Published in final edited form as:

Pediatr Blood Cancer. 2009 March ; 52(3): 351–356. doi:10.1002/pbc.21845.

Predictive Factors Of Invasion in Eyes with Retinoblastoma Enucleated After Eye Salvage Treatments

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Abstract

Background—The impact of chemotherapy, focal therapies, radiation and co-existing ocular morbidities on histology of eyes with retinoblastoma enucleated following chemoreduction is not well known.

Procedure—25 eyes (23 patients) with retinoblastoma enucleated after failing eye-salvage therapy were evaluated. Reasons for enucleation (tumor progression, subretinal or vitreous seeds) and co-morbid conditions (neovascular glaucoma, cataract, vitreous hemorrhage and retinal detachment) were documented. All specimens were reviewed for evidence of ciliary body, choroidal, optic nerve, and scleral invasion.

Results—The median age at diagnosis was 14 months (range, 1 to 37 months). Twenty eyes were classified as Reese-Ellsworth Group IV-V at diagnosis. Twenty-four eyes had recurrent disease at enucleation; one eye was enucleated for neovascular glaucoma and vitreous hemorrhage. Co-existing ocular morbidities at enucleation included vitreous hemorrhage (n=6), retinal detachment (n=9), neovascular glaucoma (n=9) and cataracts (n=3). Histologic findings included choroidal invasion (n=7), ciliary body invasion (n=4), optic nerve invasion (n=6) and scleral invasion (n=3). The median time from diagnosis to enucleation was 11 months. No treatment rendered prior to enucleation significantly increased the likelihood of invasion. However, co-existing retinal detachment and vitreous hemorrhage significantly increased the likelihood of optic nerve invasion (p=0.014 and p=0.011, respectively). Prolonged time to

enucleation was significantly associated with the likelihood of choroidal ($p=0.010$) and ciliary body ($p=0.021$) invasion as well as invasion of multiple sites.

Conclusion—In eyes with retinoblastoma enucleated after chemoreduction, co-existing ocular morbidities and time to enucleation are predictive of extra-retinal extension.

Keywords

Retinoblastoma; Chemoreduction; Focal treatments; Invasion

INTRODUCTION

Treatment of retinoblastoma aims to save life and preserve vision, and thus needs to be individualized. Factors that need to be considered include laterality of the disease, potential for vision, and intraocular and extraocular staging. The majority of patients with unilateral retinoblastoma are treated with enucleation. For patients with bilateral disease (or early stage unilateral), standard of care includes a judicious use of chemotherapy combined with aggressive focal consolidation techniques with the goal of preserving vision and delaying or avoiding radiation and enucleation. (1;2) The decision to enucleate can often be delayed until the response to therapy and the potential visual outcome have been assessed. Using this approach, ocular salvage rates of 70-75% can be achieved.(1)

Despite these efforts, 30-40% of the eyes in patients with bilateral disease are eventually enucleated. Histopathological examination of enucleated eyes shows different degrees of tumor regression and maturation.(3-5) However, there is limited information on the significance of active disease at the time of enucleation; up to one-third of enucleated specimens may show pathological risk factors of extraocular dissemination, although the overall outcome does not seem to be affected. (3-6)

Significant damage to the ocular coats may occur as a result of focal treatments. Disruption of the normal eye structures may facilitate the dissemination of retinoblastoma; this is particularly relevant considering that tumors failing therapy may have a more aggressive clinical behavior. Chemoreduction and focal treatments might be selecting chemoresistant clones while facilitating tumor invasiveness due to disruption of the blood-eye barrier. To better describe the changes occurring in the eyes of children with retinoblastoma failing eye salvage treatments, and to evaluate the factors that increase the risk of high-risk pathology, we reviewed of a series of enucleated eyes after therapy.

METHODS

Twenty-five eyes from 23 patients with retinoblastoma who failed chemoreduction and focal treatments were enucleated at St. Jude Children's Research Hospital between January 1999 and February 2004. Institutional Review Board approval was obtained for this retrospective study.

Patient data collected included demographics, laterality, Reese-Ellsworth group at diagnosis, chemotherapy, local treatment, external-beam radiation therapy (EBRT), and the reason for enucleation. All specimens were reviewed by two of the investigators (J.D.K. and J.M.), and

the following histological parameters were documented: percentage of eye involvement by tumor, percentage of necrosis, rosette formation, nuclear atypia, calcification and invasion of choroid, sclera, ciliary body, anterior chamber, or optic nerve. Choroidal invasion was considered to be massive when tumor was invading the full thickness of the choroid up to the sclera. Co-morbid conditions reviewed included the presence of retinal detachment, vitreous hemorrhage, cataract and neovascular glaucoma.

Demographic characteristics for the 23 patients and the 25 eyes (80% R-E IV-V) are shown in Supplemental Table I, and treatment characteristics in Supplemental Table II. The majority of patients (n=19; 83%) received 8 cycles of chemotherapy. Most patients (n=20; 87%) received a two-drug regimen with vincristine and carboplatin. Nearly half of the enucleated eyes (n=12; 48%) had received EBRT at doses of 44 Gy (n=1) or 45 Gy (n=11). Focal treatments included cryotherapy (14 eyes; 56%), transpupillary thermotherapy (TTT) (16 eyes; 64%), and brachytherapy (4 eyes; 16%). Most eyes received chemotherapy with focal treatments (no EBRT) (n=10; 40%) or chemotherapy with both EBRT and focal treatments (n=9; 36%). All patients responded to initial chemotherapy; progressive disease requiring EBRT occurred after discontinuation of chemotherapy in all cases.

Fisher's exact test was used to explore associations between treatment (EBRT, focal treatments) and reasons for enucleation and between invasive disease and co-morbid conditions. Times to enucleation were compared among groups using the exact Wilcoxon rank sum test. Exact Kruskal-Wallis tests were used to explore the association between invasive disease and number of co-morbid conditions (the number of conditions was considered an ordinal factor). No adjustments were made for multiple comparisons in this exploratory study.

RESULTS

The median time from diagnosis to enucleation was 11 months (range 3 to 31 months); it was 14 months (range, 10-25 months) for the 5 eyes with RE grouping II or III and 10 months (range, 3-31 months) for the 20 advanced eyes. Clinical findings at the time of enucleation are shown in Table I. Twenty-four of 25 eyes (96%) were enucleated for recurrence, but 23 of them had associated co-morbidities. One eye was enucleated for reasons other than disease activity; this eye had glaucoma, retinal detachment, hemorrhage and phthisis, and pathology showed an acellular calcified mass attached to sclera and choroid. There was evidence that more eyes enucleated for glaucoma had received EBRT ($p=0.033$); 64% of eyes that received EBRT had glaucoma at the time of enucleation compared to 15% of eyes that did not receive EBRT (Supplemental Table III). Likewise, there was a trend towards the presence of vitreous hemorrhage in patients treated with EBRT; 5 of 11 eyes (45%) compared to 1 in 13 eyes (8%) in patients without EBRT ($p=0.061$).

Table II summarizes the histological findings. The tumors appeared largely necrotic, with varying degrees of dystrophic calcification. Rosette formation and nuclear atypia were present in 44% and 28% of the cases, respectively. Some degree of invasion of the ocular coats or the optic nerve was present in 44% of the enucleated eyes. Invasion of the choroid,

optic nerve, ciliary body and sclera was present in 28%, 24%, 16%, and 12% of the cases respectively. Choroidal invasion was present in 7 enucleated eyes; it was focal in 2 cases, massive in 2, and in 3 cases occurred in an area where the ocular coats were thinned by focal treatments, whereby the tumor reached the sclera despite small choroidal invasion. Invasion of the optic nerve was seen in 6 cases; it was prelaminar in 4 and postlaminar in 2. In addition to active tumor, most eyes had associated co-morbid conditions; histological documentation of retinal detachment and vitreous hemorrhage were present in 40% and 28% of the cases, respectively. There were no differences in histological findings between eyes that did or did not receive EBRT (data not shown). Four patients received adjuvant chemotherapy due to high-risk histopathology seen in the enucleated eyes. No recurrences occurred, and all patients are alive and without disease.

There was evidence that longer times to enucleation were associated with invasive disease (Table III). The median time from diagnosis to enucleation for patients with ciliary body invasion (n=4) was 24 months, compared to 10 months for those patients without ciliary body invasion; this difference was statistically significant ($p=0.021$). Patients with choroidal invasion also had longer times to enucleation ($p=0.010$). There were only 3 patients with scleral invasion but these patients had longer times to enucleation (median, 20 months) compared to those without scleral invasion (median, 10 months). We also summed the number of invasion sites (choroid, ciliary body, sclera, and optic nerve) and documented the median times to enucleation according to the number of invasive sites. Although few patients had multiple sites of invasion, the median times to enucleation increased for patients with 1, 2, and 3 invasive sites (7.8 months vs. 17.0 months vs. 25.4 months respectively).

