CHEMOREDUCTION FOR RETINOBLASTOMA: ANALYSIS OF TUMOR CONTROL AND RISKS FOR RECURRENCE IN 457 TUMORS

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ABSTRACT

Purpose: To evaluate individual tumor control following chemoreduction for retinoblastoma.

Methods: Prospective nonrandomized single-center case series of 457 retinoblastomas managed with six cycles of chemoreduction (vincristine, etoposide, and carboplatin). The tumors were then managed with chemoreduction alone (group A) or chemoreduction combined with thermotherapy (group B), cryotherapy (group C), or both thermotherapy and cryotherapy (group D). The main outcome measure was development of tumor recurrence.

Results: Of 457 retinoblastomas, 63 (14%) were in group A, 256 (56%) in group B, 127 (28%) in group C, and 11 (2%) in group D. The tumor was located in the macula in 33 (52%) of group A, 109 (43%) of group B, 3 (2%) of group C, and 1 (9%) of group D. Using Kaplan-Meier analysis, recurrence of the individual retinoblastoma at 7 years was found in 45% of group A and in 18% of combined groups B, C, and D. Treatment of the 93 tumor recurrences included thermotherapy, cryotherapy, or plaque radiotherapy in 62 cases (67%) and external beam radiotherapy or enucleation in 31 cases (33%). Risk factors predictive of tumor recurrence by multivariate analysis included macular tumor location for all groups and, additionally, female sex for group A and increasing tumor thickness for groups B, C, and D.

Conclusions: Chemoreduction alone or combined with cryotherapy and/or thermotherapy is effective for treatment of retinoblastoma, but tumor recurrence is greatest for those located in the macula and those with greater thickness. Globe salvage is usually achieved despite tumor recurrence.

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INTRODUCTION

Chemoreduction plus focal consolidation treatment is an important therapeutic approach for retinoblastoma.[1,2] The goal of such therapy is to reduce tumor size with chemotherapy and then consolidate the regressed tumor with thermotherapy or cryotherapy to ensure permanent control. This approach offers globe salvage for approximately 85% of eyes classified as Reese-Ellsworth groups I to IV, but it is less successful for group V because globe salvage is achieved in only 47% of eyes.[3] Previous publications on the subject of chemoreduction have addressed various issues, some of which include tumor control with chemotherapy alone,[4,5] tumor control with chemotherapy and focal consolidation,[6-10] and risks for failure with need to resort to enucleation or external beam radiotherapy.[3]

Chemotherapy alone has been found to control only 8% of eyes with retinoblastoma in various stages, on account of problems with tumor and related seed progression and recurrence.[4] When assessing specifically only retinal tumor control using chemotherapy alone, without the confounding factors of vitreous or subretinal seed control, it was reported that 56 (72%) of 78 tumors responded favorably at a mean follow-up of 29 months.[5] Similarly in this analysis, we evaluate specific tumor control of 457 retinoblastomas following chemoreduction, but further investigate the role of tumor consolidation with thermotherapy or cryotherapy in offering more complete tumor control.

METHODS

All patients with retinoblastoma who were treated initially

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Bold type indicates AOS member.

with chemoreduction (institutional review board approved CHP #582) on the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, in conjunction with the Division of Oncology at The Children's Hospital of Philadelphia, were identified. The eligibility criteria for treatment with chemoreduction[9] were children with intraocular retinoblastoma in whom either eye would ordinarily require enucleation or external beam radiotherapy for cure of the disease based on published indications.[2,11] Patients whose tumor(s) could be properly controlled with focal methods alone (cryotherapy, laser photocoagulation, thermotherapy, plaque radiotherapy) were not eligible for inclusion in the chemoreduction protocol. Exclusion criteria for treatment with chemoreduction included biomicroscopic evidence of iris neovascularization, neovascular glaucoma, tumor invasion into the anterior chamber, iris, optic nerve, choroid, or extraocular tissues as documented by clinical, ultrasonographic, and neuroimaging modalities. Exclusion criteria from a systemic standpoint were those patients with evidence of systemic metastasis, prior chemotherapy, prior treatment for retinoblastoma, or inadequate organ function of the kidney, liver, or auditory apparatus. The chemotherapeutic agents included intravenous vincristine, etoposide, and carboplatin (VEC), as shown in Table 1. The duration of treatment was planned for six monthly cycles. The potential risks and benefits of the chemoreduction protocol were discussed with the patient's family, and informed consent was obtained.

Ocular oncologic follow-up was provided at examination under anesthesia every 1 to 2 months after initiation of chemoreduction until all tumors showed complete control. Thereafter, examinations were provided every 2 to 4 months as needed. At each examination, the status of the individual retinal tumors, vitreous seeds, subretinal seeds, and subretinal fluid was noted, and detailed retinal drawings and photographic documentation were performed. At cycle 1, all initial data was recorded and chemoreduction was instituted. At cycles 2 through 6, some tumors were managed with chemoreduction alone and no adjuvant treatment (group A), whereas other tumors received additional thermotherapy (group B), additional cryotherapy (group C), or additional thermotherapy and cryotherapy (group D). The patients were not randomized to treatment. Nearly all tumors outside the macular region received additional therapy (groups B, C, or D). The macula was defined as a circular area within 3 mm of the foveola. Patients with tumors anterior to the equator of the eye generally received additional cryotherapy (group C), and those posterior to the equator received additional thermotherapy (group B). If an inadequate response was achieved following thermotherapy, then cryotherapy was provided (group D). Tumors in the macular region were treated with chemoreduction alone (group A) if the opposite eye had severe visual deficit such as macular retinoblastoma or enucleation, or they were treated with chemoreduction plus additional thermotherapy (group B) if the macula in the opposite eye was intact with potential for good visual acuity.

