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Systemic Neoadjuvant Chemotherapy for Group B Intraocular Retinoblastoma: ARET0331: A Report from the Children's Oncology Group

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Abstract

Purpose—To evaluate a chemoreduction regimen using systemic vincristine and carboplatin and local ophthalmic therapies to avoid external-beam radiotherapy (EBRT) or enucleation in patients with Group B intraocular retinoblastoma.

Patients and Methods—Twenty-one patients (25 eyes) were treated with 6 cycles of vincristine and carboplatin, accompanied by local ophthalmic therapies after cycle 1. The primary study

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objective was to determine the 2-year event-free survival (EFS) where an event was defined as the use of systemic chemotherapy in addition to vincristine or carboplatin, EBRT and/or enucleation.

Results—All patients had tumor regression after the first cycle of vincristine and carboplatin and only two patients had progression during therapy. There were 7 treatment failures within 2.0 years of study enrollment, resulting in 2-year EFS of 65% and early study closure in accordance with the statistical design. The 2-year cumulative incidence of enucleation was 15%; for external beam radiation therapy was 10% and for chemotherapy to control progressive disease was 10%. All patients sustaining a treatment failure were salvaged with additional therapy.

Conclusions—For the majority of patients with Group B intraocular retinoblastoma, chemoreduction with vincristine and carboplatin, without etoposide, in conjunction with local therapy provides excellent opportunity for ocular salvage. Local therapy given with every chemotherapy cycle and incorporation of etoposide may provide improved ocular salvage rates. Central review of group at diagnosis is critical in assigning appropriate therapies.

Keywords

ARET0331; systemic neoadjuvant chemotherapy; Children's Oncology Group; Group B intraocular retinoblastoma; retinoblastoma

Retinoblastoma occurs in 6% of children with cancer less than 5 years of age [1]. Enucleation and external beam radiotherapy enabled survival to increase from 30% in the 1930's to almost 100% at the present time in high-income countries [2,3], but this increased survival is accompanied by long-term morbidity and mortality. Survivors are at risk for visual impairment, cataract, dry eye, midface and orbital deformities, and most significantly, subsequent neoplasms (SMN) [4–15]. In order to avoid these complications, retinoblastoma therapy has undergone a dramatic change during the past two decades, with the introduction of systemic chemotherapy (chemoreduction) together with local ophthalmic therapies and, more recently, regionally administered subtenon and selective intra-arterial and intra-vitreous chemotherapy [3,16–29]. Data from studies utilizing carboplatin, etoposide with or without vincristine demonstrated excellent results for patients with Reese-Ellsworth Groups I – III or International Classification Group A and B [17–24], but concern about the use of etoposide has been raised due to its association with secondary leukemia. The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) reported cumulative 6-year incidence rates of secondary leukemia for low, moderate, and higher cumulative etoposide dose groups of 3.3%, 0.7% and 2.2% respectively [30], with most intraocular retinoblastoma chemotherapy regimens falling into the low dose group. In a review of children treated for retinoblastoma, 15 cases of therapy-related acute myeloblastic leukemia were identified, eight of whom had received etoposide although, together with other chemotherapy agents, not in a regimen of six cycles of carboplatin, etoposide and vincristine alone [9]. Therefore, we designed this study to assess the efficacy of a systemic chemotherapy regimen for patients with unilateral or bilateral Group B retinoblastoma that did not include systemic etoposide.

Patients and Methods

Children's Oncology Group (COG) ARET0331, approved by the National Cancer Institute (NCI) Adult/Pediatric Central Institutional Review Board (IRB) and at the IRBs of participating sites, was a single arm trial, comparing the event-free survival experience of the patients receiving the proposed treatment with the event-free survival expected with regimens that included carboplatin, etoposide and vincristine. After undergoing an evaluation under anesthesia (EUA) to confirm disease and eligibility, patients were treated with one cycle of vincristine and carboplatin, without local ophthalmic therapy, to assess early response to systemic chemotherapy. At the conclusion of the first cycle of chemotherapy, patients were evaluated by ophthalmoscopy for response. Those who had no progression of disease continued to receive this 2-drug therapy, for a total of six cycles. Patients continued to receive EUA's at least every two cycles to assess response. Additional ophthalmic examinations were performed at the discretion of the treating ophthalmologist. All systemic chemotherapy delivered in cycles 2 through 6 could be accompanied by local ophthalmic therapies, such as cryotherapy, diode laser thermotherapy or episcleral plaque radiotherapy (brachytherapy), as required. Most treating ophthalmologists administered these therapies to areas of active tumor with each cycle of chemotherapy, delivered 28 days apart. The study schema is shown in Figure 1. The primary objective of the study was to estimate the 2-year event-free survival (EFS), where an event was defined as the need for non-protocol therapy, which included 1) use of any systemic chemotherapy other than vincristine or carboplatin as defined in the protocol; 2) enucleation; or 3) external beam radiation (EBRT).

