Title: Adjuvant use of laser in eyes with macular retinoblastoma treated with primary intravenous chemotherapy

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Synopsis: Adjuvant laser in combination with intravenous chemotherapy for the treatment of retinoblastoma is safe and results in few long-term complications. Laser use is not a significant factor in determining long-term visual prognosis of children with retinoblastoma.

Keywords: retinoblastoma, chemotherapy, laser

Abstract

Background: Adjuvant use of laser with systemic chemotherapy for treatment of retinoblastoma may reduce recurrence rates while also causing local side effects. Information is lacking on the effect of laser on visual outcomes.

Methods: A retrospective review of two retinoblastoma centers in the United Kingdom was conducted. Patients were included if there was a macular tumor in at least one eye. Eyes that received chemotherapy alone were compared to eyes that received chemotherapy plus adjuvant laser.

Results: A total of 76 patients and 91 eyes were included in the study. Systemic chemotherapy alone was used in 71 eyes while chemotherapy plus laser was used in 20 eyes. Demographic characteristics of both groups were similar. Macular relapse rates were similar between groups: 22/71 (31%) eyes in chemotherapy group, 9/20 (45%) eyes in laser group (p=0.29). There was no increase in vitreous relapses in the laser group (2/20 eyes), compared to the chemotherapy group 10/71 eyes (p=0.99). Survival analysis demonstrated similar time to first relapse between groups. Final visual acuity was equal between groups with 6/15 or better present in 31.1% of eyes in the chemotherapy group and 37.5% of eyes in the laser group (p=0.76). Presence of tumor at the fovea was predictive of final visual acuity, regardless of treatment group.

Conclusion: Adjuvant laser in the treatment of retinoblastoma is safe and does not lead to increased rate of vitreous recurrence. Final visual acuity is determined by presence of tumor at the fovea and not the use of laser.

Introduction

Laser treatment of intraocular retinoblastoma has been an important therapy for many years. Lasers are used for primary treatment of small tumors[1], adjuvant treatment of larger tumors in combination with chemotherapy[2,3], and as primary treatment of local recurrences[4]. Laser treatment combined with intravenous chemotherapy was shown to eliminate the need for external beam radiotherapy while maintaining high rates of local tumor control.[5–7]

Controversy exists regarding the use of laser for the treatment of retinoblastoma. The vast majority of tumors (72%) respond favorably to chemotherapy alone and do not require laser[8]. The addition of laser causes a progressive scar that may affect vision[9], may increase the rate of vitreous recurrence[10], and has been shown to result in orbital recurrence[11]. Conversely, combining thermal laser with systemic chemotherapy increases the rate of tumor control compared to chemotherapy alone[12,13] and recent research suggests that the foveal anatomy can be preserved with foveal-sparing laser even with parafoveal tumors[14]. There have been no clinical trials testing the effectiveness and long term side effect profile of adjuvant laser for the treatment of retinoblastoma[15]. There is a lack of information on the visual outcomes of children treated with adjuvant laser. The goal of this study was to evaluate the effectiveness of adjuvant laser for the treatment of retinoblastoma on outcomes including globe salvage, recurrence rate, and visual acuity.

Materials and methods

After ethics approval, a retrospective review was conducted in both retinoblastoma centers in the United Kingdom. The review included medical records of all patients diagnosed with retinoblastoma at the Royal London Hospital between 1999 and 2009 and at the Birmingham Children's Hospital between 2002 and 2006. These dates were determined independently by each center with the goal of allowing for long term follow-up of final vision. Inclusion criteria for the study included presence of a macular tumor, defined as any part of a tumor posterior to the superior or inferior arcades, in at least one eye at the time of presentation and use of intravenous chemotherapy as the primary treatment. Eyes undergoing primary treatment with enucleation or radiation were excluded.

