

# OUTCOME OF 6 CYCLES OF PRIMARY INTRAVENOUS CHEMOTHERAPY OF RETINOBLASTOMA PATIENTS IN TERMS OF RECURRENCE IN A TERTIARY HEALTH CARE HOSPITAL

## ABSTRACT

**Objective:** To determine the frequency of recurrence after 6 cycles of primary intravenous chemotherapy of retinoblastoma patients in a tertiary health care hospital.

**Materials and Methods:** This study was conducted at the Department of Ophthalmology, Lahore General Hospital, Lahore from March 15, 2020 to September 15, 2020. A total of 81 patients were selected randomly from outpatient department. Proforma designed was used to collect data including name, age, gender, registration number, laterality, age at diagnosis, group of disease, treatment given and outcomes of given treatment. International Intraocular Retinoblastoma Classification (IIRC) was used for classification of the disease. The chemotherapy regimen used was vincristine, etoposide and carboplatin (VEC). A total of 6 cycles were given at 3 weekly intervals. Serial monitoring of the tumors was done to rule out any local recurrence or side effects of therapy.

**Results:** Total 81 children presenting with retinoblastoma were enrolled in this study. There were 52 (64.2%) male and 29 (35.8%) female. The mean age of patients was  $3.41 \pm 1.45$  year. Unilateral disease was in 61 (75.30%) patients while 20 (24.70%) patients had bilateral retinoblastoma. Among 81 children, 20 (24.7%) had recurrence of the disease.

**Conclusion:** Development of recurrence after intravenous chemotherapy was noted in 24.7 % of all retinoblastoma eyes. Younger patients with more advanced, posteriorly located tumors and subretinal seeds at presentation were at increased risk, but recurrence can often be managed with globe-sparing therapy.

**Key Words:** Retinoblastoma, Intravenous chemotherapy, Recurrence.

## **INTRODUCTION:**

“Retinoblastoma is the most common primary intraocular malignancy of childhood”.<sup>1-2</sup> It represents almost 3% of all paediatric malignancies.<sup>3</sup> With multidisciplinary approach more than 95% of patients can be successfully treated before extra-ocular spread of tumor. Survival rate of retinoblastoma is about 95% in developed countries whereas only 50% worldwide.<sup>3</sup> Delayed presentation, diagnosis and increasing number of cases every year in developing countries lead to decreased survival rate.<sup>4</sup>

The diagnosis of retinoblastoma is based on characteristic clinical features,<sup>5</sup> leukocoria being the most common sign.<sup>6</sup> Binocular indirect ophthalmoscopy, B scan, CT scan and MRI orbit<sup>5</sup> helps in diagnosis. Management of retinoblastoma has evolved over a period of 100 years with the aim of salvage of life, eye and vision<sup>7</sup> and it depends upon group of the disease at the time of presentation. In past, enucleation remained only treatment for advanced retinoblastoma particularly in developing countries.

Over the past two decades, first-line conservative management of retinoblastoma has moved from external beam radiotherapy (EBR) to intravenous chemotherapy<sup>8</sup> with focal treatments (cryotherapy, laser photocoagulation). In recent past intravitreal and intra-arterial chemotherapy have been introduced leading to more targeted treatment of retinoblastoma without compromising patient survival.<sup>9</sup> Intravitreal chemotherapy has revolutionized the management of eyes with recurrent vitreous seeding requiring enucleation.<sup>10-14</sup> Intra-arterial chemotherapy is an alternative to enucleation and EBR in cases with tumor recurrences.<sup>15</sup>

We wanted to conduct this study to determine the frequency of recurrence after 6 cycles of primary intravenous chemotherapy at a single tertiary care hospital in Lahore as there are a number of patients with retinoblastoma being treated at this hospital and we wanted to identify an optimal approach for retinoblastoma patients as no local study has been conducted before.

## **MATERIALS & METHODS:**

After taking ethical consent from hospital committee, the study was conducted at the Department of Ophthalmology, Lahore General Hospital, Lahore from March 15, 2020 to September 15, 2020. A total of 81 diagnosed cases of retinoblastoma whether unilateral or bilateral between the ages of 6 months

to 5 years were included in the study. Patients who underwent enucleation or who are currently receiving any local or systemic therapy and those with vitreous hemorrhage, secondary glaucoma, bleeding disorders were excluded from the study. The patients were selected randomly from outpatient department. A performa designed was used to collect data including name, age, gender, registration number, laterality, age at diagnosis, group of disease, treatment given and outcomes of given treatment.

Metastatic work included haematological investigations, bone marrow aspiration, cerebrospinal fluid analysis, computerized tomography and/or magnetic resonance imaging (MRI) of the brain was carried out.

International Intraocular Retinoblastoma Classification (IIRC) was used for classification of the disease. There were 26 (32.09%) eyes with group B disease; 31 (38.27%) eyes had group C, 18 (22.23%) eyes with group D and 06 (7.41%) eyes had group E disease.

The chemotherapy regimen used was vincristine, etoposide and carboplatin (VEC). It comprises of vincristine (1.5 mg/m<sup>2</sup>), etoposide (600 mg/m<sup>2</sup>), and carboplatin (300 mg/m<sup>2</sup>), all administered on the same day. A total of 6 cycles were given at 3 weekly intervals. After evaluating the initial response to 2 or 3 cycles of chemotherapy, patients were followed up periodically. Serial monitoring of the tumors was done with ophthalmic ultrasound and examination under anaesthesia. At each visit, the size and extent of lesion, regression, or progression was recorded. After completion of therapy, follow-up examination was done every 4 weekly for 3 months to rule out any local recurrence or side effects of therapy.

Recurrence was defined as progression in tumor size or reappearance or new lesion 3 months after completion of primary therapy plus adjuvant therapy.

The data were entered and analysed by SPSS v25.0. