Original Article

Effects of Primary Chemotherapy, Radiotherapy plus Local Treatments on Regression Patterns of Posterior Pole Retinoblastoma

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Purpose: To document the types of regression patterns of intraocular retinoblastoma following primary chemotherapy, radiotherapy and local treatments.

Material and Methods: The medical records of 31 patients diagnosed with intraocular posterior pole retinoblastoma at the Department of Paediatric Ophthalmology Al-Shifa Trust, Eye Hospital, Rawalpindi between January 2006 and January 2010 were reviewed retrospectively. The size of the tumour before and after the treatment (with chemotherapy, radiotherapy and local therapy) and types of regression patterns were evaluated. Regression patterns were classified as type 0 (no residua), type 1 (fully calcified residua), type 2 (non calcified residua), type 3 (partially calcified), type 4 (flat scar). Cases were also observed for any relapse of tumour.

Results: 37 eyes of 31 children were included in the study. Out of which 6 (19.4 %) had bilateral presentation of posterior pole retinoblastoma and 25 (80.6%) had unilateral. Tumour size, location and groupings were noted according to the International Intraocular retinoblastoma classification. After treatment with chemotherapy, radiotherapy and local treatments the types of regressions noted were type 0 in 1 eye (2.7 %), type 1 in 2 eyes (5.4 %), type 2 in 7 eyes (18.9 %), type 3 in 19 eyes (51.3 %) and type 4 in 8 eyes (21.6 %). In 3 eyes tumour relapse occurred.

Conclusion: Most large intraocular tumours showed type 3 regression pattern. Small tumours resulted in flat atrophic scars.

The primary aim of the management of retinoblastoma is to preserve life[1]. Since the management of retinoblastoma has evolved over the past decade from enucleation to radiotherapy to current regimen of chemotherapy, children with retinoblastoma having access to modern medical care have a very good prognosis for survival with greater emphasis being given to salvaging the globe and preserving the vision[2]. Eyes with massive retinoblastoma filing the globe without macroscopic or microscopic extra ocular disease are still managed with enucleation. Systemic administration of chemotherapy has been noted to reduce tumour volume, allowing for consolidative ablation therapy with laser and cryotherapy[3-5]. Current regimens include systemic injections of carboplatin, vincristin and etoposide. Children receive intravenous drug administration every three weeks for four to nine cycles of chemotherapy along with local tumour laser or cryoablation. This combination therapy allows globe preservation in 85% of eyes with less advanced tumours that is those classified as Reese-Ellsworth group I to IV[6]. Conservative approaches have been developed in order to increase the eye preservation

rate and improve the visual prognosis[7,8].

Retinoblastoma shows a variety of regression patterns after treatment. Tumour regression was initially described following radiotherapy. On regression, the retinoblastoma assumes a smaller size with stable margins and, frequently, some degree of calcification. Regression patterns include Type 0, in which the tumour completely disappears, leaving no retinal scar. Type 1, with a completely calcified mass appearing like cottage cheese. Type 2, with a completely noncalcified mass. Type 3, with a partially calcified mass and type 4, with a flat atrophic scar[9,10]. We conducted a retrospective study to evaluate the type of regression patterns seen in intraocular retinoblastoma grouped as A, B, C and D according to International Intraocular Retinoblastoma Classification (IIRC) after treatment with chemotherapy, radiotherapy and fovea sparing laser therapy[11].

MATERIAL AND METHODS

In this study we observed the patterns of regression of posterior pole intraocular retinoblastomas following primary chemotherapy, radiotherapy and local treatment with laser therapy or cryotherapy. The study was approved by the ethical committee of the hospital. The medical records of the patients diagnosed with retinoblastoma at the Paediatric Ophthalmology department of Al-Shifa Trust, Eye Hospital, Rawalpindi, from January 2006 to January 2010 were reviewed retrospectively. Of these patients, only the newly diagnosed cases of retinoblastoma, which were intraocular with posterior pole involvement (tumour entirely or partially in the area within the major vascular arcades), which had been treated with primary chemotherapy, radiotherapy and local treatments like laser therapy or cryotherapy were selected and included in this study. Patients with evidence of group E presentation according to IIRC, extra ocular extension, systemic metastasis or which had been treated with enucleation were excluded from the study.

At our institution, following guidelines for examination and diagnosis in all the children with suspected retinoblastoma were observed. Each patient was evaluated for age at diagnosis, familial or sporadic hereditary pattern of retinoblastoma and tumour laterality. Firstly a limited non sedated examination with attention to visual acuity, pupillary examination, extra ocular movements was carried out and it gave an idea of whether the patient can fixate and to what extent eye motility was affected. It also helped in taking family history and assessing what therapies may be practical. All paediatric patients with suspicion of retinoblastoma underwent examination under anaesthesia, consisting of measuring intraocular pressure, portable slit-lamp examination for evidence of iris neovascularisation, hyphema, or hypopyon, indirect ophthalmoscopy with 360 degrees of sclera indentation and documenting all the lesions with drawings indicating the location and size of the tumours and presence and extent of vitreous or sub retinal seedlings and sub-retinal fluid. Photographs of anterior chamber and fundus were taken of all the patients by RET CAM. This was followed by diagnostic testing by ultra sound, CT scan and magnetic resonance imaging to exclude extra ocular extension and trilateral retinoblastoma where needed.

Each affected eye was classified according to the International Intraocular Retinoblastoma Classification (IIRC) and Reese Ellsworth Classification of Retinoblastoma. The potential risks and benefits of the planned treatment were discussed with the patient's family and an informed consent was obtained. Treatment options considered were chemotherapy (with carboplatin, vincristin and etoposide) and radiotherapy was considered for those patients who required further aggressive chemotherapy but had evidence of inadequate organ function of the kidney or liver. Examination under anaesthesia was carried out every 6 weekly after the initiation of chemo reduction therapy and tumour consolidation was provided using local treatment with laser thermotherapy or cryotherapy until tumour control was achieved. Cryotherapy was used in large tumours extending anteriorly and the adjuvant fovea sparing thermotherapy was provided using the indirect ophthalmoscope diode laser, with varied duration, power and spot size of 1.2mm. Chemotherapy and radiotherapy were given in collaboration with clinical oncologist.

The Variables recorded for each patient included age at presentation and gender. The parameters noted of the retinoblastoma were laterality, tumour location (macular, extra macular, or both in cases of multiple tumours), tumour size (tumour area in disc diameters) and tumour grouping (A to E) according to IIRC at the time of diagnosis. We planned our patient treatment according to the International Intraocular Retinoblastoma Classification (IIRC) which is based mainly on extent of tumour seeding in the vitreous cavity and subretinal space with minor consideration

Table 1: International classification of retinoblastoma

Group	Sub group	Quick reference	Specific features
A	A	Small tumour	Retinoblastoma =3 mm in size*
B	B	Larger tumour	Retinoblastoma >3 mm in size* or
		Macula	Macular retinoblastoma location (=3 mm to foveola)
		Juxtapapillary	Juxtapapillary retinoblastoma location (=1.5 mm to disc)
		Subretinal fluid	Clear subretinal fluid =3 mm from margin
C		Focal seeds	Retinoblastoma with
	C1		Subretinal seeds =3 mm from retinoblastoma
	C2		Vitreous seeds =3 mm from retinoblastoma
	C3		Both subretinal and vitreous seeds =3 mm from retinoblastoma
D		Diffuse seeds	Retinoblastoma with
	D1		Subretinal seeds >3 mm from retinoblastoma
	D2		Vitreous seeds >3 mm from retinoblastoma
	D3		Both subretinal and vitreous seeds >3 mm from retinoblastoma
E	E	Extensive retinoblastoma	Extensive retinoblastoma occupying >50 percent globe or
			Neovascular glaucoma
			Opaque media from haemorrhage in anterior chamber, vitreous, or subretinal space
			Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

* Refers to 3 mm in basal dimension or thickness.