Patients were eligible for study if they were less than six years old, newly diagnosed with Group B intraocular retinoblastoma and had not received any prior anti-neoplastic or local ophthalmic therapy. These included patients with unilateral disease with a Group B tumor, or bilateral disease with a Group B tumor in one eye and either a Group A, B, or an already enucleated other eye. A CT or MRI of the brain and orbits was required within 4 weeks prior to study entry and an ophthalmic EUA to confirm the diagnosis of a Group B intraocular tumor within 3 weeks of study entry. Patients were registered on study based on the local EUA performed for diagnostic purposes prior to study entry. RetCam images were submitted from the diagnostic EUA for central review within three weeks following study entry. With assistance of the Quality Assurance Radiotherapy Center (QARC), these images were independently reviewed by three ophthalmologists, specializing in retinoblastoma management, within six weeks from study entry to confirm eligibility per the International Retinoblastoma Classification System. Subsequent RetCam images were submitted and centrally reviewed, utilizing the same mechanism, during and following therapy to assess response.

Statistical methods

The primary aim of the study was to demonstrate that the proposed treatment regimen, with 2-drug chemoreduction with vincristine and carboplatin (VC), resulted in EFS of 96% at 2 years with few subsequent failures by ruling out an EFS less than 88% at 2 years. The difference between the number of observed and expected failures was approximately

normally distributed with independent increments and thus could be used for interim monitoring using standard group sequential boundaries. Outcome data was formally reviewed, using the Lan-DeMets α -spending function implementation of sequential boundaries, after every expected failure, corresponding approximately to 33%, 66% and 100% of the expected information. An alpha spending function of (α_t) was used, as it is of interest to detect early indications of increased harm relative to an outcome we considered sufficient for this stage of disease [31].

Accounting for a 10% drop-out rate, a target accrual of 85 patients was set in order to assure 80% power to rule out a two-year EFS below 90%, assuming that the two-year EFS for the current therapy was actually 96%, at a one-sided α -level of 0.10.

Event-free survival (EFS) was taken as the time from enrollment to the first occurrence of an analytic event, considered to be external beam radiation therapy, enucleation of the affected eye, administration of systemic chemotherapy to control progressive disease, diagnosis of a second malignant neoplasm or death, or last contact. Patients who did not experience an analytic event by the date of last contact were considered censored for EFS; in all other cases, an EFS event was considered to have occurred. Survival was defined as the time from enrollment to death or last contact. Patients who were alive at last contact were considered censored for survival; in all other cases, a survival event was considered to have occurred.

EFS and survival, as a function of time since enrollment were calculated by the method of Kaplan and Meir. The distribution of the complementary log-log transformation of the Kaplan-Meier estimate was used for the construction of confidence intervals [32].

The cumulative incidence of each type of analytic event, *viz.*, external beam radiation therapy, enucleation of the affected eye or administration of systemic chemotherapy to control progressive disease, was calculated according to the method of Gray [33].

Results

Patients

Twenty-eight patients were registered for the study. Patients began treatment at a mean of 7.7 days from date of EUA with a range of 0 – 27 days. Of 41 eyes evaluated by central review, 10 (25%) central review eye group classifications disagreed with the institutional group resulting in 7 patients (25%) being determined to be ineligible for the study. Of the 7 patients, one was determined to have only a Group A involved eye and the other 6 had an intact eye that was group C or D. A consort diagram is shown in Figure 2. Of the 21 eligible patients, there were 12 (57%) females and 9 (43%) males with the following age distribution: 12 (57%) were less than 6 months of age, six (28%) were 6 months to one year, two (10%) were 1 – 2 years and on) was older than age 2 years. Distribution by sex and reported race was consistent with United States (US) incidence data [1]. Details on tumor presentation, number and location of tumors, age, time to event and follow up is shown in Table 1, showing 10 unilateral and 11 bilateral cases. Among the bilateral cases, seven had a Group E eye that had been enucleated prior to starting protocol treatment. In these patients,

the treatment success was determined solely by the response in the remaining Group B eye. A summary of local therapies received by study patients is shown in Table 2.

Response and Outcome

Data current to June 30, 2015 are presented below. At the first interim analysis conducted on December 19, 2008, three events had occurred with 0.43 expected events based on 96% EFS, so that the null hypothesis could be rejected ($p < .001$). Following this statistical design, the study was therefore closed in June 2009 by the COG Data Safety and Monitoring Committee.

In 25 eyes in 21 patients, there was evidence of tumor regression after the first cycle of vincristine and carboplatin and all patients proceeded to receive five subsequent courses of chemotherapy and local ophthalmic therapy per the protocol specifications. In addition, response was noted at the end of therapy in all but 3 eyes in 2 patients where progression was noted. Regression patterns I-IV were noted. The 2-year EFS, defined as use of non-protocol chemotherapy, EBRT or enucleation was 65% (95% confidence interval [CI] 40%, 82%) (Figure 3). Overall survival was 100%. There were seven local treatment failures and data on these patients is found in Table 2. All failures occurred within 2 years of study enrollment. Five of the patients with treatment failures had bilateral disease, and of those, two had enucleated Group E eyes. Four of the seven patients with treatment failures and four of the fourteen patients without treatment failure started therapy 10 or more days after diagnosis. The hazard ratio for an event associated with time from diagnosis to start of therapy was 0.43 (95% CI 0.12, 1.5) ($p = 0.18$). All patients who sustained a treatment failure were salvaged with additional therapy, which included enucleation, radiation therapy or additional chemotherapy, or combinations thereof. The 2-year cumulative incidence of enucleation was 15%; for external beam radiation therapy was 10% and for chemotherapy to control progressive disease was 10%. There were no metastatic recurrences and one patient was found to have minimal episcleral disease on enucleation. No patients required bilateral enucleation.

A total of 19 patients completed therapy per protocol, with seven patients removed by physicians after study termination as they felt it to be in the patient's best interest. Details of treatment subsequent to termination of protocol therapy of these patients were not reported.

Toxicity

Therapy was well tolerated. Eight patients (38%) experienced grade 3 or 4 toxicity (using the Common Toxicity Criteria, v3), the most common of which was hematologic. There were two infections, one allergic reaction with urticaria and one case of dehydration. These toxicities were not unexpected with the chemotherapy regimen and the age of the enrolled patients.

Discussion

While this study was closed due to an excess number of failures, based on an EFS of 65% compared with the projected EFS of 96%, all treatment failures were local. Overall patient survival was 100%. No patients developed metastatic disease or a subsequent malignancy

and no bilateral enucleations were required. Of the seven patients who entered the study with only one intact eye, there were only two failures and both were salvaged by additional systemic chemotherapy combined with local ophthalmic therapy.

Because intraocular retinoblastoma has cure rates that approach 100%, and treatment with vincristine, etoposide and carboplatin is highly successful in patients with Group B intraocular disease [3,17–24], our stopping criteria were particularly stringent. We also did not want an excess number of patients to be exposed to additional chemotherapy or radiotherapy, both of which are associated with significant long-term toxicities, most particularly, SMN [4–15].

However, as used in this small group of patients, systemic chemotherapy with vincristine and carboplatin alone did not afford the same rate of EFS as previous published studies with vincristine, etoposide and carboplatin [3,17–24]. This may in part be due to this being a multi-institutional study, as opposed to single institution studies where therapies are delivered at highly specialized centers with high retinoblastoma patient volume and expertise.