Adjuvant thermotherapy was provided using the indirect ophthalmoscopic system using 1.2-mm spot size. Duration and power varied so that a light gray-white appearance could be achieved at the end of the session.[2,12] The entire tumor was treated in a slow fashion over several minutes with adjustment of the power to reach a satisfactory appearance at end point. The only exception to treating the entire tumor was with macular tumors for which foveal-sparing thermotherapy was employed to minimize central vision loss.[13] Cryotherapy was applied using transscleral triple freeze-thaw technique directly over the tumor with ophthalmoscopic visualization using a retinal cryoprobe.[14]

All data were collected in a prospective fashion. At initial examination, each patient was evaluated for age at diagnosis, race, male or female sex, and hereditary pattern of the retinoblastoma (sporadic, familial). The eye was assessed for laterality of involvement (unilateral, bilateral) and Reese-Ellsworth classification (I, II, III, IV, V).[15] The tumor was assessed for anteroposterior location (macula, macula to equator, equator to ora serrata), quadrant location (superotemporal, inferotemporal, inferonasal, superonasal), and size in basal dimension (mm) and thickness (mm). At final examination, each tumor was assessed for basal dimension (mm), thickness (mm), regression type (0, 1, 2, 3, 4),[16] and tumor recurrence. Regression type 0 is complete disappearance with no remnant, type 1 is completely calcified remnant, type 2 is completely noncalcified remnant, type 3 is a combination of calcified and noncalcified remnant, and type 4 is flat chorioretinal atrophic scar but no tumor remnant. The interval from initiation of chemoreduction to the tumor recurrence was calculated. The tumor follow-up was continued until the date the patient was last examined or until the date of enucleation of the eye.

TABLE 1. CHEMOREDUCTION REGIMEN FOR INTRAOCULAR RETINOBLASTOMA GIVEN FOR A TOTAL OF SIX MONTHLY CYCLES

DAY	VINCRISTINE (0.05 mg/kg)	ETOPOSIDE (5 mg/kg)	CARBOPLATIN (18.6 mg/kg)
0	x	x	x
1		x	

Statistical Analysis

The clinical data were then analyzed with regard to the single outcome of retinoblastoma recurrence for each

group (A, B, C, and D) and for the entire cohort of 457 tumors as a whole. The effect of each individual clinical variable recorded at the time of patient presentation on the Ocular Oncology Service and the effect of the treatment strategy on the development of this outcome were analyzed by a series of univariate Cox proportional hazards regressions. The correlation among the variables was determined by using Pearson correlations. All variables were analyzed as discrete variables (continuous variables were analyzed by grouping them into discrete categories). Variables that were significant on a univariate level ($P \leq .05$) were entered first into the multivariate Cox regression analysis. For variables that showed a high degree of correlation, only one variable from the set of associated variables was entered at a time into subsequent multivariate models. A final multivariate model tested variables that were identified as significant predictors ($P \leq .05$, Wald's statistic or 95% confidence interval [CI] of the relative risk) from the initial model as well as variables deemed clinically important for the outcome of retinoblastoma recurrence. In the final model, a predictor was considered a significant risk factor if the 95% CI of its relative risk did not contain a risk value of 1. The time to retinoblastoma recurrence using Kaplan-Meier life table analysis was performed.

RESULTS

There were 457 retinoblastomas in 193 eyes of 125 patients managed with six cycles of this chemoreduction protocol (Table 1) between January 1995 and May 2003. Group A (chemoreduction alone) consisted of 63 tumors (14%), group B (chemoreduction plus thermotherapy) consisted of 256 tumors (56%), group C (chemoreduction plus cryotherapy) consisted of 127 tumors (28%), and group D (chemoreduction plus thermotherapy and cryotherapy) consisted of 11 tumors (2%). The demographic features of all 457 tumors are listed in Table 2. The mean patient age at treatment was 9 months, and the hereditary pattern was sporadic in 75% and familial in 25%. The Reese-Ellsworth classification of each eye is listed in Table 3.

A description of the clinical features of the retinoblastomas at initial examination is listed in Table 4. The tumor base and thickness were greater for those in group A (mean, 11 mm and 7 mm, respectively) than those in groups B (mean, 7 mm and 4 mm, respectively), C (mean, 3 mm and 2 mm, respectively), and D (mean, 5 mm and 3 mm, respectively). Macular retinoblastoma represented 52% of group A, 43% of group B, 2% of group C, and 9% of group D. Peripheral retinoblastoma near the ora serrata represented 11% of group A, 5% of group B, 72% of group C, and 18% of group D. A comparison of tumors in group A versus groups B, C, and D revealed that there were significant differences in patient age and race, tumor basal dimension and thickness, and tumor location (Table 5). A description of the retinoblastoma's appearance following therapy at last examination is listed in Table 6. Type 1 regression was noted in 30% of group A, 9% of group B, 2% of group C, and 0% of group D. Regression pattern was most commonly type 3 for group A (46%) and type 4 for groups B (45%), C (85%), and D (82%). Recurrence at last follow-up was found in 20% of all 457 tumors.

Kaplan-Meier estimates of recurrence by 5 years follow-up was 45% for group A, 18% for combined groups B, C, and D, and 22% for the entire group of 457 retinoblastomas (Table 7). The Kaplan-Meier estimates

TABLE 2. DEMOGRAPHIC FEATURES OF PATIENTS TREATED WITH CHEMOREDUCTION FOR RETINOBLASTOMA (n = 125)

Age (mo)	
Mean	9
Median (range)	7 (<1-41)
Sex	
Male	74 (59%)
Female	51 (41%)
Race	
Caucasian	100 (80%)
African American	17 (14%)
Hispanic	4 (3%)
Asian	4 (3%)
Heredity	
Sporadic	94 (75%)
Familial	31 (25%)
Laterality	
Unilateral	35 (28%)
Bilateral*	90 (72%)
Eye affected†	
Right	99 (51%)
Left	94 (49%)

*Of the 90 patients with bilateral retinoblastoma, 22 eyes were not entered into this study because they were initially treated with enucleation.
†No. of eyes = 193.

TABLE 3. REESE-ELLSWORTH CLASSIFICATION OF 193 EYES TREATED WITH CHEMOREDUCTION FOR RETINOBLASTOMA

REESE-ELLSWORTH GROUP	NO. OF EYES (%)
Ia	8 (4)
Ib	5 (3)
IIa	34 (18)
IIb	19 (10)
IIIa	13 (7)
IIIb	18 (9)
IVa	5 (3)
IVb	52 (27)
Va	13 (7)
Vb	26 (13)

TABLE 4. RETINOBLASTOMA FEATURES AT INITIAL EXAMINATION

TUMOR FEATURE	GROUP A: CHEMOREDUCTION ALONE (n = 63) TUMORS	GROUP B: CHEMOREDUCTION + THERMOTHERAPY (n = 256) TUMORS	GROUP C: CHEMOREDUCTION + CRYOTHERAPY (n = 127) TUMORS	GROUP D: CHEMOREDUCTION + THERMOTHERAPY + CRYOTHERAPY (n = 11) TUMORS	TOTAL (n = 457) TUMORS
Base (mm)					
Mean	11	7	3	5	7
Median (range)	10 (<1-25)	5 (<1-23)	2 (<1-23)	4 (1-12)	4 (<1-25)
Thickness (mm)					
Mean	7	4	2	3	4
Median (range)	7 (<1-15)	3 (<1-13)	1 (<1-13)	3 (1-7)	3 (<1-15)
Anteroposterior location					
Macula	33 (52)	109 (43)	3 (2)	1 (9)	146 (32)
Macula to equator	23 (37)	134 (52)	32 (25)	8 (72)	197 (43)
Equator to ora serrata	7 (11)	13 (5)	92 (72)	2 (18)	114 (25)
Quadrant location					
Macula	33 (52)	109 (43)	3 (2)	1 (9)	146 (32)
Superotemporal	6 (10)	28 (11)	19 (15)	2 (18)	55 (12)
Inferotemporal	12 (19)	30 (12)	29 (23)	2 (18)	73 (16)
Inferonasal	5 (8)	52 (20)	34 (27)	4 (36)	95 (21)
Superonasal	7 (11)	37 (14)	42 (33)	2 (18)	88 (19)

for recurrence were stable for up to 7 years follow-up. Treatment of 93 tumor recurrences included cryotherapy in 14 cases (15%), thermotherapy in 9 (10%), plaque radiotherapy in 39 (42%), external beam radiotherapy in 25 (27%), and enucleation in 6 cases (5%). Those eyes managed with external beam radiotherapy or enucleation usually had additional diffuse vitreous and/or subretinal seed recurrence. Factors predictive of tumor recurrence for the 457 tumors using multivariate analysis included non-Caucasian race, macular tumor location, and increasing tumor thickness (Table 8). Multivariate analysis for factors predictive of recurrence for the 63 patients in group A included female sex and tumor location in the macula (Table 9). Multivariate analysis for factors predictive of recurrence for the 256 patients in group B included macular tumor location (Table 9). Multivariate analysis for factors predictive of recurrence for the 394 patients in combined groups B, C, and D included macular tumor location and increasing tumor thickness (Table 8).

