CASE SERIES

Outcome of focal treatment to residual retinoblastoma after chemotherapy (Experience with Focal Treatment of Retinoblastoma)

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Abstract

We report a prospective case series on the anatomical, and functional outcomes, and complications of focal treatment of retinoblastoma to residual tumors in patients who had already received chemotherapy.

We examined the patients of retinoblastoma under general anaesthesia with Ret Cam II. Patients with lesions from Group 1 to Group 5 of Reese Ellsworth classification at presentation. They were first given chemotherapy according to VEC (Vincristine, Etoposide and Carboplatin) protocol and then focal treatment.

Solid State Green laser photocoagulation and/or cryotherapy were applied to the lesions with help of indirect ophthalmoscope.

Thirty one eyes of 26 children were treated. The mean age at presentation was 35.5 ± 6.4 (median = 24, IQR = 36) months. Fourteen (57.7%) were male and 12 (42.3%) were female. Twenty three (88.5%) children had bilateral retinoblastoma and 3 (11.5%) had unilateral involvement. Complete regression was achieved in 25 (80.6%) eyes. Only 6 (19.4%) eyes had to be enucleated. Final mean LogMAR visual acuity after treatment was0.6 ± 0.64. Transient Corneal oedema was the most commonly observed adverse effect seen immediately after laser photocoagulation in 12 (38.7%) eyes.

Focal treatment is a good and effective adjuvant to systemic treatment and ophthalmologists should be aware of this modality of treatment and competent enough to use these modalities appropriately to improve the outcome of RB patients in our population.

Keywords: Retinoblastoma, Cryotherapy, Chemotherapy, Radiotherapy.

Introduction

Retinoblastoma (RB) is the most common intraocular malignancy of childhood with reported universal incidence of 3.4 to 42.5 per million children.[1,2] Radiotherapy or enucleation was primarily used for treatment earlier.[3] Chemotherapy was described by Shields et al in 1996 as primary management of intraocular RB to avoid enucleation or External Beam Radiation Therapy (EBRT).[4] EBRT remained as a globe salvaging treatment after chemotherapy failure.[5] EBRT has its own disadvantages of radiation induced complications with minimal chances of retaining useful vision. Other modalities of treatment are being used as an adjunct to chemotherapy as globe and vision salvaging modalities. These include laser photocoagulation,[6,7] cryotherapy,[8-10] subconjuctival carboplatin[11] and intra arterial chemotherapy in ophthalmic artery.[12,13]

We describe our experience with focal laser photocoagulation and cryotherapy after chemotherapy to avoid enucleation or EBRT.

Patients and Methods

This is a prospective case series. Patients with definitive diagnosis of RB (newly or previously diagnosed and referred from elsewhere) registered at Civil Hospital Karachi from February 2009 to December 2012, were included in the study. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Dow University of Health Sciences, Karachi. Patients with prior history of any focal or globe salvaging treatment like EBRT, cryotherapy or laser photocoagulation were not included in the study. We applied focal treatment to those eyes which did not respond well to chemotherapy and were noted to have residual active tumour after completion of chemotherapy. Eyes with anterior segment seedlings, rubeosisiridis, posterior synechiae, complicated cataract, ciliary body involvement and retinal detachment with massive vitreous and/or subretinal seedlings were excluded from the study. These eyes were enucleated without any focal intervention. Parents were explained about the treatment and an informed consent was obtained from them.

The examination was performed under general anaesthesia with Ret Cam II (Clarity Medical Systems, Inc.

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Pleasanton, CA, USA). This was saved as baseline data. This examination was complemented by indirect ophthalmoscopy to have overall stereoscopic view of the lesions in the fundus. Lesions were classified according to Reese Ellsworth (RE) Classification. Brain and distant metastases were excluded by MRI brain, bone scan, bone marrow analysis and CSF analysis. All patients were referred for chemotherapy to Children Cancer Hospital Karachi. After completion of chemotherapy, if residual tumour was found on Ret Cam examination, local therapy was applied.