As we observed invasive disease to be associated with longer times to enucleation, we wanted to explore associations between co-morbid conditions and times to enucleation, postulating that eyes with more co-morbid conditions would be those eyes that had delayed enucleation. Co-morbid conditions of interest included cataracts, glaucoma, retinal detachment, and vitreous hemorrhage. Table IV shows the results of these analyses. Significant differences in times to enucleation were not observed with respect to various co-morbid conditions. Although eyes with cataracts had relatively long times to enucleation (median, 17 months), there were only 3 eyes with cataracts. The median time to enucleation was longer for eyes with glaucoma (medians, 20 months vs. 10 months), but the difference was not statistically significant ($p=0.155$). We summed the number of co-morbid conditions observed for each eye. We compared times to enucleation between eyes with 0 or 1 co-morbid conditions to eyes with 2 or more co-morbid conditions; although eyes with more co-morbid conditions had longer times to enucleation, the difference was not statistically significant (16 months vs. 10 months) ($p=0.38$). There was no evidence that treatment received (EBRT or focal therapies) increased the likelihood of invasive disease (data not shown).

There was evidence of associations between some co-existing morbidities and invasive disease (Table V). Eyes with vitreous hemorrhage and retinal detachment were more likely to have optic nerve invasion ($p=0.011$ and $p=0.014$, respectively). Although there were only 3 eyes with cataracts, two of those eyes also had scleral invasion. There was evidence that

the number of co-morbidities in a given eye was associated with optic nerve invasion ($p=0.020$); eyes with optic nerve invasion were more likely to have more co-morbidities.

DISCUSSION

The last two decades have witnessed major changes in the management of retinoblastoma. Treatments have become increasingly sophisticated, and improvements in technology and cancer care have facilitated a more conservative approach to the management of intraocular disease. Despite this progress, approximately 20-30% of the eyes in patients with bilateral disease are enucleated. (1;7-10) Importantly, by the time enucleation occurs, the tumor has progressed despite aggressive systemic and focal treatments, which could potentially further disrupt the normal eye anatomy. Thus, evaluation of the remaining disease activity needs to be performed and interpreted considering this unique context.

In order to define tumor and treatment related changes, and factors predictive of extraretinal extension, we investigated the histological changes occurring in eyes with retinoblastoma that were enucleated after conservative treatment. Clinically detectable vitreoretinal complications are reported to occur in less than 10% of patients with retinoblastoma, but those complications appear to be more often seen when systemic chemotherapy is combined with external beam radiation, cryotherapy, and local chemotherapy. (11) In our series, all the eyes but one were enucleated for disease progression, but importantly, 92% of them had associated co-morbidities that influenced the decision to enucleate. The vitreoretinal complications of therapy cannot thus be underestimated as they likely influence the decision to enucleate. While the advanced intraocular disease at diagnosis is most likely responsible for the development of these associated problems, many elements used in treatment likely disrupt normal eye anatomy and physiology. In our series, eyes with glaucoma or vitreous hemorrhage were more likely to have received EBRT. Neovascularization glaucoma and bleeding are common causes for enucleation in patients with uveal melanoma treated with radiation, (12-14) and a similar phenomenon seems to occur in retinoblastoma. (3;15)

A more aggressive behavior may be expected from neoplasms progressing after such intensive treatments, and a careful evaluation of the histological findings must be performed. At a cellular level, one-third of the tumors displayed nuclear atypia, which could be interpreted as a sign of a more aggressive disease, and rosette formation was found in approximately 40% of the cases. The presence of rosettes has been traditionally considered to be a sign of tumor differentiation in retinoblastoma; this finding is commonly seen in eyes with retinoblastoma enucleated after therapy, and it is usually interpreted as a sign of response to therapy. (3-5) However, in our series, 7 of the 11 cases with obvious rosette formation had less than 40% necrosis, and nuclear atypia was present in 4 of them. Stannard et al (16) found rosettes to be related with tumors with less invasive features, but recent data suggests that rosette formation is not a hallmark of retinoblastoma differentiation, it rather reflects extensive cell-cell contacts between retinoblastoma cells in both early-stage (differentiated) and late-stage (dedifferentiated) tumors. (17)