Our data compare favorably to those reported by Rodriguez-Galindo and colleagues in a study conducted at St. Jude's Children's Research Hospital. In that study, patients were treated with eight cycles of systemic vincristine and carboplatin with no concomitant local cryotherapy or laser. Local therapies were instituted only at the time of tumor progression [21]. Similar to our results, all but two patients showed regression of tumor while receiving chemotherapy and EFS was inferior to regimens containing vincristine, etoposide and carboplatin, with events classified as the need for enucleation or external beam chemotherapy. Among 24 eyes in R-E groups I – III, five were treated with external beam radiotherapy and four with both external beam radiotherapy and enucleation, resulting in a 2-year EFS of $85.7\% \pm 14.5\%$ for R-E group I, $53.3\% \pm 16.3\%$ for group II and $30.0\% \pm 17.7\%$ for group III [21]. In contrast, in our study, among 25 eyes, two were treated with external beam radiotherapy, three with enucleation and two patients responded to additional systemic chemotherapy with vincristine, etoposide and carboplatin with local therapy, without the need for radiotherapy or enucleation. In another report from the St. Jude group, in a study of 20 patients (36 eyes), eight cycles of vincristine and carboplatin were given over a 6-month period, with focal therapy only delivered with disease progression. Ninety-two percent of eyes progressed after completion of chemotherapy [34]. Thus, early institution of local ophthalmic therapies seems critical for effective long-term control of retinoblastoma with the subsequent few progressions or recurrences easily controlled with additional local therapies and systemic therapies. Local ocular therapy may be more important in disease control than additional cycles of systemic chemotherapy with vincristine and carboplatin. However, the choice and timing of local ophthalmic therapies should also take into account the risk of vitreous relapse when diode laser treatment is used very early in the course of the disease [35].

In a Phase II randomized trial of neoadjuvant vincristine-carboplatin versus etoposide-carboplatin prior to local ophthalmic therapy, in 65 eyes in 55 children, 69.7% versus 81.2% of eyes, respectfully per study arm, were salvaged without the need for enucleation or external beam radiotherapy. Fifty percent of the eyes in this study were Group B in each of

the study arms, but there were also patients with Groups A, C and D eyes [23]. In another study by this group of investigators, 83 children (115 eyes) were treated with cycles of carboplatin with transpupillary thermotherapy, of whom 66 had treatment with neoadjuvant carboplatin and etoposide for two cycles. This study included patients with RE Groups I – V and 84% of eyes did not require enucleation or external beam radiotherapy [24]. When limited to the group of patients with RE Groups I – III eyes, our results are inferior compared to a regimen of carboplatin and etoposide, as reported by Beck and colleagues, where all 14 patients with Groups I – III eyes were successfully treated with carboplatin and etoposide with local therapy [22]. These data suggest that etoposide does contribute to improved external beam radiotherapy and enucleation free survival in children with retinoblastoma, although there remain a significant number of patients who respond well without the addition of this agent.

A group of patients for which carboplatin and vincristine therapy can be considered are those in low and middle-income countries (LMIC), where the additional systemic toxicity of etoposide requires supportive therapies not always readily available. Chantanda and colleagues evaluated this regimen, together with local ophthalmic therapy in children with RE Groups I – III eyes. Among 26 patients, with receipt of a median of four cycles (range 2 – 8) of this chemotherapy, the 5 – year probability of enucleation-free and external beam radiotherapy-free survival were 0.9 and 0.41 respectively. Two patients required the addition of etoposide for ocular salvage. These data suggest that this is an acceptable regimen in developing countries with results in selected high volume centers not too dissimilar to those from this COG study [36].

While certainly advantageous to start therapy promptly after diagnosis, increased time between diagnosis and start of therapy (range 0 – 27 days) only nominally increased risk of an event, but this was not significant. In our study, local therapies were allowed with the second course of chemotherapy to assess response to the first course of systemic chemotherapy and correlate the response to the outcome. Thus delays between time of diagnosis and start of treatment represented a delay in the start of systemic chemotherapy only. All patients in our study demonstrated tumor response after a single cycle of chemotherapy and all but two responded to six cycles. This is consistent with data from a study of 36 tumors measured after cycles of systemic carboplatin, where the cumulative decrease in area and diameter of tumors was greatest after 1–2 cycles, with less change thereafter [37]. Therefore, the delay in instituting local therapy in our study adversely affected outcome, as failures were local. It is well known that local control for most solid malignancies is optimal earlier in therapy, corresponding to the time period of optimal cytoreduction and prior to the development of chemoresistance. In addition, there appears to be a synergistic effect of the concurrent use of chemotherapy and local ophthalmic therapies. The sequential administration of carboplatin and thermotherapy enhances the antitumor effect by increasing the platinum-DNA adducts, and is commonly utilized in such a manner in the treatment of intraocular retinoblastoma [38–39]. Cryotherapy increases the intraocular penetration of carboplatin, presumably through disruption of the blood-vitreous barrier [40–41]. Laser ablation and diode laser hyperthermia may also act through this mechanism. We would suggest that local therapy be applied with every cycle of systemic chemotherapy.