of tumour size and location since the chemoreduction is effective despite these variables. The potential risks and benefits of the planned treatment were discussed with the patient's family and an informed consent was obtained. Examination under anaesthesia was carried out every 6 weekly after the initiation of chemoreduction therapy and tumour consolidation was provided using laser therapy or cryotherapy until tumour control was achieved. After the completion of chemotherapy the tumour regression patterns were then documented as type 0 (no residua), type 1 (fully calcified residua), type 2 (non calcified residua), type 3 (partially calcified), type 4 (flat scar). Cases were followed at 4 monthly intervals till for the first year and relapse in any case if present was noted. In cases of tumour recurrences, further two to four cycles of chemotherapy were given in minor relapses and enucleation was carried out in cases of major relapses. Data was analyzed by Statistical Program for social sciences SPSS version 17.

RESULTS

Between January 2006 and January 2010, 37 eyes with intraocular retinoblastoma of 31 children were treated with chemoreduction, radiotherapy and local adjuvant methods. All eyes were classified according to IIRC (Table 1). The age of presentation ranged from 5 months to 9 years. The mean age at presentation in months was 34.48 ± 25.27. The frequencies and

Table 2: The frequencies and percentages of gender and laterality

Variables		Frequency (n=31) n (%)
Gender	Males	19 (61.3)
	Females	12 (38.7)
Laterality of retinoblastoma	Unilateral	2 (6.5)
	Bilateral	29 (93.5)
Laterality of posterior pole retinoblastoma	Unilateral	25 (80.6)
	Bilateral	6 (19.4)

Table 3: Retinoblastoma grading, size and location

Variables	Frequency (n=37) n %)
Tumor Grouping	
A	2 (5.4)%
B	4 (10.8)
C	5 (13.5)
D	26 (70.3)
E	-
Tumor Size	
1-5 DD	23 (62.2)
6-10 DD	13 (35.1)
11-15 DD	1 (2.7)
Tumor location	
Macular	19 (51.4)
Extramacular	15 (40.5)
Mixed (macular + extramacular)	3 (8.1)

percentages of gender and laterality in these 31 patients are given in Table 2. Out of 29 children (93.5%) with bilateral retinoblastoma 6 (20.7%) had bilateral presentation of posterior pole retinoblastoma and treatment was initiated to preserve both the eyes

Table 4: Different treatment modalities and their percentages

Treatment Modalities	Frequency n = 37 n (%)
Chemotherapy	6 (16.2)
Laser + Chemotherapy	26 (70.3)
Laser + Chemotherapy + Radiotherapy	5 (13.5)

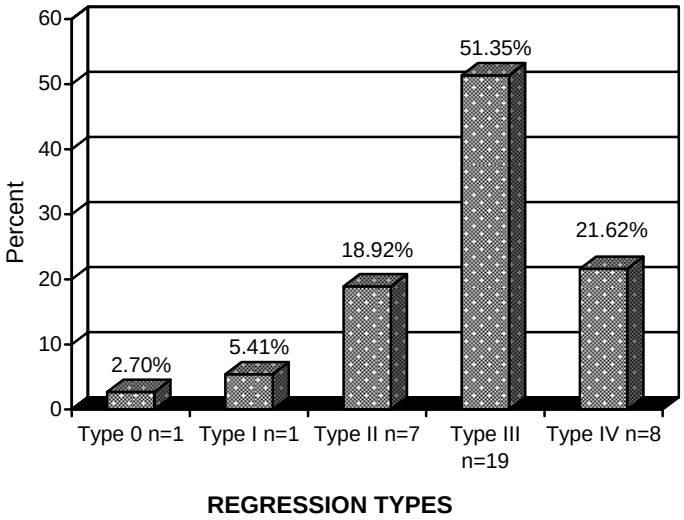

Fig. 1: Types of Regression in Reinblastomas

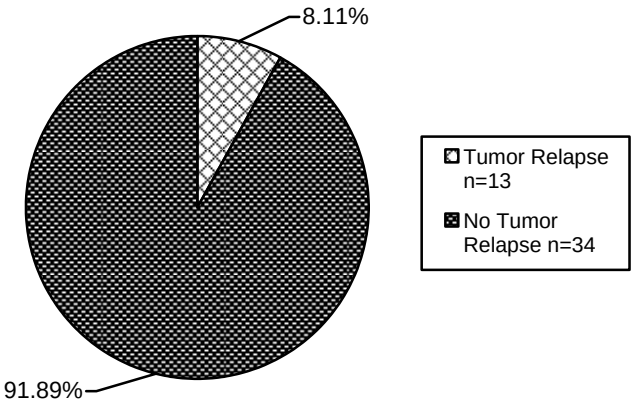

Fig. 2: Relapse of Retinoblastoma

of these patients, while 23 (79.3%) patients presented with unilateral posterior pole retinoblastoma and the other eye needed enucleation due to advance presentation. Two (6.5%) patients presented with unilateral retinoblastoma that involved posterior pole. The details of initial tumour features, IIRC grading,

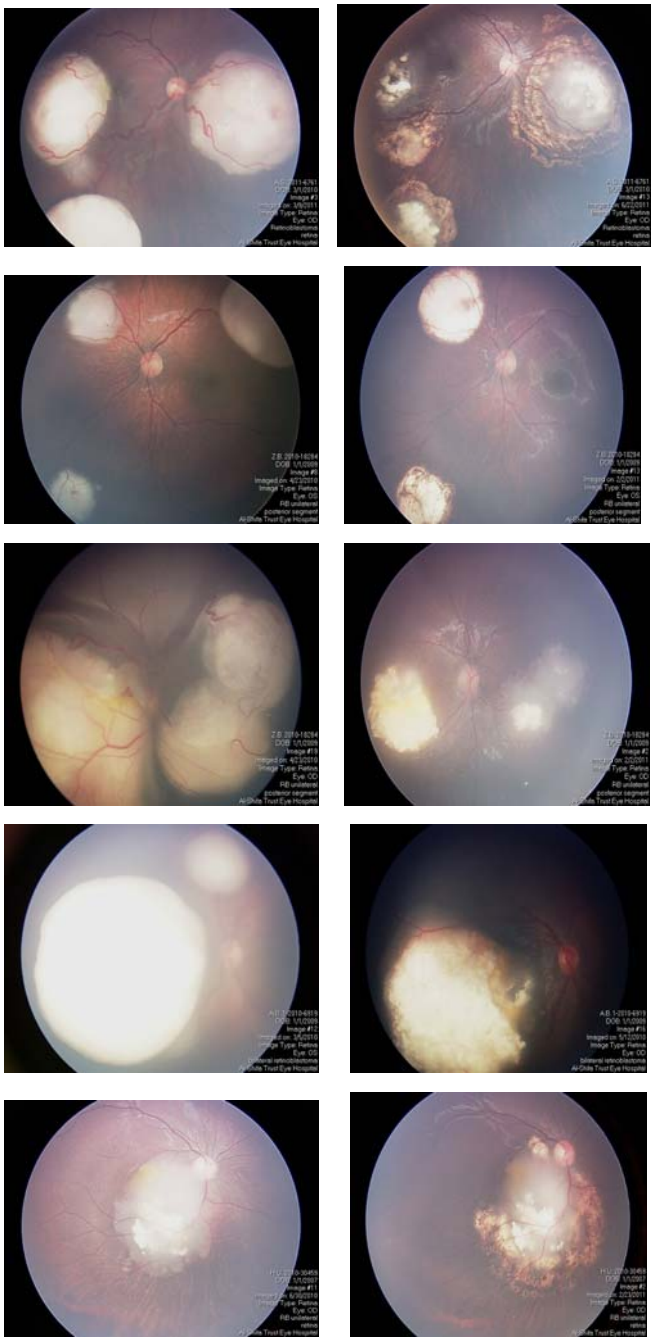

Fig. 3: Different retinoblastomas showing regression.

sizes and locations are listed in Table 3. Majority of retinoblastoma presented in group D (70.3%). The basal diameter of all retinoblastomas ranged from 1 to 15 disc diameters (1mm to 23mm). The average basal diameter of the tumours involving macula was 5 disc diameter (7.5mm). The different treatment modalities and their percentages are shown in Table 4.