The more important reason for a careful evaluation of the intraocular extent of the tumor in the enucleated specimen is for the assessment of the risk of extraocular dissemination. In our

series, 44% of the enucleated eyes displayed signs of invasiveness, such as involvement of the choroid (28%), optic nerve (24%), ciliary body (16%) or sclera (12%). Four patients received adjuvant chemotherapy for these reasons, and no metastatic disease eventually developed in any of the cases. While the clinical significance of extraocular extension is obvious, there is no uniform agreement on the prognostic implications of the different histologic characteristics. (18-22) Many studies have attempted to evaluate the risk associated to the different histologic variables. The metastatic risk and mortality rate appear to be proportional to the extent of invasion of the ocular coats and the optic nerve. (18;19;23) Optic nerve involvement is found in 25%-45% of eyes with retinoblastoma who undergo up-front enucleation, but its impact on outcome appears to be limited to the involvement beyond the lamina cribrosa and to the extension up to the transection line. (18;19;23-26) Involvement of the optic nerve does not seem to occur more often in eyes that have failed therapy; in our series, 24% of the eyes had optic nerve invasion, although retrolaminar involvement occurred in 2 of the 6 cases. Choroidal involvement is found in up to 40% of the eyes enucleated up-front, although massive invasion occurs in less than 10% of the cases. (22;23;27) This is an important distinction, since although choroidal invasion might have prognostic implications, (18;25;28;29) its impact appears to be limited to those cases with massive replacement. (23) In our series, choroidal involvement was present in 28% of the cases, a proportion that is comparable to eyes enucleated prior to any therapy. It is important to note that in 3 of the 7 cases with choroidal invasion, it occurred in areas thinned by previous treatments, which resulted in access of tumor cells to the superficial layers of the sclera with minimal choroidal involvement.

Delayed enucleation and the presence of some co-morbid conditions were associated with the presence of more invasive features. This is likely a reflection of the persistent efforts at eye salvage in cases with advanced disease, and should raise a cautionary sign as desperate efforts resulting in delayed enucleation could compromise survival. In a series of 122 patients with retinoblastoma who underwent enucleation after failing chemoreduction, tumor invasion of the ocular coats or optic nerve was found in 34% of the cases, and it was also associated with longer time to enucleation. (6) The presence of scleral invasion and the need for bilateral enucleations (which resulted in delayed procedures) were associated with the development of extraocular relapse. Overall, the outcome was excellent, and the 5-yr EFS estimate for this group of 122 patients was $96\% \pm 1\%$. (6) Thus, although invasive features are found in 30-40% of enucleated eyes after failed conservative therapy, the possibility of extraocular relapse is low.

Finally, we must not forget the impact that the aggressive management of retinoblastoma has on patients and families; children endure multiple procedures, with the associated risks and emotional impact. Thus, a careful consideration of the risks associated with delayed enucleation, has to be performed also in the light of those factors. (30) In summary, the successful management of retinoblastoma requires a multidisciplinary approach with aggressive treatment and close surveillance. An ongoing evaluation of the co-morbid conditions developing in these eyes and the risks associated with delayed enucleation should be performed as treatment progresses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by the National Cancer Institute, Bethesda, Maryland (grant nos. CA 23099, 21765 [Cancer Center Support Grant]); American Lebanese Syrian Associated Charities (ALSAC), Memphis, Tennessee; Research to Prevent Blindness, New York, New York; and St. Giles Foundation, New York, New York.

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Table I

Clinical Findings at the Time of Enucleation

Findings	N (%)	Findings	N (%)
Reason for Enucleation		Sub-retinal Seeds	
Recurrence only	1 (4%)	Yes	2 (8%)
Recurrence + other reasons	23 (92%)	No	22 (88%)
Other reasons only	1 (4%)	Unknown	1 (4%)
Recurrence		Vitreous Hemorrhage	
Yes	24(96%)	Yes	6 (24%)
No	1 (4%)	No	18 (72%)
		Unknown	1 (4%)
Glaucoma		Cataracts	
Yes	9 (36%)	Yes	3 (12%)
No	15 (60%)	No	22 (88%)
Unknown	1 (4%)		
Retinal Detachment		Vitreous Seeds	
Yes	9 (36%)	Yes	9 (36%)
No	16 (64%)	No	15 (60%)
		Unknown	1 (4%)

Table II

Summary of histologic changes observed in enucleated eyes

Characteristic	N (%)	Characteristic	N (%)
LOCAL CHANGES			
% of Globe Involved	14 (56%)	% Necrosis	8 (32%)
20%	6 (24%)	<20%	6 (24%)
>20% - <40%	2 (8%)	20% - <40%	2 (8%)
>40% - <60%	2 (8%)	40% - <60%	3 (12%)
>60% - <80%	1 (4%)	60% - <80%	5 (20%)
>80%		80%	1 (4%)
		Not available	
Rosette Formation	11 (44%)	Nuclear Atypia	7 (28%)
Yes	11 (44%)	Yes	1 (4%)
No	3 (12%)	No	17 (68%)
Unknown		Unknown	
INVASION			
Optic Nerve Invasion	6 (24%)	Ciliary Body Invasion	4 (16%)
Yes	15 (60%)	Yes	19 (76%)
No	4 (16%)	No	2 (8%)
Unknown		Unknown	
Choroid Invasion	7 (28%)	Sclera Invasion	3 (12%)
Yes	16 (64%)	Yes	20 (80%)
No	2 (8%)	No	2 (8%)
Unknown		Unknown	
	Invasion (overall)		11 (44%)
	Yes		10 (40%)
	No		4 (16%)
	Unknown		
CHANGES IN EYE ANATOMY			
Retinal Detachment	10 (40%)	Calcification	23 (92%)
Yes	12 (48%)	Yes	2 (8%)
No	3 (12%)	No	
Unknown			
Vitreous Hemorrhage	7 (28%)		
Yes	18 (72%)		
No			

Table III

Invasive disease and time to enucleation

	N	Months from diagnosis to enucleation*	p
Choroid invasion	7	19.9 (10.1 – 31.5)	0.010
Yes	16	9.1 (3.4 – 24.2)	
Ciliary body invasion	4	24.0 (10.1 – 31.5)	0.021
Yes	19	9.6 (3.4 – 24.2)	
Scleral invasion	3	19.9 (17.0 – 31.5)	0.076
Yes	20	9.9 (3.4 – 25.4)	
Optic nerve invasion	6	8.7 (3.5 – 25.4)	0.47
Yes	15	11.1 (3.4 – 31.5)	
# of invasive sites	13	10.4 (3.4 – 26.2)	
0	5	7.8 (3.5 – 11.1)	
1	3	17.0 (10.1 – 19.9)	
2	3	25.4 (22.5 – 31.5)	
3	0	-	
4			

* Times are shown as median (range)

Table IV

Co-morbid conditions and time to enucleation

	N	Months from diagnosis to enucleation*	p
Cataracts			
Yes	3	17.0 (14.0 – 31.5)	0.151
No	22	10.3 (3.4 – 26.2)	
Glaucoma			
Yes	9	19.9 (7.4 – 25.4)	0.155
No	15	9.6 (3.4 – 31.5)	
Retinal detachment			
Yes	9	14.8 (3.5 – 25.4)	0.98
No	16	10.7 (3.4 – 31.5)	
Vitreous hemorrhage			
Yes	7	19.9 (7.4 – 25.4)	0.50
No	18	10.3 (3.4 – 31.5)	
# of co-morbid conditions			
0	1	7.8 (–)	
1	12	9.9 (3.4 – 31.5)	
2	6	15.9 (3.5 – 24.2)	
3	5	13.5 (7.4 – 25.4)	
4	1	20.3 (–)	
5	0	-	
6	0	-	
7	0	-	
# of co-morbid conditions			
0 or 1	13	9.6 (3.4 – 31.5)	0.38
2 or more	12	15.9 (3.5 – 25.4)	

* Times are shown as median (range)

Table V

Co-morbid Conditions and Invasive Disease

	Choroid invasion		Ciliary body invasion		Optic nerve invasion		Scleral invasion	
	No	Yes	No	Yes	No	Yes	No	Yes
Cataracts								
No	15	P=0.21	17	P=0.45	13	P=1	19	P=0.034
Yes	1	5	2	3	2	6	1	1
		2		1		0		2
Glaucoma								
No	11	P=0.34	12	P=0.60	11	P=0.35	12	P=1
Yes	4	3	6	2	4	3	7	2
		4		2		3		1
				2				
Phthisis								
No	13	P=1	15	P=1	13	P=1	17	P=0.37
Yes	2	6	3	4	2	6	2	2
		1		0		0		1
Retinal detachment								
No	9	P=0.66	12	P=1	12	P=0.014	11	P=0.25
Yes	7	5	7	2	3	1	9	3
		2		2		5		0
Subretinal seeds								
No	15	P=0.091	17	P=0.34	13	P=1	17	P=1
Yes	0	5	1	3	2	6	2	3
		2		1		0		0
Vitreous hemorrhage								
No	13	P=0.32	15	P=0.27	14	P=0.011	15	P=1
Yes	3	4	4	2	1	2	5	2
		3		2		4		1
Vitreous seeds								
No	8	P=0.193	10	P=0.25	9	P=1	11	P=0.27
Yes	7	6	8	4	6	4	8	3
		1		0		2		0
# of Co-morbidities								
0	1	P=0.120	1	P=0.54	1	P=0.020	1	P=0.83
1	9	0	9	0	9	0	10	0
2	4	2	6	2	4	1	4	1
3	1	2	2	0	1	2	4	2
4	1	3	1	2	0	3	1	0
		0		0		0		0