DISCUSSION

Chemoreduction with or without focal tumor consolidation treatment is now the most commonly employed conservative (nonenucleation) therapeutic regimen for retinoblastoma.[1,2,17] Despite its popularity, long-term tumor control is often less than desired. Most eyes show favorable initial response within one or two cycles of chemotherapy,[6-9] but over time tumor and associated vitreous and subretinal seeds can recur.[3-5,10,13,18-20] We had noted that by 3 years following chemoreduction, tumor recurrence was found in 51% of eyes.[10] Of those eyes with subretinal seeds at initial examination, subretinal seed recurrence was found in 46% of eyes, and of those with initial vitreous seeds, recurrence was detected in 62% of eyes by 3 years follow-up. These findings did not increase much by 5 years follow-up, so it was presumed that most recurrence following chemoreduction would be clinically visible by 3 years following treatment. These findings underscore the difficulty with this therapy and the need for long-term cautious monitoring of these patients by experienced clinicians. Even though these results seem unfavorable, recurrence is usually detected at an early stage and can be controlled with further salvage measures, avoiding enucleation and external beam radiotherapy.[3]

Tumor change following two cycles of chemoreduction has been reported at approximately 35% reduction in basal dimension and 50% reduction in thickness.[9] In this analysis, we found that tumor basal dimension reduction following completed six cycles and consolidation (if any) was 36% for group A, 43% for group B, 67% for group C, and 60% for group D. Tumor thickness reduction following completed six cycles and consolidation (if any) was 57% for group A, 50% for group B, 75% for group C, and 67% for group D. A few cases showed very little change in size following chemoreduction. It has been speculated that minimal response following chemoreduction may be a feature of well-differentiated retinoblastoma.[9,21] Follow-up of such patients has documented that these poorly responsive tumors remain stable. Unpublished observations from our department have also identified that the presence of intratumoral cysts is a potential sign of tumor

TABLE 5. COMPARISON OF CLINICAL FEATURES IN PATIENTS WITH RETINOLASTOMA AT INITIAL EXAMINATION

CLINICAL FEATURE	GROUP A: CHEMOREDUCTION ALONE (n = 24 PATIENTS, 63 TUMORS)	GROUPS B, C, D: CHEMOREDUCTION + THERMOTHERAPY, CRYOTHERAPY, OR BOTH (n = 101 PATIENTS, 394 TUMORS)	*P* VALUE
Patient age (mo): mean (median, range)	13 (11, 1-41)	8 (6, <1-39)	.02†
Race			
Caucasian*	13 (54%)	87 (86%)	.04†
African American	8 (33%)	9 (9%)	
Hispanic	2 (8%)	2 (2%)	
Asian	1 (4%)	3 (3%)	
Sex			
Male	12 (50%)	74 (73%)	.4
Female	12 (50%)	27 (27%)	
Heredity			
Sporadic	20 (83%)	72 (73%)	.3
Familial	4 (17%)	27 (27%)	
Laterality			
Unilateral	5 (21%)	30 (29%)	
Bilateral	19 (79%)	71 (70%)	.8
Total number tumors per eye: mean (median, range)	3.3 (3, 1-9)	2.9 (3, 1-15)	.1
Base (mm): mean (median, range)	11 (11, <1-25)	6 (6, <1-23)	.0001†
Thickness (mm): mean (median, range)	7 (7, <1-15)	3 (3, <1-13)	.0001†
Anteroposterior location			
Macula*	33 (52%)	113 (29%)	
Macula to equator	23 (37%)	174 (44%)	.008†
Equator to ora serrata	7 (11%)	107 (27%)	.001†
Quadrant location			
Macula*	33 (52%)	113 (29%)	
Superotemporal	6 (10%)	49 (12%)	.02†
Inferotemporal	12 (19%)	61 (16%)	.3
Inferonasal	5 (8%)	90 (23%)	.001†
Superonasal	7 (11%)	81 (21%)	.005†
Proximity to optic disk (mm): mean (median, range)	1.2 (0, 0-16)	2.4 (0, 0-17)	.2
Proximity to foveola (mm): mean (median, range)	1.0 (0, 0-16)	2.5 (0, 0-19)	.2

*Reference variable.
†Indicates clinical features significantly different between the two groups.

differentiation and less dramatic response to chemoreduction.

Following therapy, judgment of tumor response is based on reduction of tumor size, resolution of subretinal fluid, and change in tumor appearance. The appearance is classified into five regression patterns from type 0 to type 4, based on presence of tumor calcification and appearance of the residual tumor scar (defined in the "Methods" section). Tumor regression patterns depended on the initial tumor size and treatment. Retinoblastomas in group A most commonly showed regression type 3 (46%) and type 1 (30%), whereas those in group B showed regression type 3 (42%) and type 4 (45%). Tumors in groups C and D showed most commonly regression type 4 (85% and 82%, respectively). Regression type 4 is the most satisfying pattern to the clinician, because there is no tumor remnant and the site is atrophic without blood supply. As indicated in this report, this pattern was generally found following chemoreduction and cryotherapy (85%) and less often following chemoreduction and thermotherapy (45%) or chemoreduction alone (5%). Complete calcification of the retinoblastoma following therapy was found in 30% of group A, 9% of group B, 2% of group C, and 0% of group D. This is another pattern that provides satisfaction to the clinician because there is a completely calcified scar, implying tumor necrosis with dystrophic calcification. The

TABLE 6. RETINOBLASTOMA FEATURES AT LAST EXAMINATION

TUMOR FEATURE	GROUP A: CHEMOREDUCTION ALONE (n = 63)	GROUP B: CHEMOREDUCTION + THERMOTHERAPY (n = 256)	GROUP C: CHEMOREDUCTION + CRYOTHERAPY (n = 127)	GROUP D: CHEMOREDUCTION + THERMOTHERAPY + CRYOTHERAPY (n = 11)	TOTAL (N = 457)
Base (mm)					
Mean	7	4	1	2	3
Median (range)	6 (0-20)	3 (0-18)	0 (0-13)	0 (0-10)	0 (0-20)
Thickness (mm)					
Mean	3	2	<1	1	2
Median (range)	3 (0-10)	1 (0-9)	0 (0-7)	0 (0-9)	0 (0-10)
Regression type*					
0	8 (13)	2 (1)	4 (3)	0 (0)	14 (3)
1	19 (30)	23 (9)	3 (2)	0 (0)	45 (10)
2	4 (6)	10 (4)	1 (1)	0 (0)	15 (3)
3	29 (46)	107 (42)	11 (9)	2 (18)	149 (33)
4	3 (5)	114 (45)	108 (85)	9 (82)	234 (51)
Recurrence					
Yes	28 (44)	51 (20)	11 (9)	3 (28)	93 (20)
No	35 (56)	205 (80)	116 (91)	8 (72)	364 (80)

*Type 0 = tumor has disappeared; type 1 = tumor is completely calcified; type 2 = tumor is noncalcified; type 3 = tumor is partly calcified; type 4 = tumor is flat with chorioretinal scar.

TABLE 7. KAPLAN-MEIER ESTIMATES OF TIME TO RECURRENCE OF RETINOBLASTOMA

TIME OF RECURRENCE	GROUP A CHEMOREDUCTION ALONE % FAILED* (n = 63)	GROUP B CHEMOREDUCTION + THERMOTHERAPY % FAILED* (n = 256)	GROUPS B, C, D CHEMOREDUCTION + ADJUVANT THERAPY % FAILED* (n = 394)	TOTAL CHEMOREDUCTION WITH OR WITHOUT ADJUVANT THERAPY % FAILED* (N = 457)
1 yr	39% (24/37)	18% (43/188)	13% (50/309)	17% (73/347)
2 yr	45% (27/18)	20% (49/163)	17% (61/258)	20% (88/276)
3 yr	45% (27/15)	21% (50/122)	17% (62/191)	21% (89/202)
4 yr	45% (27/10)	22% (51/101)	18% (64/153)	22% (91/164)
5 yr	45% (27/10)	22% (51/72)	18% (64/99)	22% (91/105)
6 yr	45% (27/10)	22% (51/39)	18% (64/57)	22% (91/66)
7 yr	45% (27/8)	22% (51/16)	18% (64/31)	22% (91/40)

*(No. of events/No. still in risk set.)

least satisfying tumor regression pattern is type 2, which appears as a noncalcified residua, sometimes quite similar to the original tumor. Type 2 pattern is also termed "fish flesh appearance" and has a grey, translucent minimally vascular surface that is different from an active tumor, which is usually more opaque, pink-white, and highly vascular. Type 2 regression pattern was found in 6% of group A, 4% of group B, 1% of group C, and 0% of group D. The lack of calcification or chorioretinal atrophy raises the question of tumor viability at each examination, but lack of change on follow-up suggests tumor regression. Even though it might be suspected that tumors showing regression type 2 were more likely to show ultimate recurrence, the statistical analysis did not support this conclusion. There was no relationship between tumor regression type and tumor recurrence. All regressed retinoblastomas, despite the tumor regression pattern, require meticulous periodic observation to monitor for recurrence.

In this analysis, we specifically evaluated control of each individual retinal tumor following chemoreduction. By 7 years follow-up, we found overall tumor control of 78%, without the need for external beam radiotherapy or enucleation. More specifically, by 7 years, tumors treated with chemoreduction alone showed 55% tumor control,

TABLE 8. RISK FACTORS PREDICTIVE OF TUMOR RECURRENCE IN COMBINED GROUPS A, B, C, AND D

RISK FACTORS	NO RECURRENCE (n = 87 PATIENTS 364 TUMORS)	RECURRENCE (n = 38 PATIENTS, 93 TUMORS)	*P* VALUE	RISK*	CONFIDENCE INTERVALS
Univariate analysis					
Race (non-Caucasian vs Caucasian†)	71 (82%)	29 (76%)	.02	2.07	(1.11,3.85)
Tumor basal dimension (mm): mean (median, range) (per 1 mm increase)	6 (3, <1-25)	10 (9 ,<1-25)	<.0001	1.10	(1.07,1.13)
Tumor thickness (mm): mean (median, range) (per 1 mm increase)	3 (3, <1-15)	6 (4, <1-15)	<.0001	1.19	(1.12,1.26)
Tumor location					
Macula	101 (28%)	45 (48%)			
Macula vs macula to equator†	161 (44%)	36 (39%)	.011	1.79	(1.14,2.81)
Macula vs equator to ora†	102 (28%)	12 (13%)	.0002	3.49	(1.80,6.79)
Tumor quadrant (macula vs extramacular†)	101 (28%)	45 (48%)	.0003	2.22	(1.45,3.40)
Proximity to optic disk: mean (median, range) (per 1 mm decrease)	2.6 (0, 0-17)	0.9 (0, 0-6)	.012	1.13	(1.03,1.24)
Proximity to foveola: mean (median, range) (per 1 mm decrease)	2.8 (0, 0-19)	0.5 (0, 0-7)	.005	1.27	(1.08,1.51)
Therapy (group A vs groups B, C, D†)	36 (10%)	27 (30%)	<.0001	3.53	(1.92,6.49)
Multivariate analysis					
Tumor thickness (mm) (per 1 mm increase)	—	—	<.001	1.13	(1.07,1.20)
Race (non-Caucasian vs Caucasian†)	—	—	.029	1.85	(1.07,3.22)
Tumor quadrant (macula vs superotemporal†)	—	—	.012	3.58	(1.32,9.73)
Therapy (group A vs groups B, C, D†)	—	—	.053	1.96	(1.00,3.86)

*Risk ratio computed from Cox proportional hazards model.
†Reference variable.

whereas those treated with chemoreduction combined with focal consolidation of thermotherapy or cryotherapy showed 82% control. In the overall group of 457 retinoblastomas, tumors most likely to recur were large tumors and those located in the macular region. It should be realized that in this nonrandomized study, tumors in group A were larger than those in groups B, C, and D, and this could have impacted tumor recurrence. Large tumors are not particularly amenable to tumor consolidation with thermotherapy or cryotherapy, because these focal modalities would affect only a small portion of the large mass and provide only partial treatment. Additionally, large retinoblastomas are often found in the macular region, and in many cases tumor consolidation is avoided to preserve vision for the child, especially if it is the patient's only remaining eye. For these reasons, large retinoblastomas are occasionally managed with chemoreduction alone.

In a previous report, we specifically assessed tumor control of macular retinoblastoma in a group of 68 patients.[13] We noted Kaplan-Meier estimates for tumor recurrence in 35% of those macular tumors treated with chemoreduction alone and only 17% of those treated with chemoreduction plus foveal-sparing thermotherapy. Surprisingly, tumor recurrence was most often found in smaller, relatively inactive tumors without subretinal or vitreous seeds. Gombos and colleagues[5] found similar results in their analysis of chemotherapy alone for 78 retinoblastomas. In their report, tumor recurrence was greatest for small tumors, that is, those under 2 mm in diameter. We speculate that this occurs because small tumors might be more well differentiated and show less chemotherapy response, or they may receive smaller doses of chemotherapy on account of tiny feeder vessels.

In our analysis, all patients were treated with

TABLE 9. RISK FACTORS PREDICTIVE OF TUMOR RECURRENCE FOR INDIVIDUAL GROUP A AND GROUP B, AND COMBINED GROUPS B, C, AND D

RISK FACTORS	NO RECURRENCE	RECURRENCE	*P* VALUE	RISK*	CONFIDENCE INTERVALS
Group A	(n=11 patients, 36 tumors)	(n=13 patients, 27 tumors)			
Univariate analysis					
Sex (female vs male†)	4 (36%)	8 (62%)	.025	2.92	(1.15,7.42)
No. of tumors per eye: mean (median, range)	4 (4, 1-9)	3 (3, 1-4)	.009	1.26	(1.06,1.49)
Tumor basal dimension (mm): mean (median, range) (per 1 mm increase)	9 (9, <1-25)	14 (14, 1-25)	.007	1.08	(1.02,1.14)
Tumor thickness (mm): mean (median, range) (per 1 mm increase)	6 (5, <1-15)	8 (9, <1-15)	.035	1.10	(1.01,1.19)
Tumor quadrant					
Macula	19 (53%)	14 (52%)			
Macula vs superotemporal†	6 (17%)	0 (0%)	<.0001	NE	NE
Macula vs superonasal†	1 (3%)	4 (15%)	.011	2.83	(1.27,6.32)
Multivariate analysis					
Sex (female vs male†)	—	—	.025	2.76	(1.11,6.89)
Tumor quadrant					
Macula vs superotemporal†	—	—	<.0001	NE	NE
Macula vs superonasal†	—	—	.022	2.16	(1.12,4.17)
Group B	(n = 66 patients, 205 tumors)	(n = 23 patients, 51 tumors)			
Univariate analysis					
Tumor basal dimension (mm): mean (median, range) (per 1 mm increase)	7 (4, <1-23)	9 (6, <1-23)	.01	1.05	(1.01,1.09)
Tumor thickness (mm): mean (median, range) (per 1 mm increase)	4 (3, <1-13)	5 (4, <1-12)	.02	1.11	(1.02,1.20)
Tumor location (macula vs extramacular†)	79 (39%)	30 (59%)	.01	2.06	(1.18,3.61)
Multivariate analysis					
Tumor location (macula vs extramacular†)	—	—	.01	2.06	(1.18,3.61)
Groups B, C, D	(n = 76 patients, 328 tumors)	(n = 25 patients, 66 tumors)			
Univariate analysis					
Tumor basal dimension (mm): mean (median, range) (per 1 mm increase)	5 (3, <1-23)	8 (6, <1-23)	<.001	1.08	(1.10,1.27)
Tumor thickness (mm): mean (median, range) (per 1 mm increase)	3 (2, <1-13)	5 (4, <1-13)	<.001	1.18	(1.10,1.27)
Tumor location (macula vs extramacular†)	82 (25%)	31 (47%)	.001	2.45	(1.48,4.08)
Proximity to optic nerve (mm): mean (median, range) (per 1 mm increase)	3 (0, 0-17)	<1 (0, 0-5)	.02	1.15	(1.02,1.29)
Proximity to foveola (mm): mean (median, range) (per 1 mm increase)	3 (0, 0-19)	<1 (0, 0-7)	.009	1.23	(1.05,1.43)
Multivariate analysis					
Tumor thickness (mm)	—	—	.001	1.13	(1.05,1.22)
Tumor quadrant					
Macula vs superotemporal†	—	—	.04	2.88	(1.03,8.10)
Macula vs superonasal†	—	—	.04	2.27	(1.02,5.02)