Chemotherapy

All patients received systemic chemotherapy according to VEC Protocol (Carboplatin 550mg/m^2 day 1, Vincrisitne 1.5mg/m^2 day 1 and Etoposide 100mg/m^2 day 1, 2 and 3). Almost all patients had 6 cycles of chemotherapy (maximum 8 cycles). Patients were followed up after every 2 cycles of chemotherapy with Ret Cam photographs on each follow up.

Focal therapy

Lesions were categorized according to their location with reference to optic disc in 3 categories. Active foci presenting within 1.5 disc diameter of the disc temporally were categorized as macular, lesions located near the arcuate vessels but not involving macula were labeled as paramacular and all other tumours were categorized as peripheral tumours. Solid State green laser of 532nm wavelength (Oculight TX, Iridex, USA)was applied with indirect ophthalmoscope to the lesions located at the posterior pole. The lesion was encircled by 2 rows of laser

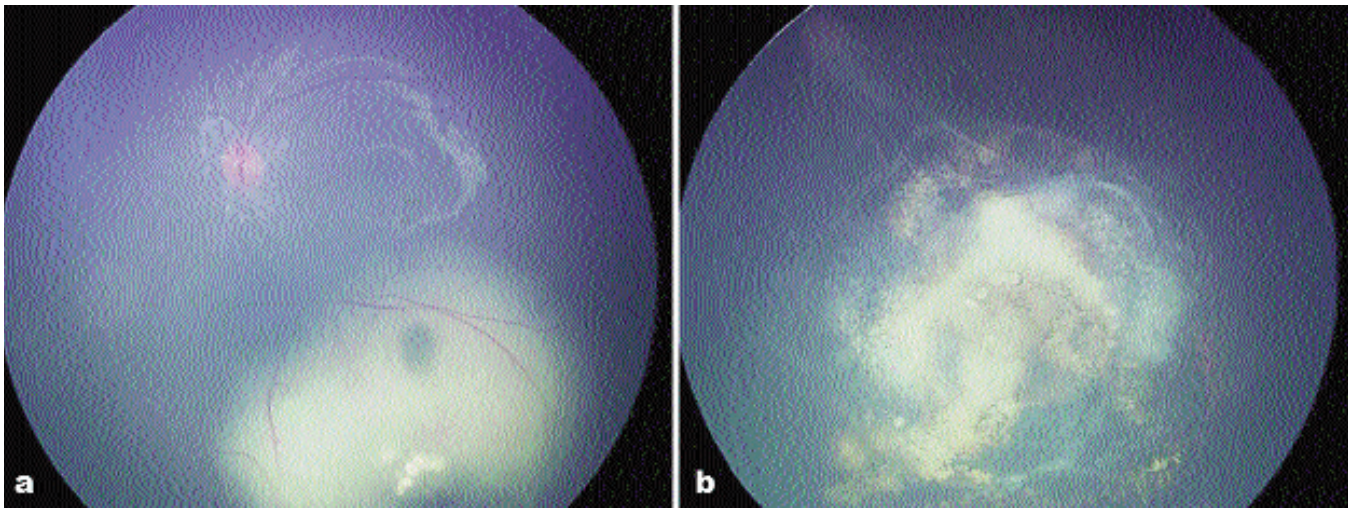

Figure-1: (a) Before Focal laser photocoagulation. (b) After 4 sessions of Laser Photocoagulation.

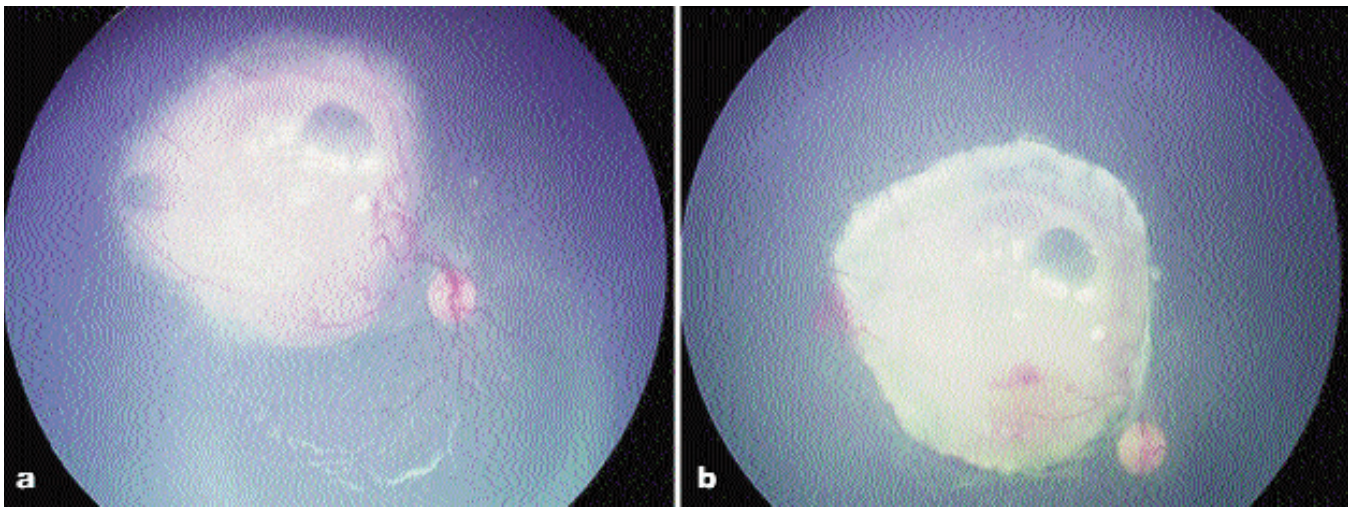

Figure-2: (a) A large residual tumour after chemotherapy . (b) Fresh laser marks are visible on the surface of tumour with localized haemorhage.

application with power of 100mW to 300mW. Surface of the lesion was also ablated with power in the range of 300mW to 1000mW starting with the lowest power and gradually increasing the power as required, depending on presumed thickness of the tumour on stereoscopic view of indirect ophthalmoscope. Cryotherapy with triple freeze thaw technique was applied to leisions located anteriorily and not fully accessible to ablation with laser. Post treatment photographs were taken each time. Patients were followed up after 4 weeks of the treatment. A completely calcified mass or an excavated scar with no dilated feeder vessels was considered as inactive or regressed lesion. If there was grey hue and/or dilated tortuous feeder vessels the lesion was considered to be active and further laser sessions were repeated until the tumours completely regressed. If lesion showed increase in size or activity with or without massive vitreous involvement at any time during the follow up visits, focal treatment was abandoned and eyes were either enucleated or EBRT was applied. Log MAR visual acuity was assessed after completion of treatment and on each follow up visit on every 3-6 months after complete regression.

Treatment was considered successful when there was complete regression with potential vision. Treatment was recorded unsuccessful when there was increased in vitreous seedlings, size of the tumour, and exudative retinal detachment with no potential vision. All these failure outcomes resulted in the need of enucleation or EBRT.

Figures-1 a and b, Figure-2 a and b are showing the fundal photographs of the patients treated.

Statistical Analysis

The data was analyzed with SPSS v.16.0. Frequencies were computed for each group of the Reese Ellsworth (RE) classification. Statistical significance of difference in outcomes, length of follow up and final Best Corrected Visual Acuity (BCVA) in each stage of RE was calculated using the Kruskall Wallis H test. A p value < 0.05 was considered significant. The data was analyzed with SPSS v.16.0. Mean, median and modes were calculated for quantitative variables. Frequencies were computed for each group of the Reese Ellsworth (RE) classification. Statistical significance of difference in outcomes, length of follow up and final Best Corrected Visual Acuity (BCVA) in each stage of RE was calculated using the Kruskall Wallis H test. A p value < 0.05 was considered significant. For the purpose of analysis Snellen's BCVA was converted to LogMAR scale.

Results

Thirty one eyes of 26 children were included. The average age at presentation was 35.5 ± 6.4 (median = 24, IQR = 36) months. Out of these children, 14 (57.7%) were male and 12 (42.3%) were female. Twenty three (88.5%) children had bilateral retinoblastoma and 3 (11.5%) had unilateral involvement. Eighteen children had only one functional eye at first session of focal treatment as other had already been enucleated. Twenty one children were treated in only one eye and 5 required treatment in both eyes. Number of eyes in different groups of Reese Ellsworth classification is given in Table-1. Twenty eyes were treated with laser photocoagulation at peripheral retina, 2 at para macular area and 10 at macula. Complete regression was noted in 25 (80.6%) eyes. Only 6 (19.4%) eyes had to be

Table-1: Number of eyes in each stage according to RE classification.