All children were treated with six courses of intravenous chemotherapy consisting of vincristine, etoposide, and carboplatin (VEC) via a central line. The decision to begin treatment with chemotherapy alone or with empiric, adjuvant laser treatments applied to the macular tumors was left to the discretion of the treating surgeon. There were no set guidelines as to whether each patient would be treated with laser initially; this decision was made based on weighing the risks of tumor recurrence vs. vision loss due to macular laser. When laser was used empirically with VEC for chemoreduction, it was applied after completion of 1-2 cycles of VEC to all macular tumors and was continued at each examination under anesthesia, occurring every 1-2 months during VEC, until the tumor was completely regressed. All surgeons treated the entire tumor surface using indirect ophthalmoscopic laser delivery, in the case of 532nm laser this was done in a dot-matrix pattern while in the case of the 810nm laser this was done with a continuous beam. Each tumor was treated to its edge. A foveal-sparing paradigm was used which included sparing the area within 1.5mm of the fovea as well as the papillomacular bundle, as previously described by Shields et al.[12] **Figure 1** demonstrates the fundus photo for a representative patient treated by the authors in both groups: chemotherapy versus laser. Additional laser treatments were provided ad hoc in the following three situations: a new posterior tumor in any patient, a posterior edge recurrence in any patient, or a tumor not responding to VEC in the group who did not initially receive laser. Laser settings varied between surgeons, with some preferring an 810nm thermal laser and others preferring 532nm green laser. Additional adjuvant treatments were also performed at the discretion of the treating surgeon and included cryotherapy, ruthenium plaque brachytherapy, external beam radiotherapy, or secondary enucleation.

Data were analyzed based on whether laser treatment was started empirically at the time of chemotherapy initiation or if local treatments were deferred until tumor recurrence or relapse. The groups were compared based on demographics and outcome measures including: age, sex, laterality, International Intraocular Retinoblastoma Classification (IIRC)[16], adjuvant treatments, globe salvage, presence and timing of recurrence, total follow up time (from date of presentation to last follow up), tumor distance to fovea and final visual acuity. Eyes that presented prior to the IIRC guidelines were classified retroactively based on data at the time of presentation, photographic documentation was used where necessary. Data were analyzed using the R Statistical Environment. Categorical data and contingency tables were evaluated with Fisher's exact test. Continuous variables were compared using Student's t-test. Kaplan-Meier survival analysis was used to estimate the time to first relapse in both groups. First relapse in this sense refers to either development of a new tumor or recurrence of a previously treated tumor. These curves were compared using a log-rank test. An alpha level of 0.05 was

assumed. In this hypothesis generating analysis the use of multiple comparison corrections was not necessary.

Results

A total of 76 patients and 91 eyes met inclusion criteria for the study. Intravenous chemotherapy alone ("chemotherapy" group) was started in 71 eyes while chemotherapy plus laser ("laser" group) was started in 20 eyes. Demographic characteristics of the two groups are reported in **Table 1.** There was no difference between groups for the following variables: age, laterality, IIRC stage, follow-up time, number of chemotherapy cycles, duration of active treatment (defined as time from first dose of chemotherapy to the last treatment of any kind), and tumor distance to fovea. There was a difference in the number eyes of male patients in the chemotherapy group, 30 out of 71 (42%), compared to the laser group, 14 of 20 eyes (70%, p=0.04).

The number of eyes requiring adjuvant or second line treatments is reported in **Table 1**. There were significantly more eyes requiring adjuvant cryotherapy in the chemotherapy group (33/71 eyes, 46%) compared to the laser group (2/20 eyes, 10%, p=0.004). There was otherwise no difference in the number of adjuvant treatments between groups including a similar number of secondary enucleations. There was no difference in the number of treatment failures (enucleation or external beam radiotherapy "EBRT"): 26/71 (37%) in chemotherapy group, 4/20 (20%) in laser group (p=0.19). The failure rate was uniform across IIRC groups in the chemotherapy group while in the laser group there were significantly more failures in Group D eyes (**Table 1**).

Tumor relapse or recurrence, which we defined as local recurrence to a treated tumor or new tumor in the retina or vitreous in any location of the eye, was seen in 48 of 71 eyes (68%) in the chemotherapy group and in 10 of 20 eyes in the laser group (50%, p=0.19). Macular relapse or recurrence specifically was seen in 22 of 71 eyes in the chemotherapy group (31%) and in 9 of 20 eyes in the laser group (45%, p=0.29). The mean number of all relapses was significantly higher in the chemotherapy group (2.0) compared to the laser group (0.9, p=0.01). This trend was not present for the mean number of macular relapses specifically (0.5 in chemotherapy group, 0.8 in laser group, p=0.42). The rate of relapse in the vitreous, including new vitreous seeds or relapse at the vitreous base, was equal between the two groups with 10 vitreous relapses in the chemotherapy group, which represents 14.1% of eyes (10/71) and 20.8% of all relapses (10/48), and 2 vitreous relapses in the laser group, representing 10% of eyes (2/20) and 20% of all relapses (2/10) (**Table 1**). Kaplan Meier survival analysis demonstrated no difference in the time to first relapse between the chemotherapy and laser group (p=0.7, **Figure 2**).