While the use of vincristine and carboplatin in the absence of etoposide in our study did not produce the same EFS as regimens with vincristine, etoposide and carboplatin or carboplatin and etoposide, the balance between efficacy and potential toxicity should be considered. While etoposide can result in short-term toxicities such as myelosuppression and allergic reaction, its association with secondary leukemia was the driving motivation to attempt avoidance of its use in children with retinoblastoma. While not absent, reports of etoposide-associated secondary leukemia in patients with retinoblastoma remain low.^[9,42] In a review by Gombos and colleagues, by physician survey and review of databases with >1600 patients, 8 cases of secondary leukemia were identified among patients receiving 360 mg/m² to 2700 mg/m² of etoposide, but all in regimens other than carboplatin, etoposide and vincristine^[9]. In a cohort of 187 patients with heritable retinoblastoma treated with carboplatin, etoposide and vincristine without radiotherapy, 4% developed SMNs at a mean of 11 years of follow-up, with only a single reported leukemia, which was promyelocytic, not commonly thought to be associated with etoposide exposure. There were no SMNs among the 58 patients with non-heritable retinoblastoma. Patients in this cohort received 10 – 12 mg/kg of etoposide^[42].

The question therefore arises whether enucleation in 3 of 21 patients outweighs the benefit to 16/21 patients not receiving etoposide and thus avoiding, a very small increased risk of secondary leukemia. Although only two patients in our study required external beam radiotherapy as salvage therapy and all retained at least one eye, these salvage therapies might have been necessary in other patients who fail vincristine and carboplatin therapy. As radiotherapy, particularly in the first year of life, clearly increases the risk of SMN in patients with the genetic form of retinoblastoma^[10], this is of particular importance. If avoiding etoposide results in the need for external beam radiotherapy, this would be disadvantageous. Our patients who required salvage therapy were all less than 6 months of age at diagnosis and 7 to 22 months of age at time of recurrence and radiotherapy was delayed until after 12 months of age.

Particularly as this study proposed a reduction in therapy from what had been considered the standard for chemoreduction therapy, the role of central review for eligibility also proved critical. Of the seven patients excluded from this study, six would have been significantly under-treated by this therapy, as they had Group C or D eyes. For future cooperative group trials in retinoblastoma such consensus based central reviews are essential, particularly when therapy is based on clinical characteristics at the time of diagnosis.

When considering treatment for retinoblastoma, considerations must include survival of the child, retention of the affected eye and useful vision. Survival was 100% and ocular salvage was 85%. However, these results are somewhat limited by the lack of vision outcomes, as these were not collected as part of this clinical trial.

In summary, while this study was closed prematurely as per the statistical design, due to an excess number of failures, the EFS target was set very high. Ocular response was excellent and the majority of patients retained their eyes and were not exposed to the potential toxicities of etoposide or external beam radiotherapy. For Group B disease, when considering intravenous chemoreduction, the optimal chemoreduction therapy choice must

consider that the inclusion of etoposide with vincristine and carboplatin does offer better ocular salvage and avoids the need for salvage chemotherapy. However, this consideration should be balanced with the very small but not absent risk for secondary malignancy associated with etoposide. In general, etoposide-related leukemia has been reported in cohorts of patients treated for malignancies other than retinoblastoma with higher doses than that delivered in retinoblastoma therapy, and sometimes in combination with radiotherapy [30,43–44].

With advances in intra-arterial chemotherapy, available still only in select centers, changes in approach to treating retinoblastoma is evolving [25–29,45–46]. It is now reasonable to consider the use of intra-arterial chemotherapy for Group B eyes, as ocular salvage and disease control rates are favorable. However, chemoreduction with systemic chemotherapy together with combined local ophthalmic therapy remains an important treatment modality, for children too small for an intra-arterial approach or who do not have access to such therapies. For children too small for safe delivery of intra-arterial therapy, a study of 11 children (19 eyes) with RE Group I – V demonstrated efficacy of intravenous carboplatin alone until children were 3 months of age and 6 kg [47]. However, there have not yet been large studies to determine the best intravenous chemotherapy regimen to serve as a bridge to intra-arterial therapy.

For disease limited to Group B eyes, vincristine and carboplatin, although potentially less effective in ocular salvage, can continue to be considered, with a defined regimen that includes etoposide utilized only for a minority who have multiple tumors, particularly those located in areas less amenable to local therapies, or for those without adequate initial response to vincristine and carboplatin alone after 1–2 cycles. A vincristine-carboplatin regimen without etoposide may also serve as a bridge for young infants until they are old enough to receive intra-arterial therapy or for those in LMIC, where supportive care is more limited and myelosuppressive effects of etoposide may lead to unacceptable toxicity. When systemic chemotherapy is utilized, local ophthalmic therapy, which is safe and effective, should be considered with systemic chemotherapy to optimize response rate.