After primary chemotherapy, radiotherapy and local treatments the types of regression documented in those 37 eyes are shown in (Fig 1). Majority of retinoblastomas showed type 3 (n=19, 53.35%) and type 4 (n=8, 21.62%) regression. Large tumours mostly regressed to type 3 (n=7, 18.92%). Small tumours, which were consolidated with laser therapy or cryotherapy resulted in flat atrophic scars. Only in 3 eyes (8.1%) the relapse of the retinoblastoma was documented (Fig 2). The relapse was seen at the mean interval of 11 months (range of 2-48 months) after completing the initial treatment of chemotherapy. The relapse was seen in those tumours that were initially graded as group D according to IIRC with subretinal and vitreous seeds and lying in close proximity of optic nerve head. These tumours showed type 2 and type 3 regression patterns. No relapse was recorded in type 0, type 1 and type 4. Different tumours before and after treatment are shown in (Fig 3).

DISCUSSION

There has been a significant change in the treatment approaches to retinoblastoma[12,13]. Attempts to avoid enucleation and complications associated with external beam radiotherapy have focused on globe preserving techniques. Systemic chemotherapy and focal treatments like laser photocoagulation and cryotherapy, are becoming the primary treatment modality[14-16]. The options for management of intraocular retinoblastoma include enucleation, external beam radiotherapy, plaque radiotherapy, laser photocoagulation, thermotherapy, cryotherapy and chemoreduction with or without adjuvant thermotherapy. Eyes with large tumours, especially if associated with extensive subretinal fluid, subretinal seeds or vitreous seeds are managed with enucleation. However, eyes with less advanced retinoblastoma are being managed with non-enucleation measures, most commonly involving chemoreduction followed by focal tumour consolidation. Currently used chemotherapeutic protocols involving intravenous administration of vincristin sulfate, etoposide and carboplatin have been proven effective in reduction of tumour size[17]. The tumour size and location are most important in predicting tumour regression patterns. According to IIRC group E unilateral retinoblastoma should be enucleated, while group D eyes are safe to attempt a combination of chemotherapy, focal therapy and low dose radiation. The attempt to preserve an eye with retinoblastoma requires careful classification and selection of eyes with good prospect for success (IIRC group A, B and some C)[18].

Abramson and colleagues first described the globe preserving treatment for unilateral retinoblastoma using radiotherapy. They stressed the need for proper patient selection[19]. They evaluated 89 eyes, which were treated with EBRT, for long term stability of regression patterns with a follow-up period of 7 years. They noted that the regression patterns slowly changed over time and that there was an increase in type 0, 1 and 4 patterns by approximately 10% each, whereas type 2 and 3 decreased by 19% and 8% respectively. In their observation smaller tumours were most likely to become type 0, while larger tumours were more likely to become type 1 pattern. Singh et al reported the distribution of regression patterns of retinoblastoma treated with EBRT to be 18% for the type 0, 50 % for type 1, 17% for type 2 and 14% for type 3[20]. They did not comment on type 4 regression patterns.

Regression patterns have changed as chemotherapy has replaced EBRT as the primary treatment. Shields et al reported the regression patterns of retinoblastoma treated with chemotherapy to be 2% to 3% for type 0, 10% to 13% for type 1, 3% to 5% for type 2, 23% to 33% for type 3 and 51% to 57% for type 4 tumours[21,22]. In our study the regression pattern mostly observed was type 3 (51.53%) and type 4 (21.62%), which is comparable with the studies mentioned earlier. The relapse of retinoblastoma was seen in 3 eyes (8.11%). In these eyes the retinoblastoma initially regressed to type 2 and type 3. The presence of vitreous seeds and subretinal seeds were the factors resulting in recurrence of retinoblastoma in these eyes. However there are few limitations in our study. Firstly, the extent of the tumour treated with laser therapy, it varied depending on its relation to the fovea and close proximity to the optic nerve head. Secondly the changes in visual acuity were not assessed as most of our patients were infants.

