invasion was classified as prelaminar, at the lamina cribrosa, postlaminar, and/or to the site of transection. Additional invasion into the sclera and extrascleral structures, including the orbit, were recorded. Patients with high-risk RB who received postenucleation adjuvant chemotherapy with VEC, and with a minimum follow-up of 1 year, were included in this study. High-risk RB patients treated with chemotherapeutic agents other than VEC and patients enrolled in Children's Oncology Group study ARET-0332 were excluded.

The medical records were reviewed for clinical and histopathologic findings. The demographic data included age at diagnosis (months), sex, and race. Genetic results (germline or somatic) for RB were recorded when available. The hereditary pattern (sporadic or familial) and prior local or systemic treatment for RB was noted. The presenting symptoms, duration of symptoms (days), and visual acuity were recorded. The tumor laterality (unilateral or bilateral), total number of tumors per eye, International Classification of Retinoblastoma group, Reese-Ellsworth classification, intraocular pressure (milimeters of mercury by Schiotz tonometry), and status of the anterior chamber, iris, ciliary body, optic nerve, choroid, and vitreous were noted. Each tumor was measured for greatest basal dimension (millimeters), thickness (millimeters), and proximity to the optic disc and foveola (millimeters). Clinical features of anterior chamber seeding, hyphema, iris neovascularization, vitreous seeding, vitreous hemorrhage, subretinal seeding, tumor calcification, retinal detachment, neovascularization of the optic disc, neovascularization elsewhere, optic disc edema, and choroidal invasion were noted. All findings were documented by large fundus drawings, fundus photography with RetCam camera (Massie Industries, Dublin, California), fluorescein angiography, and ultrasonography.

The initial treatment and reason for enucleation were recorded. The eyes were sent for histopathologic assessment, and the findings were reviewed for high-risk features. Other histopathologic findings noted were growth pattern (exophytic, endophytic, or combined exophytic-endophytic), tumor location (quadrant), presence of necrosis and dystrophic calcification, depth and lateral extent of choroidal invasion (millimeters), depth of postlaminar optic nerve invasion (millimeters), and tumor differentiation.

Table 1. Postenucleation Adjuvant Chemotherapy in the Treatment of High-Risk Retinoblastoma[a]

	Chemotherapeutic Regimen		
Day	Vincristine, 0.05 mg/kg	Etoposide Phosphate, 5 mg/kg	Carboplatin, 18.6 mg/kg
0	x	x	x
1	. . .	x	. . .

[a]The regimen was planned for 4 to 6 cycles.

In patients with high-risk RB, postenucleation adjuvant therapy by intravenous VEC was administered. Dosage (**Table 1**), number of cycles, and complications of VEC systemic chemotherapy were recorded. After VEC chemotherapy, metastatic evaluation included history and physical examination, computed tomography, and/or magnetic resonance imaging of the orbit and brain repeated at 6-month intervals until age 5 years and yearly thereafter. Systemic findings from the metastatic evaluation, duration of follow-up (months), and the final systemic outcome (alive without metastasis, alive with metastasis, alive with second malignant neoplasm, dead from metastasis, dead from second malignant neoplasm, or dead from other causes) were recorded.

RESULTS

Of 406 eyes enucleated for RB during this period, 66 eyes (16.3%) had 1 or more high-risk histopathologic features predictive of systemic metastasis. Of these 66 eyes, 52 eyes (79%) of 51 patients were treated with VEC with a minimum follow-up of 1 year and were included in this study. The demographic data are listed in **Table 2**.

The clinical features at presentation are listed in **Table 3**. Five patients (10%) had a history of previous intraocular surgery, which included vitrectomy and sclera buckle (n=2), vitrectomy alone (n=2), and anterior chamber tap (n=1).

The classification of each eye using Reese-Ellsworth classification revealed 51 group Vb (98%) and 1 group Va (2%). According to the International Classification of Retinoblastoma, all 52 eyes (100%) were group E.

Enucleation was preceded by systemic chemotherapy in 4 patients (8%), external beam radiotherapy in 1 (2%), plaque radiotherapy in 1 (2%), and subconjunctival carboplatin in 1 (2%). The reason for enucleation included massive tumor involving 50% or more of the vitreous with no visual potential in 45 eyes (87%), recurrence after chemoreduction in 4 (8%), recurrence after external beam radiotherapy in 1 (2%), recurrence after plaque in 1 (2%), and necrotic tumor with orbital inflammation in 1 (2%).

The histopathologic features are listed in **Table 4**. All cases with scleral and/or extrascleral invasion had additional postlaminar and/or massive choroidal invasion. High-risk features were noted in the right eye in 24 patients (47%), left eye in 26 (51%), and both eyes in 1 (2%). The optic nerve stump at enucleation was a mean length of 15 mm (median [range], 14 [8-22] mm).

All 51 patients received intravenous chemotherapy using VEC standard dose (Table 1). The mean number of VEC cycles per patient was 6 (median [range], 6 [4-6]). There were 4 patients (8%) who received 4 cycles of VEC, and the remaining patients received 6 cycles of VEC. The only chemotherapy-related complication was pneumonia in 1 patient (2%). There was no case of etoposide-related leukemia. One patient (2%) had extrascleral extension along with the high-risk feature of combined optic nerve and choroidal invasion, for which chemotherapy and additional orbital external beam radiotherapy was given after enucleation.

All patients (100%) were followed up for more than 1 year, and the mean duration of follow-up after adjuvant chemotherapy was 66 months (median [range], 55 [12-202] months). Of 51 patients, 43 (84%) had more than 2 years' follow-up, 41 (80%) had more than 3 years' follow-up, and 22 (43%) had more than 5 years' follow-up. The incidence (95% confidence interval) of metastasis was 0% (0%-6%) at 1 year, 0% (0%-7%) at 3 years, and 0% (0%-14%) at 5 years. There was no second malignant neoplasm or death in any case.

Table 2. Demographic Features of 51 Patients Receiving Treatment for High-Risk Retinoblastoma[a]

Demographic Feature	Value
Age	
Mean (median [range]), mo	42 (28 [4-368])
≤12 mo	9 (18)
>12 mo	42 (82)
Sex	
Male	30 (59)
Female	21 (41)
Race/ethnicity	
White	35 (69)
African American	6 (12)
Hispanic	10 (20)
Heredity	
Sporadic	49 (96)
Familial	2 (4)
Genetic testing[b]	
Somatic	9/14 (64)
Germline	5/14 (36)
Laterality	
Unilateral	32 (63)
Bilateral	19 (37)
Eye with high-risk features	
Right	24 (47)
Left	26 (51)
Both	1 (2)

[a]Data are given as number (percentage) of patients unless otherwise specified.
[b]Genetic testing was available in only 14 of 51 patients.

COMMENT

In nations with advanced medical care, the incidence of metastasis in children with RB is less than 10%.[15] The risk for metastasis greatly increases with histopathologic evidence of high-risk features. In a study from our institution, Honavar and associates[10] found that untreated patients with high-risk histopathologic features developed metastases in 24% of cases, often leading to death. This risk could be much greater in undeveloped nations where

Table 3. Clinical Features at Presentation of 51 Patients Receiving Treatment for High-Risk Retinoblastoma

Clinical Feature	Value[a]
Presenting symptom	
Leukocoria	33 (63)
Strabismus	10 (19)
Decreased vision	6 (12)
Blind painful eye	3 (6)
Red eye	2 (4)
Heterochromia	2 (4)
Duration of symptoms, mean (median [range]), days	114 (38 [0 to 730])
History of previous intraocular surgery	
Anterior chamber tap	1 (2)
Vitrectomy with or without scleral buckle	4 (8)
Visual acuity	
Fix and follow	15 (29)
No fix or follow	37 (71)
Intraocular pressure, mean (median [range]), mm Hg	22 (21 [<4 to 50])
Clinical sign	
Secondary glaucoma	23 (44)
Anterior chamber seeding	16 (31)
Neovascularization iris	22 (42)
Hyphema	4 (8)
Vitreous seeds	37 (71)
Subretinal seeds	12 (23)
Subretinal fluid	16 (31)
Vitreous hemorrhage	8 (15)
Basal diameter of largest tumor, mean (median [range]), mm	20 (21 [10 to 24])
Ultrasonographic thickness, mean (median [range]), mm	12 (13 [3 to 18])

[a] Data are given as number (percentage) unless otherwise indicated. Total may not equal 100% because 4 patients had more than 1 presenting complaint.