RE Stage	No. of Eyes (n)	Percentage (%)
1	3	9.7
2	5	16.1
3	11	35.5
4	7	22.6
5	5	16.1
Total	31	100

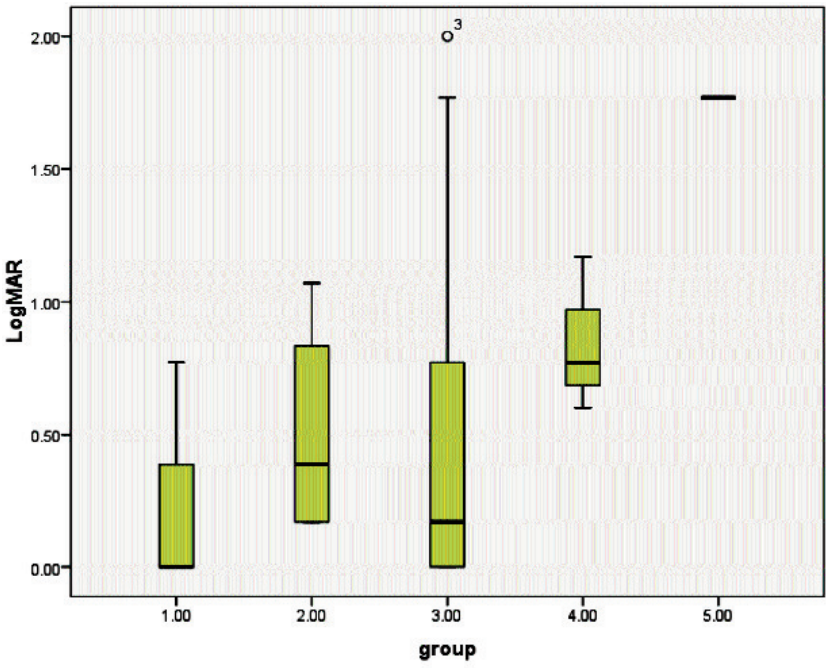

Figure-3: Box Plot showing comparison of visual acuities in each group after complete treatment.

Table-2: Characteristics of patients.