NE, nonestimable (zero cell).
*Risk ratio computed from Cox proportional hazards model.
†Reference variable.

multi-agent chemotherapy for retinoblastoma to minimize chemoresistance in eyes with often extensive disease.[22] Others have investigated single-agent chemotherapy for retinoblastoma using carboplatin.[23] Lumbroso and coworkers[23] found that carboplatin plus thermotherapy for selected small to medium-sized retinoblastomas (median tumor diameter, 3.5 mm) provided control in 89.5% of patients at 2 years follow-up. However, eyes with large tumors or those with localized or diffuse vitreous or subretinal seeding were excluded from their protocol owing to anticipated concerns for recurrence. Their selected cohort differs from ours in that we were more inclusive to provide a general picture of tumor control with chemoreduction strategies. We included eyes with small, medium, and large retinoblastomas, and we included eyes with localized and diffuse vitreous and subretinal seeding.

There are limitations to this study that should be realized. We specifically evaluated only retinal tumor control and did not evaluate vitreous seed or subretinal seed control. Seed recurrence is a common cause for chemoreduction failure, so this should be anticipated when treating patients with such features. We also did not evaluate for the development of new retinoblastomas, because this has been previously reported.[24,25] In addition, many patients had more than one tumor per eye. There may be unknown factors within a single patient's tumor(s) that could lead to excessive resistance or sensitivity to treatment and could bias the results. Finally, these tumors were not randomized to treatment, because treatment selection was based on many features of the patient, the eye(s), and the tumor(s). Randomization would have been difficult because of the many variables from case to case. This report was not designed to be a comparison of various treatment methods. Our goal was to assess the singular outcome of tumor recurrence following four chemoreduction strategies.

In summary, chemoreduction with or without focal tumor consolidation is effective therapy for retinoblastoma. Each treated tumor had approximately 22% risk for recurrence. Most recurrences were detected within 1 year of initiation of chemoreduction, and no recurrences occurred after 4 years follow-up. Meticulous examination in the first few years following chemoreduction and consolidation is critical to early detection of recurrence and salvage of the eye. Long-term follow-up is advised in all cases.

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DISCUSSION

Dr Barrett G. Haik. In the past decade, systemic chemotherapy has replaced external beam radiotherapy as the primary treatment for patients with multifocal intraocular retinoblastoma. Different combinations of carboplatin, vincristine, etoposide or teniposide, and cyclosporine form the basis of most current treatment regimens for intraocular retinoblastoma. Although no two institutions have had identical experiences, reports thus far have been encouraging. Just as chemotherapy protocols have varied, so have the methods and timing of consolidation for individual tumors. Even the need for consolidation is debated: Some investigators have favored intensive, early focal consolidation while others have elected to defer it. This is due in part to difficulty in predicting an individual tumor's response to chemotherapy. Lesions that demonstrate the classic patterns of regression described by Reese and Ellsworth following radiotherapy do not necessarily behave in a similar manner following chemotherapy.

We agree with Dr Shields and colleagues that primary systemic chemotherapy alone does not successfully treat most eyes with multifocal intraocular retinoblastoma. Consolidation with external beam radiotherapy, episcleral plaque brachytherapy, diode laser, argon laser photocoagulation, and/or cryotherapy is usually needed. However, we did observe individual tumors in those eyes that required no consolidation following chemotherapy. Those tumors were more often located in the posterior pole. Treatment of those lesions with chemotherapy alone spared visually sensitive areas from the destructive effects of consolidation, hopefully ensuring maximal preservation of vision.

Dr Shields and colleagues have analyzed local tumor control and factors predictive of recurrence in a group of 457 retinoblastomas occurring in 193 eyes of 125 patients. Twenty-eight percent of the patients had unilateral disease; 50 percent of the eyes had advanced retinoblastoma. The authors analyzed the effectiveness of different combinations of therapies for local control and concluded that chemotherapy alone or combined with focal treatments is effective, but large tumors and those occurring in the macula have higher rates of recurrence.