Table 4. Histopathologic Features of 51 Patients Receiving Treatment for High-Risk Retinoblastoma

Histopathologic Feature	No. (%) of Patients
Growth pattern	
Endophytic	12 (23)
Exophytic	6 (12)
Both endophytic and exophytic	27 (52)
Diffuse infiltrating	7 (13)
Tumor differentiation	
Well differentiated	5 (10)
Moderately differentiated	0
Poorly differentiated	43 (83)
Undifferentiated	4 (8)
Necrosis	45 (87)
Dystrophic calcification	48 (92)
Main histopathologic high-risk features	
Anterior segment invasion[a]	7 (13)
Isolated posterior uveal invasion ≥3 mm	6 (12)
Isolated postlaminar optic nerve invasion[b]	15 (29)
Any posterior uveal and optic nerve invasion	24 (46)
Total histopathologic high-risk features	
Anterior segment	7 (13)
MUI with no ONI	6 (12)
MUI with nonpostlaminar ONI	4 (8)
Combined MUI and postlaminar ONI	3 (6)
Postlaminar ONI and no UI	15 (29)
Postlaminar ONI and nonmassive UI	2 (4)
Combined nonmassive UI and nonpostlaminar ONI	15 (29)
Other features	
Iris infiltration	16 (31)
Ciliary body infiltration	12 (23)
Prelaminar optic nerve invasion	6 (12)
Laminar optic nerve invasion	6 (12)
Scleral infiltration	3 (6)
Extrascleral infiltration	1 (2)

Abbreviations: MUI, massive posterior uveal invasion; ONI, optic nerve invasion; UI, posterior uveal invasion.
[a] All patients with anterior chamber seeding had iris and/or ciliary body infiltration.
[b] One patient had invasion up to optic nerve surgical transection.

high-risk features are more extreme, with macroscopic rather than microscopic invasion. The use of postenucleation adjuvant chemotherapy has been recommended for patients with high-risk features on histopathologic analysis to eradicate presumed micrometastases before they are clinically manifest and to reduce ultimate death.[10,13]

There is considerable controversy in the definition of risk factors for RB metastasis based on histopathologic features. There is also debate regarding the most effective treatment strategies for affected patients. In previous studies, histopathologic risk factors for RB metastasis included anterior segment invasion, massive uveal invasion (defined as ≥2 mm), scleral infiltration, extrascleral invasion, postlaminar optic nerve invasion, and invasion to the site of surgical transection of the optic nerve.[12,16,17] Following enucleation, the incidence of high-risk histopathologic features has varied from 7% to 9% for anterior segment invasion,[8,17] 12% to 42% for choroidal invasion,[5,7-9,17] 8% to 12% for scleral invasion,[5,8,9,17] 2% to 20% for extrascleral invasion,[5,8,9,17] 6% to 28% for invasion of the postlaminar optic nerve,[5,6,8,9,17,18] and 1% to 38% for involvement of the optic nerve to surgical transection.[5-9,17,18]

In a recent comprehensive report on histopathologic findings following enucleation in 297 untreated eyes of RB, Eagle[16] identified high-risk features in 55 eyes (18.5%). In these 55 eyes, these features included massive (defined as ≥3 mm) uveal invasion with no optic nerve invasion (8 [14.5%]), massive uveal invasion with prelaminar optic nerve invasion (7 [12.7%]), massive uveal invasion with postlaminar optic nerve invasion (10 [18.2%]), postlaminar optic nerve invasion with no uveal invasion (18 [32.7%]), postlaminar optic nerve invasion with nonmassive uveal invasion (3 [5.5%]), combined nonmassive uveal invasion without postlaminar optic nerve invasion (2 [3.6%]), and anterior segment involvement (8 [14.5%]).