S. No.	Gender	Age at presentation (months)	Laterality of Retinoblastoma	Stage of treated eye	Only eyed	Site of application	No. of sessions	Outcome	LogMAR	Complication
1	Male	24	Bilateral	3A	Y	Peripheral	1	Lost to follow up		Corneal oedema
2	Female	12	Bilateral	3A	Y	Peripheral	6	Complete regression	0	Localized haemorrhage+ corneal oedema
3	Female	36	Unilateral	5A	N	Macular	2	Enucleation	--------	Corneal Oedema+ Exudative retinal detachment + Increased activity
4	Male	24	Bilateral	2A	Y	Periphery	4	Complete regression	1	Death due to respiratory infection
5	Male	60	Bilateral	2B (OD)	N	Periphery	6	Complete regression	0.60	----------
				5B(OS)		Periphery	4	Enucleation	-------	Increased vitreous seedling with no remaining fundal view
6	Male	48	Bilateral	4A	Y	Macular	6	Enucleation	--------	Increased vitreous seedling+ increased number of masses+anterior segment infiltration
7	Female	36	Bilateral	1A	Y	Peripheral	4	Complete regression	0.77	Corneal oedema
8	Male	12	Bilateral	3A	Y	Peripheral	3	Complete regression	0.60	----------
9	Female	4	Bilateral	5A	N	Para macular	3	Completer egression	0.87	----------
				4A		Peripheral	5	Enucleation	------	----------
10	Female	24	Bilateral	3A	Y	Peripheral	2	Complete regression	0.00	Localized haemorrhage
11	Female	24	Bilateral	3A	Y	Peripheral	1	Complete regression	0.00	Localized haemorrhage
12	Male	24	Bilateral	4A	Y	Peripheral	4	Complete regression	0.00	Localized haemorrhage + Corneal oedema
13	Male	24	Unilateral	2A	Y	Peripheral	2	Complete regression	0.60	
14	Female	24	Bilateral	3A	Y	Macular	2	Complete regression	1	Localized haemorrhage
15	Female	3	Bilateral	2A	N	Peripheral	1	Complete regression	0.16	Corneal oedema
				3A		Macular	3	Complete regression	1.69	Localized haemorrhage+ corneal oedema
16	Female	7	Bilateral	5B	Y	Macular	4	Enucleation		Massive vitreous seedling + Corneal odema
17	Male	36	Bilateral	2A	Y	Macular	8	Complete regression	1	Localized tractional retinal detachment
18	Female	60	Bilateral	4A	Y	Macular	3	Complete regression	0.77	Localized tractional retinal detachment+ Corneal odema
19	Male	36	Bilateral	4A	N	Macular	2	Complete regression	0.60	
20	Male	12	Bilateral	5B	Y	Macular	2	Enucleation		Vitreous haemorrhage + Corneal oedema
21	Female	96	Bilateral	3A (OD)	N	Peripheral	1	Complete regression	0.60	
				3A (OS)		Macular	1	Complete regression	Perception of light	
22	Female	48	Unilateral	1B	N	Peripheral	4	Complete regression	0.00	----------
23	Male	142	Bilateral	3B	N	Peripheral	2	Complete regression	0.00	
24	Male	24	Bilateral	4A	N	Peripheral + Para macular	4	Complete regression		Corneal oedema
				4A		Peripheral	3	Complete regression		
25	Male	41	Bilateral	3B	Y	Peripheral	3	Complete regression	0.00	Localized haemorhage
26	Male	6	Bilateral	1A	Y	Peripheral	1	Complete regression	0.00	

(OD= Right Eye, OS=Left Eye, Y=yes, N= NO)

Table-3: Frequency of Complications of focal treatment (Eyes).

Complications	No. of Eyes (n)	Percentage of total Number of eyes treated (%)
Corneal oedema	12	38.7
Localized haemorrhage	7	22.6
Increased vitreous seedling	2	6.4
Localized Tractional RD	2	6.4
Vitreous haemorrhage	1	3.2
Exudative retinal detachment	1	3.2
Total	25	

enucleated eventually due to progression of tumour despite treatment. Table-2 shows the individual characterstics of all the patients.

Average LogMAR BCVA after treatment was 0.60 ± 0.64 (Median = 0.60, IQR = 0.92). Figure-1 shows the group wise final LogMARBCVA. It may be noted that the outcome in terms of BCVA is highly dependent on the region of the retina involved for example an eye with a macular pathology treated successfully by a single session of treatment will have a poor final BCVA as compared to an eye with a paramacular or peripheral tumour requiring multiple sessions of treatment for eventual regression but preserved macula. VA tended to be better with lesser stages of the disease in which the tumour is small except in stage 3 which incidentally contained most patients without macular involvement. The difference in Visual outcomes across groups was statistically insignificant (p = 0.26, Kruskall Wallis test). Table-2 shows characteristics of our patients. Patient 3 was treated for a large macular retinoblastoma. It showed regression after first session. When patient was seen after 2nd session, there was total exudative retinal detachment with severe activity in the vitreous and finally the eye had to be enucleated.

Patient 5, 6 and 16 were given focal laser photocoagulation after completion of chemotherapy. They showed marked regression in after first 3 sessions but thereafter developed increased activity and massive vitreous seedling. Patient 6 also developed anterior segment seedling. EBRT was first given in these patients but the tumour activity did not reduce and eventually these eyes were enucleated.

Patient 9 responded very well initially. After about 1 year of complete regression, she had recurrence in her left eye with large tumours. She was again given chemotherapy. Lesions did not regress and finally the eye was enucleated. After few months of enucleation, she developed pinealoblastoma and died of cerebral metastases.

We found very poor response with group 5 in which 80% (4 out of 5) of the eyes had to be enucleated even after EBRT (Figure-2). The difference in outcome (Regression or EBRT or Enucleation) across different stages was statistically significant (p=0.003, Kruskall Wallis H test).

The mean length of follow up across our patient

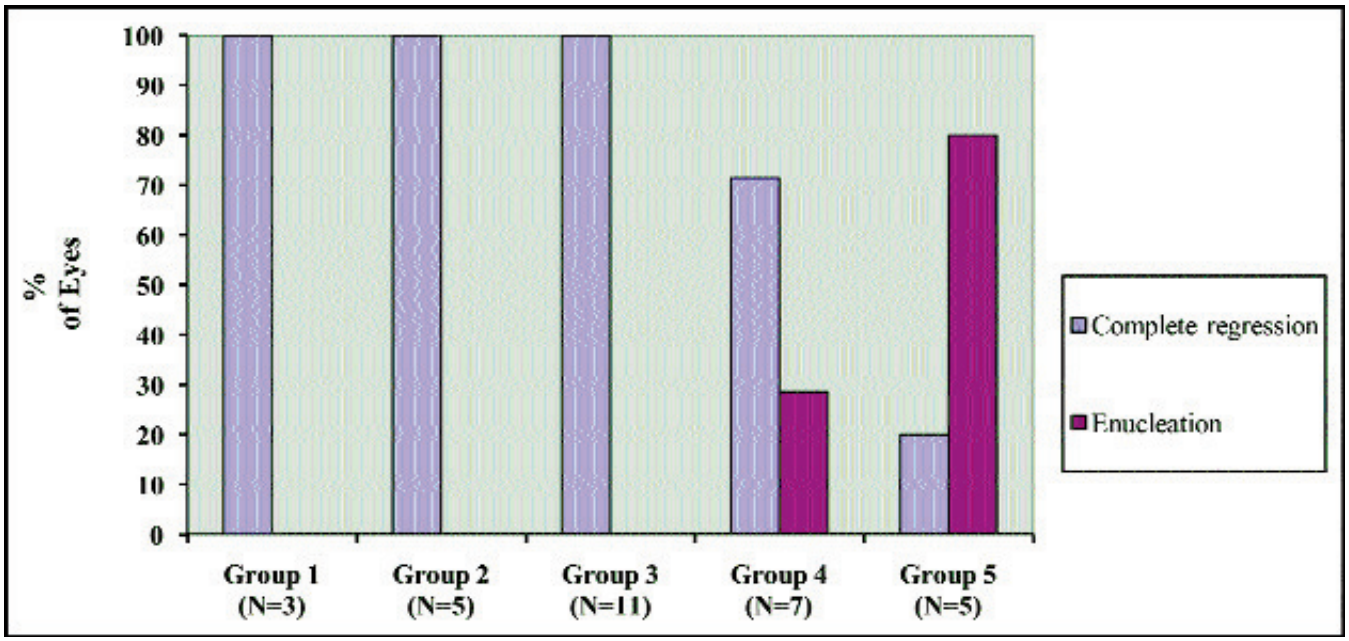

Figure-4: Bar Chart showing outcome with reference to stage.

population was 32.1±3.9 months. The difference in followup periods across different stages was statistically insignificant (p = 0.054, Kruskall Wallis H test) (Figure 3-4).

Observed complications of focal treatment are given in Table-3. Corneal oedema frequently developed per operatively, halting the view of the fundus for further application. It settled on its own after 24 hours. Localized haemorrhages developed sometimes in few patients at some sessions. These haemorrhages resolved after 6-8 weeks.

Discussion

This study was conducted to assess the efficacy of local therapy after chemotherapy failure or after partial response and to find the role of focal therapy to avoid enucleation or EBRT. Side effects of EBRT are dose related and include dry eye, radiation induced cataract, vitreous haemorrhage, radiation retinopathy and neuropathy, poor orbital development and most dangerous is radiation induced secondary malignancies.[14-16] Reported rates of globe preservation after EBRT are stage dependent e.g 91% for group 1 and 29% for group 5 of RE classification.[17,18]

Initially Xenon arc photocoagulation was used to treat RB. The use of laser was limited to small tumours of less than 3 mm in diameter and those which were away from the macula.[19] EBRT remained a common modality for large visually threatening RB. Trends grew for combined chemotherapy and focal therapy to avoid radiation and its side effects. Trends in focal therapy include thermotherapy, laser photocoagulation, cryotherapy, intra arterial chemotherapy and local periorbital or intravitreal chemotherapy.[20,21]