Eyes treated with enucleation or EBRT were excluded from the visual acuity analysis. Vision was assessed categorically using two thresholds similar to previous reports of vision in young children with retinoblastoma[17]: "Good" vision with Snellen-equivalent acuity of 6/15 or better, and "Poor" vision with Snellen-equivalent acuity of 6/60 or worse. The proportion of eyes with final "Good" vision was similar between groups: 14 of 45 (31.1%) of eyes in the chemotherapy group and 6 of 20 (30%) of eyes in the laser group (p=0.76). The proportion of eyes with final "Poor" vision was also similar between groups: 20 of 45 eyes (44.4%) in the chemotherapy group and 14 of 20 eyes (70%) in the laser group (p=0.25, **Table 1**).

Tumor location was a significant risk factor for final visual acuity. Of the 20 eyes with "Good" final vision, 5 (25%) had tumor involvement at the fovea while in eyes with "Poor" final vision 27 out of 30 eyes (90%) had tumor at the fovea (p=0.000004, **Table 2**). The same trend was present and equal in both the

chemotherapy and laser groups. There was no statistical difference between the final visual acuity of the chemotherapy and laser group when analyzed based on presence of foveal tumor involvement (p=0.99, **Table 2**)

An argon laser with 532 nanometer (nm) wavelength was used as initial treatment in 11 of the 20 eyes in the laser group while diode laser (810nm) was used in the remaining 9 eyes. The characteristics of these two groups were compared. One eye that was initially treated with each laser type (532nm and 810nm) was switched to the other laser type for subsequent treatments due to non-response of the tumor. There was no difference in the mean number of laser treatments required between the two laser types (mean number of treatments in 532nm group 5.6 vs. 5.2 in the 810nm group, p=0.78). There was no difference in the number of relapses between groups (4 of 11 in the 532nm group, 5 of 9 in the 810nm group, p=0.65). There was no difference in the final visual acuity between groups (9 or 11 eyes had final acuity or 20/50 or better in the 532nm group, 4 of 9 had good vision in the 810nm group, p=0.33)

Discussion

Despite its widespread use, there is limited information regarding potential toxicity and the long-term visual effects of adjuvant laser for treatment of retinoblastoma. Laser has been shown to improve the success of systemic chemotherapy [5–7] and reduce local recurrence rates[12]. However, it has also been implicated in causing increased rates of vitreous relapse[10] and extra-scleral spread[11]. The results of this two-centered study show no difference between recurrence rates of eyes treated with chemotherapy alone versus chemotherapy plus adjuvant laser. In contrast to previous reports, we did not see an increase in the rate of new vitreous seeds in eyes treated with laser. In those reports showing increased risk of vitreous relapse[10] the laser settings were often longer with a mean of 9 minute applications compared to the shorter durations modern laser delivery systems.

In this study, the rate of treatment failures (enucleation or external beam radiotherapy) was similar between the chemotherapy group and the laser group. There was no statistical difference in treatment failure across IIRC classification in the chemotherapy group: Group A (33%), Group B (24%), Group C (27%), Group D (50%). However, all treatment failures in the laser group were found in Group D eyes, where all four eyes in the study resulted in treatment failure. A possible explanation of this finding may be that the addition of laser can improve outcomes in less advanced eyes where seeding (subretinal and vitreous) is less prevalent but has less effect on more advanced eyes with more seeding. This explanation would be supported by previous reports of improved outcomes in early stage eyes with addition of adjuvant laser[12]. Cryotherapy was required more frequently in the chemotherapy group. This would likely be explained by the presence of more peripheral tumors in this group but would not likely be a result of differences in the macular tumors between groups.

Findings of the present study showed that the application of laser did not affect the long-term visual prognosis. After an average of 70 months of follow-up, eyes that received adjuvant laser demonstrated similar rates of “good” and “poor” vision compared to eyes treated with chemotherapy only. The location of the tumor, however, was a significant predictor of long-term visual outcome. Eyes with tumor at the fovea had very high rates of “poor” final vision while eyes without tumor at the macula had high rates of “good” final vision. This was true for the entire cohort as well as both the chemotherapy group and the laser group independently. Final visual outcome is dependent on whether a tumor has invaded the fovea and does not appear to be related to the use of adjuvant laser.

This study has several limitations. The data were obtained retrospectively. There authors did not have access to optical coherence tomography images to assess foveal anatomy before and after treatment, something that has been shown to be affected by laser[14]. The patients and eyes in this study were treated by four different retinoblastoma specialists at two different centers. The methodology and treatment strategies of each consultant are independent of one another. There was no formal guideline provided to determine which eyes would be treated with adjuvant laser. This may introduce bias into the two groups. However, the demographic data were largely similar between groups including tumor characteristics (size, location). There were more males in the laser group (70%) compared to the chemotherapy group (42%, p=0.04), but sex differences are unlikely to affect outcomes.

Another limitation is the diversity in laser techniques. Nearly half of the eyes treated with laser (9 out of 20) were treated with a diode 810nm beam while the rest (11 out of 20) were treated with an argon 532nm beam. The dose and duration of laser was not standardized, and each specialist treated according to their own experience. These factors may also introduce bias into the results. However,

there was no statistical difference in the tumor characteristics nor in the treatment outcomes of eyes treated with 810nm laser versus eyes treated with 532nm laser.

The study was conducted using patients who presented between 1999 and 2009 in order to obtain long term visual outcomes. These patients were treated prior to the time of intra-arterial and intra-vitreal chemotherapy. While the delivery method and globe salvage rates may be different today than in 2009, we believe the utility, safety, and visual risks of laser remain the same.

Conclusion

Adjuvant laser in the treatment of retinoblastoma is safe and does not lead to increased rate of vitreous recurrence. Final visual acuity appears to be determined by presence of tumor at the fovea and not by whether laser is used, as long as a foveal-sparing paradigm is used.

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Competing Interests Statement

The authors have no competing interests to disclose

Contributorship Statement

MAH, JA, MS, and MP conceived of the study, treated the patients, and provided critical review of the manuscript. BM, ZN, VS, HK, and ST treated patients and provided critical review of the manuscript. MT, IDF, and AWS analyzed the data and wrote the manuscript.

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Table 1: Demographics and treatment outcomes between chemotherapy group and chemotherapy plus laser group in 91 eyes of 76 retinoblastoma patients.

	Chemotherapy Group (n=71 eyes)	Laser Group (n=20 eyes)	P value
Male	30/71 (42%)	14/20 (70%)	
Female	41/71 (58%)	6/20 (30%)	0.04
Bilateral	50/71 (70%)	15/20 (75%)	0.79
Unilateral	21/71 (30%)	5/20 (25%)	0.79
Mean age at diagnosis (months, range)	9.9 (0.2-72.8)	8.1 (0.2-20.2)	0.31
Mean duration of treatment (months, range)	18.2 (3.5-78.2)	12.7 (3.7-74.6)	0.17
Mean total follow up (months, range)	88.9 (32-188)	70.3 (12-152)	0.09
Mean number of chemotherapy cycles (range)	6.3 (4-8)	6 (2-8)	0.26
ADJUVANT AND SECONDARY TREATMENTS			
Second line chemotherapy	10/71 (14%)	1/20 (5%)	0.44
Cryotherapy	33/71 (46%)	2/20 (10%)	0.004
Plaque Brachytherapy	12/71 (17%)	1/20 (5%)	0.28
Orbital floor carboplatin	3/71 (4%)	2/20 (10%)	0.3
Intra-arterial chemotherapy	2/71 (3%)	0/20 (0%)	>0.99
EBRT	15/71 (21%)	1/20 (5%)	0.18
Enucleation	14/71 (20%)	4/20 (20%)	1
Treatment failure (EBRT or Enucleation)	26/71 (37%)	4/20 (20%)	0.19
TREATMENT FAILURE BY ICRB GROUP			
Group A: Total (% Overall)	3 (4%)	3 (15%)	
Group A: Failures (% of Group)	1 (33%)	0 (0%)	
Group B: Total (% Overall)	21 (30%)	9 (45%)	
Group B: Failures (% of Group)	5 (24%)	0 (0%)	
Group C: Total (% Overall)	15 (21%)	4 (20%)	
Group C: Failures (% of Group)	4 (27%)	0 (0%)	
Group D: Total (% Overall)	32 (45%)	4 (20%)	0.08
Group D: Failures (% of Group)	16 (50%)	4 (100%)	
RELAPSE			
Relapse in eye	48/71 (68%)	10/20 (50%)	0.19
Relapse in macula	22/71 (31%)	9/20 (45%)	0.29
Mean number of relapses	2	0.9	0.01
Mean number of macular relapses	0.5	0.8	0.42
Number of vitreous relapses	10	2	0.99
FINAL VISUAL ACUITY			
Final vision 6/15 or better (overall)	14 / 45	6 / 16	0.76
By ICRB Group: Group A	1 / 2	2 / 3	
Group B	8 / 16	4 / 9	
Group C	3 / 11	0 / 4	
Group D	2 / 16	All Failures	
Final vision 6/60 or worse (overall)	20 / 45	10 / 16	0.25
By ICRB Group: Group A	1 / 2	1 / 3	
Group B	4 / 16	5 / 9	
Group C	5 / 11	4 / 4	
Group D	10 / 16	All Failures	