Careful and diligent follow-up is the mainstay to ensure the success of retinoblastoma treatment. Chemoreduction and local therapy helps in regression of retinoblastomas and can be considered as a treatment of choice especially in bilateral cases with one eye already requiring enucleation.

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REFERENCE

1. **Sanders BM, Draper GJ, Kingston JE**. Retinoblastoma in Great Britain 1969-1980: incidence treatment and survival. Br J Ophthalmol. 1988; 72: 576-83.
2. **Kopelman JE, Mclean IW, Rosenberg SH.** Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. Ophthalmology. 1987; 94: 371-7.
3. **Shields CL, Shields JA.** Basic understanding of current classification and management of retinoblastoma. Curr Opin Ophthalmol. 2006; 17: 228-34.
4. **Abramson DH.** Retinoblastoma in the 20th century: past success and future challenges the Weisenfeld lecture. Invest Ophthalmol Vis Sci. 2005; 46: 2683-91.
5. **Murphree AL Villablanca JG, Deegan WF 3rd, et al.** Chemotherapy plus local treatment in the management of intraocular retinoblastoma. Arch Ophthalmol. 1996; 114: 1348-56.
6. **Kingston JE, Hungerford JL, Madreperla SA, et al.** Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Arch Ophthalmol. 1996; 114: 1339-47.
7. **Buckley EG, Heath H.** Visual acuity after successful treatment of large macular retinoblastoma. J Pediatr Ophthalmol Strabismus. 1992; 29: 103–6.
8. **Shields CL, De Potter P, Himelstein BP, et al.** Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol. 1996; 114: 1330–8.
9. **Ellsworth RM.** The practical management of retinoblastoma. Trans Am Ophthalmol Soc. 1969; 67: 462-534.
10. **Abramson DH, Jereb B, Ellsworth RM.** External beam radiation for retinoblastoma. Bull N Y Acad Med. 1981; 57: 787-803.
11. **Murphree AL.** Intraocular retinoblastoma: The case for a new group classification. Ophthalmol Clin North Am. 2005; 18: 41-53.
12. **Abramson DH, Schefler AC.** Update on retinoblastoma. Retina. 2004; 24: 828-48.
13. **DePotter P.** Current treatment of retinoblastoma. Curr Opin Ophthalmol. 2002; 13: 331-6.
14. **Shields JA, Shields CL, Meadows AT.** Chemoreduction in the management of retinoblastoma. AM J Ophthalmol. 2005; 140: 505-6.
15. **Shields CL, Mashayekhi A, Au AK, et al.** The international classification of retinoblastoma predicts chemo reduction success. Ophthalmology. 2006; 113: 2276-80.
16. **Chan HS, Gallie BL, Munier FL, et al.** Chemotherapy for retinoblastoma. Ophthalmol Clin North Am. 2005; 18: 55-63.
17. **Friedman DL, Himelstein B, Shields CL, et al.** Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol. 2000; 18: 12-7.
18. **Mallipatna AC, Sutherland JE, Gallie BL, et al.** Management

and outcome of unilateral retinoblastoma. JAAPOS 2009; 13: 546-50.
19. **Abramson DH, Marks RF, Ellsworth RM, et al.** The management of unilateral retinoblastoma without primary enucleation. Arch Ophthalmol. 1982; 100: 1249-52.
20. **Singh AD, Garway-Heath D, Love S, et al.** Relationship of regression patterns to recurrence in retinoblastoma. Br J Ophthalmol. 1993; 77: 12-6.
21. **Shields CL, Mashayekhi A, Carter J, et al.** Chemoreduction for retinoblastoma. Analysis of tumour control and risk for recurrence in457 tumours. Am J Ophthalmol 2004;138:329-37.
22. **Shields CL, Palamar M, Sharma P, et al.** Retinoblastoma regression patterns following chemo reduction and adjuvant therapy in 557 tumours. Arch Ophthalmol. 2009; 127: 282-90.