These are important observations. However, several of these observations deserve additional evaluation:

The use and type of focal treatments for each patient, each eye, and each tumor are functions of several factors: laterality and location of the tumor, intraocular group, age of the patient, expected visual outcome, compliance status, treatment given to other tumors in the same eye, tumors in the vicinity, growth, etc.

Although the authors describe the different treatment groups, it is not clear how the decisions were made regarding the treatment of an individual tumor. It appears that consolidation therapy may have been delayed or modified in the most visually sensitive areas of the retina. While we agree with this strategy, it makes some comparisons of tumor responses extremely difficult.

This study includes patients treated over an eight-year period. Treatment practices have evolved over those years.

The authors have provided valuable information on retinal tumor control and in this study did not evaluate vitreous or subretinal seed control. We look forward to additional studies discussing the clinical management of vitreous disease in retinoblastoma patients who have received chemotherapy, since these foci are often the source of tumor control failure and eye loss.

Dr John T. Flynn. These are three very toxic drugs and you are administering them to very small children. What have been the side effects? It also seems that retinoblastoma is an ideal tumor to study with a randomized clinical trial. Are the major centers that study or treat patients with retinoblastoma considering a randomized clinical trial or are each of you resolving your medications, dosages, and regimes of treatment independently of each other?

Dr Bartley R. Freuh. With rhabdomyosarcoma, the great advances that have been made have been by pooling cases. Recognizing different research groups are using different regimens, combining your data and then fully evaluating the data might advance the treatment of retinoblastoma more quickly.

Dr Douglas A. Jabs. There is a potential treatment indication bias issue. The study demonstrated that recurrence was related to macular location, and your indication for chemotherapy alone was macular location. Your conclusion is that consolidation reduces the rate of recurrence, but you're consolidating those who are less likely to recur. Did you do a multivariate analysis, and does the conclusion that consolidation reduces the rate of recurrence still persist after a multivariate analysis that corrects for tumor location?

Dr Carol L. Shields. I'd like to thank Dr Haik for his wisdom and comments. He continues to provide us with a tremendous amount of information regarding therapy for retinoblastoma.

Regarding Dr Flynn's question on the side effects, those of us who treat retinoblastoma with systemic chemotherapy are worried about side effects. Are we trading the side effects from external beam radiation for the side effects from chemotherapy? The side effects using carboplatin in children include ototoxicity and renal toxicity. In our series of patients, we have not seen these side effects, but we monitor the medication carefully and rarely give more than six cycles. There would be nothing worse than having a child who's blind from the retinoblastoma and deaf from the chemotherapy. The main side effect from etoposide is induction of leukemia that usually occurs within the first five years after delivering the medication. Worldwide, there have been about 11 or 12 cases of secondary leukemia from etoposide. The main side effect from vincristine is neurotoxicity. We have had a few children develop neurotoxicity, usually manifested as a head droop. When we cut back on their vincristine dose, it usually resolves. I'm very interested in the carboplatin in the epibulbar gel that was discussed in the symposium today. There is a push toward delivering the chemotherapy locally to avoid these systemic side effects.

Regarding Dr John Flynn's question about a clinical trial, we made an effort to start a national clinical trial on retinoblastoma called The Retinoblastoma Study. About five or six years ago, we all met at the NIH to discuss the design of that clinical trial. At that time, we were going to be using a trial that was instituted in Toronto, but later this evolved into a trial that was developed in Los Angeles and Philadelphia in a collaborative mode similar to treating advanced eyes with rhabdomyosarcoma. Advanced eyes with retinoblastoma would receive high dose chemotherapy, three agents plus subconjunctival carboplatin, plus low dose radiation. That trial is about to begin at eight major centers in the United States. The second part of The Retinoblastoma Study will be to evaluate intermediate retinoblastoma using two agents and avoiding etoposide, the drug that might induce leukemia. Then there are other side investigations that will be in The Retinoblastoma Study such as risk factors predictive of metastatic disease and some pathology-based factors. They will not be randomized because of other complex issues. Randomizing a child who has unilateral versus bilateral disease or has unifocal versus multifocal disease is difficult. These are going to be single-armed trials where we all pool our data and come to a consensus regarding the best approach for chemoreduction for retinoblastoma.

Dr Freuh raised the question about a clinical trial and suggested a retinoblastoma trial similar to the rhabdomyosarcoma trial. The rhabdomyosarcoma trial really made giant steps in our management of rhabdomyosarcoma back in the 1970s when only 30 percent of children survived with rhabdomyosarcoma. Currently, 93 percent of children survive. With the upcoming national study of retinoblastoma, we might obtain better results in the long term by collaborating with our colleagues.

Dr Jabs queried the design of our study. This was a retrospective study to assess our results regarding the need for tumor consolidation for children with retinoblastoma. As it turns out, tumors in the macular region tended to show the highest recurrence whether or not consolidation was performed. Our study and several other studies have now shown that macular retinoblastoma tends to be the site with the greatest recurrence. This nonrandomized retrospective analysis of a rare tumor would not allow us to select out the macular tumors and compare to extramacular tumor results.

We appreciate the interest and comments of the participants in our study on chemoreduction for retinoblastoma.