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Abbreviations

COG	Children's Oncology Group
CTEP	Cancer Therapy Evaluation Program
EBRT	External-Beam Radiotherapy
EFS	Event-Free Survival
EUA	Evaluation Under Anesthesia
IRB	Institutional Review Board

LMIC	Low and Middle-Income Countries
NCI	National Cancer Institute
OS	Overall Survival
QARC	Quality Assurance Radiotherapy Center
SMN	Subsequent Neoplasm
VC	Vincristine and Carboplatin

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V = Vincristine

C = Carboplatin

Local therapy = cryotherapy, diode laser thermotherapy, episcleral plaque radiotherapy (alone or in combination)

Figure 1.
EXPERIMENTAL DESIGN SCHEMA

Figure 2.
CONSORT DIAGRAM

Outcome Measure

— EFS

- - - OS

Figure 3.
EVENT- FREE AND OVERALL SURVIVAL

Table 1

Summary of Patient Presentation and Response

Patient Number	Age at Enrollment (years)	International Class Intraocular Retinoblastoma Right/Left	Number and Location of tumors ¹	Time from Diagnosis to Enrollment (Days)	Time from Enrollment to Event (months)	Treatment for Recurrence	Time from Enrollment to Last Seen (years)
1	1.3	E/B	1 – M (L)	2	N/A	N/A	5.1
2	0.9	E/B	1 – ME (R) 2 – EO (L)	1	N/A	N/A	3.7
3	0.7	B/Normal	1 – ME (R) 1 – EO (R)	6	N/A	N/A	8.5
4	0.3	B/B	1 – M 1 – ME (R) 1 – M (L)	2	7.5	Radiation	4.9
5	0.8	B/B	1 – M (R) 1 – ME (L)	1	14.4	Enucleation	7.8
6	0.8	E/B	1 – ME (L) 1 – EO (L)	3	N/A	N/A	7.8
7	0.1	E/B	3 – M (L)	9	6.9	Chemotherapy	7.0
8	0.1	B/Normal	1 – M (R)	4	N/A	N/A	5.4
9	0.3	E/B	3 – ME (R) 2 – EO (L)	27	7.5	Chemotherapy	6.6
10	0.02	B/A	1 – M (R)	4	N/A	N/A	5.1
11	0.09	Normal/B	1 – M (L)	13	N/A	N/A	5.8
12	0.2	B/Normal	1 – M (R)	2	N/A	N/A	6.8
13	0.2	B/Normal	1 – M (R)	10	19.7	Enucleation	5.4

Patient Number	Age at Enrollment (years)	International Class Intraocular Retinoblastoma Right/Left	Number and Location of tumors /	Time from Diagnosis to Enrollment (Days)	Time from Enrollment to Event (months)	Treatment for Recurrence	Time from Enrollment to Last Seen (years)
						Chemotherapy	
14	2.0	E/B	1 - ME (L) 1 - EO (L)	14	N/A	N/A	4.8
15	0.3	B/B	1 - M (R) 1 - M (L)	3	N/A	N/A	2.7
16	1.6	B/Normal	1 - M (R)	15	N/A	N/A	7.4
17	0.8	B/Normal	1 - M (R)	12	10.2	Enucleation	3.7
18	0.2	B/Normal	1 - M (R)	21	N/A	N/A	6.7
19	0.3	E/B	1 - ME (L) 1 - EO (L)	0	22.1	Radiation	3.5
20	0.9	Normal/B	1 - M (L)	1	N/A	N/A	3.0
21	0.4	B/Normal	1 - M (R)	9	N/A	N/A	3.2

Location of tumors; M = Macula; ME = From Macula to Equator; EO = From Equator to Ora Serrata

Table 2

Local therapies received by patients

Number of patients (%)	Argon Green Laser	Diode Red Laser	Cryotherapy	Plaque Therapy
4 (19.0)	None recorded	None recorded	None recorded	None recorded
1 (4.8)			X	
1 (4.8)			X	X
5 (23.8)		X		
3 (14.3)		X	X	
3 (14.3)	X			
2 (9.5)	X	X		
2 (9.5)	X	X	X	.