According to Chantada and associates,[12] there are world disparities in risk definition and management of RB. On the basis of our previous experience, we believe that anterior segment invasion, massive posterior uveal invasion of 3 mm or greater, postlaminar optic nerve invasion, or a combination of any degree of posterior uveal and optic nerve invasion poses a risk; therefore, we include these 4 factors in our definition as high risk. The significance of isolated anterior segment involvement remains debatable, but we have previously witnessed metastasis in such cases, so this was included as a factor.[10] Some authors[5,13] have suggested that anterior segment in-

Table 5. The Role of Adjuvant Chemotherapy in Preventing Metastasis in High-Risk Retinoblastoma: Published Literature[a]

Source, y	Chemotherapeutic Drugs Used	No. of Patients	Metastasis, No. (%) of Patients
Howarth et al,[24] 1980	V, Cy	14	1 (7)
Wolff et al,[25] 1982	V, Cy	41	6 (12)
Keith,[26] 1989	V, Cy	26	1 (4)
Zelter et al,[27] 1991	V, D, Cy	24	8 (33)
Khelfaoui et al,[9] 1996	Variable[b]	75	4 (6)
Schvartzman et al,[28] 1996	V, D, Cy	29	4 (14)
Namouni et al,[29] 1997	V, Cy, C	6	1 (17)
Mustafa et al,[30] 1999	V, D, Cy	27	5 (19)
Uusitalo et al,[31] 2001	Variable[b]	11	1 (9)
Honavar et al,[10] 2002	V, D, Cy or V, E, C	46	2 (4)
Chantada et al,[13] 2004	V, D, Cy or V, I, Cy	24	4 (17)
Cuenca et al,[32] 2009	Variable[b]	32	6 (19)
Present study, 2010	V, E, C	52	0

Abbreviations: C, carboplatin; Cy, cyclophosphamide; D, doxorubicin hydrochloride; E, etoposide phosphate; I, idarubicin hydrochloride; V, vincristine sulfate.

[a] The number of patients and overall results in some of the studies may be different from the data compiled in the table because only relevant and comparable data are tabulated.

[b] More than 2 regimens were used.

volvement and isolated choroidal invasion are not risk factors for metastasis. The other major source of variation is related to the definition of massive choroidal invasion.[12] In a survey by the International Retinoblastoma Staging Working Group, composed of 58 members from 24 countries in 4 continents, at least 5 different criteria have been reported, including full-thickness choroidal invasion with at least 1 cell adherent to the sclera, full invasion greater than 50% of the thickness of the choroid or more than 1 cluster, deep invasion greater than 50% of the thickness of the choroid, diffuse choroidal invasion of more than 3 clusters, and invasion greater than 3 mm in the largest dimension or tumor noted on gross examination. For consensus in that group, the criterion for massive choroidal invasion was agreed to be maximum diameter (thickness or width) of tumor at 3 mm or greater.[12]

A search for the most effective chemotherapy for RB has been under way since the 1950s.[19-22] Previous studies on adjuvant chemotherapy for high-risk RB have revealed several protocols, including agents such as vincristine, doxorubicin hydrochloride, cyclophosphamide, etoposide, cisplatin, carboplatin, and cyclosporine.[14,23] As shown in **Table 5**, postenucleation adjuvant chemotherapy regimens have varied over the years. The metastatic rate has ranged from 4% in a study of 26 cases in which vincristine and cyclophosphamide were used to 33% in a study of 24 cases in which vincristine, cyclophosphamide, and doxorubicin were used.[26,27] Mustafa and associates[30] studied the effect of vincristine, doxorubicin, and cyclophosphamide in high-risk RB and found distant metastasis and subsequent death in 19% of cases. They concluded that alternative chemotherapeutic agents should be considered for patients with such high-risk features. Uusitalo and associates[31] studied 129 patients using variable regimens and concluded that chemoprophylaxis was beneficial in patients with tumor extending beyond the lamina cribrosa. Honavar and colleagues[10] conducted a retrospective, nonrandomized comparative study of 80 patients with high-risk RB, in which 58% of patients received adjuvant therapy and 42% did not receive adjuvant therapy for various reasons. A significant difference was found in the rate of metastasis between the group that had received adjuvant therapy (4%) and the group that had not (24%). The beneficial effect of adjuvant therapy was statistically significant in subgroups with massive choroidal infiltration and/or postlaminar optic nerve invasion.

In our study, we used a standard multiagent chemotherapeutic protocol of VEC in every case of high-risk RB. With this regimen, there was no case of metastasis or death during the mean follow-up period of more than 5 years. These same chemotherapeutic agents have proven effective as neoadjuvant chemotherapy.[33] On the basis of our results, VEC is impressively effective for postenucleation high-risk RB in the prevention of systemic metastases, thereby improving survival.

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