Gallie et al[22] reported 89% relapse free rate in patients treated with chemoreduction than focal consolidation with laser photocoagulation or cryotherapy. He found 88% relapse free rate in eyes with advanced involvement. We experienced one intraocular relapse after focal laser consolidation with pinealoblastoma and one child presented with Exudative retinal detachment with severe activity 4 weeks after focal laser treatment. It was an unusual experience as it could be due to tumour dispersion after laser treatment or natural course of RB.

Murphree et al[23] described their experience in 38 eyes with RE group 1-5B. They combined Platinum based chemotherapy with local treatments. They had complete reduction of the tumour in all eyes with group 1-4 involvement but failed in eyes with massive subretinal seedlings and vitreous involvement. Shield et al[24] succeeded in avoiding enucleation or EBRT in 25% eyes with group 5 involvement. Enucleation rate in our series was 19.35% .

Friedman et al[25] described 76% rate of avoidance of EBRT or enucleation after adjuvant local therapy. He offered cryotherapy, laser photocoagulation and plaque radiotherapy as local adjuvant. He experienced that 33 % of patients with group 1-4 RB needed to be enucleated or treated with EBRT in comparison to 53% of group 5 RB. No patient of this series developed recurrence or pinealoblastoma. We had to enucleate 4 out of 5 (80%) eyes in group 5 compared to 30% eyes in group 4.

Yoo et al[26] reported salvage of 6 out of 10 eyes with chemotherapy and local therapy only.

Schiaveti et al[27] studied response of combined chemotherapy and local therapy in 58 eyes of newly diagnosed patients. He described his experience in accordance with each stage of R E group. Twenty-nine eyes (50%) were treated without external-beam radiotherapy or enucleation. Out of these 90% were in group 1, 69% in group 2, 67% in group 3, 33% in group 4, and 6% in group 5. The difference was statistically significant among group 5 versus 1-4 and group 4-5 versus 1-3.

A review article by Shields et al[28] showed that chemoreduction and focal therapies are most successful for eyes with minimal to moderate RB. Enucleation was the final solution in less than 15% of cases. In case of advanced tumour enucleation is needed in 50 % cases.

We also experienced stage dependent outcome, both anatomically and functionally. We had 100% results in group 1-3, 70% in group 4 and 20% in group 5. Only 1 patient of our study relapsed with pinealoblastoma. The most important complication, we observed was tractional retinal detachment but no patient needed surgery till the last follow up as these were localized and not threatening the macula. Ultimate treatment failure and increase in aggressiveness of the tumour was observed in 06 eyes (19.35%).

Conclusion

This study showed a favourable response to Focal Treatment in eyes with residual Retinoblastoma after completion of Chemotherapy but the response was dependent upon the stage of the disease and advanced stage was less responsive to treatment.

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References

1. Bunin GR, Orjuela M. Geographic and environmental factors. In: Singh AD, Damato BE, Peer J, eds. Clinical ophthalmic oncology. Philadelphia: Saunders-Elsevier, 2007; pp 410-6.
2. Parkin DM, Krama rova E, Draper GJ, eds. International Incidence of Childhood Cancer Vol2. IARC Science Publication, No. 144 Lyon, France, 1998; pp 1-391.
3. Dondey JC, Staffieri S, McKenzie J, Davie G, Elder J. Retinoblastoma in Victoria, 1976-2000: changing management trends and outcomes.Clin Exp Ophthalmol. 2004; 32: 354-9.
4. Shields CL, De Potter P, Himelstein BP, Shields JA, Meadows AT, Maris JM. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol. 1996; 114:1330-8.
5. Chan MP, Hungerford JL, Kingston JE, Plowman PN. Salvage external beam radiotherapy after failed primary chemotherapy for bilateral retinoblastoma: rate of eye and vision preservation.Br J Ophthalmol. 2009; 93: 891-4.
6. Shields CL, Shields JA, Kiratli H, De Potter PV. Treatment of retinoblastoma with indirect ophthalmoscope laser photocoagulation. J Pediatr Ophthalmol Strabismus. 1995; 32: 317-22.
7. Shields CL, Santos MC, Diniz W, Gündüz K, Mercado G, Cater JR, et al. Thermotherapy for retinoblastoma. Arch Ophthalmol. 1999; 117: 885-93.
8. Shields JA, Parsons H, Shields CL, Giblin ME. The role of cryotherapy in the management of retinoblastoma. Am J Ophthalmol. 1989; 108: 260-4.
9. Abramson DH, Ellsworth RM, Rozakis GW. Cryotherapy for retinoblastoma. Arch Ophthalmol. 1982; 100: 1253-6.
10. Lincoff H, McLean J, Long R. The cryosurgical treatment of intraocular tumors.Am J Ophthalmol. 1967; 63: 389-99.
11. Abramson DH, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology.1999; 106: 1947-50.
12. Abramson DH, Dunkel IJ, Brodie SE, Marr B, Gobin YP. Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). Ophthalmology. 2010; 117: 1623-9.
13. Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology. 2008; 115: 1398-404.
14. Shields CL, Shields JA, Minelli S, De Potter P, Hernandez C, Cater J, et al. Regression of retinoblastoma after plaque radiotherapy. Am J Ophthalmol. 1993; 115: 181-7.
15. Pradhan DG, Sandridge AL, Mullaney P, Abboud E, Karcioglu ZA, Kandil A, et al. Radiation therapy for retinoblastoma: a retrospective review of 120 patients. Int J Radiation Oncology BiolPhys.1997; 39: 3-13.
16. Egbert PR, Donaldson SS, Moazed K, Rosenthal AR. Visual results and ocular complications following radiotherapy for retinoblastoma. Arch Ophthalmol. 1978; 96: 1826-30.
17. Hernandez JC, Brady LW, Shields JA, Shields CL, DePotter P, Karlsson UL, et al. External beam radiation for retinoblastoma: results, patterns of failure, and a proposal for treatment guidelines.Int J Radiat Oncol Biol Phys. 1996; 35: 125-32.
18. Ellsworth RM. Retinoblastoma. Mod Probl Ophthalmol 1977; 96: 1826-30.
19. Shields JA. The expanding role of laser photocoagulation for intraocular tumors. The 1993 H. Christian Zweng memorial lecture. Retina. 1994; 14: 310-22.
20. Shields JA. Misconceptions and techniques in the management of retinoblastoma. The 1992 Paul Henkind Memorial Lecture. Retina. 1992; 12: 320-30.
21. Shields JA, Shields CL, Parsons H, Giblin ME. The role of photocoagulation in the management of retinoblastoma. Arch Ophthalmol.1990; 108: 205-8.
22. Gallie BL, Budning A, DeBoer G, Thiessen JJ, Koren G, Verjee Z, et al. Chemotherapy with focal therapy can cure intraocularf retinoblastoma without radiotherapy. Arch Ophthalmol.1996; 114: 1321-8.
23. Murphree AL, Villablanca JG, Deegan WF 3rd, Sato JK, Malogolowkin M, Fisher A, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. Arch ophthalmol.1996; 114: 1348-56.
24. Shields CL, Shields JA, Needle M, de Potter P, Kheterpal S, Hamada A,et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. Ophthalmology. 1997; 104: 2101-11.
25. Friedman DL, Himelstein B, Shields CL, Shields JA, Needle M, Miller D, et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol. 2000; 18: 12-7.
26. Yoo KH, Sohn WY, Sung KW, Jung HL, Koo HH, Oh SY, et al. Chemoreduction followed by local therapy and adjuvant chemotherapy for advanced intraocular retinoblastoma: a pilot study in a single center. J Korean Med Sci. 2002; 17: 817-22.
27. Schiavetti A, Hadjistilianou T, Clerico A, Bonci E, Ragni G, Castello MA. Conservative therapy in intraocular retinoblastoma: response/recurrence rate. J Pediatr Hematol Oncol. 2005; 27: 3-6.
28. Shields CL, Shields JA. Diagnosis and management of retinoblastoma. Cancer Control. 2004; 11: 317-27.