[1]Intravenous chemotherapy only

[2]Intravenous chemotherapy plus adjuvant laser therapy

Table 2: Visual outcomes based on tumor involvement at the fovea

		Good Vision (6/15 or better)	Poor Vision (6/60 or worse)	P-value
Whole Cohort	Fovea not involved (n=)	15	3	
	Fovea involved (n=)	5	27	<0.001
Chemotherapy Group	Fovea not involved (n=)	10	2	
	Fovea involved (n=)	4	18	<0.001
Laser Group	Fovea not involved (n=)	5	1	
	Fovea involved (n=)	1	9	0.008

Figure 1: Representative fundus images of patients treated by the authors that would be analyzed in the (A) chemotherapy alone group and the (B) chemotherapy plus laser group (these patients were not treated in the years of this study). The patient treated with laser (B) was treated with continuous 810nm laser for 3 total treatments during routine chemotherapy cycles. Laser was applied to the superior aspect of the macular tumor, sparing the parafoveal, inferior portion of the tumor.

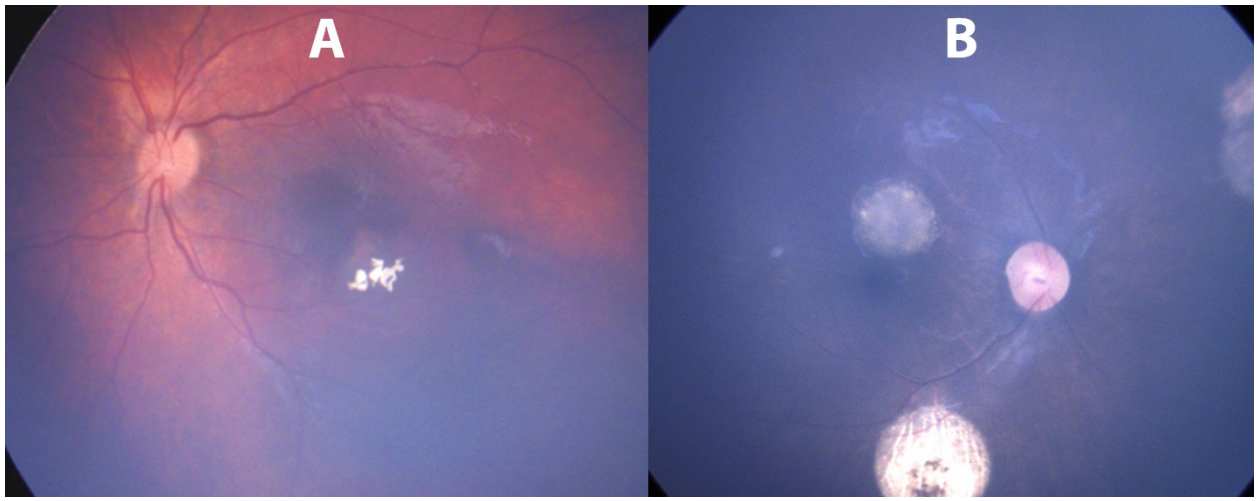

Figure 2: Kaplan-Meier estimate of relapse free survival for the chemotherapy group and the chemotherapy plus laser group. There was no statistical difference between groups.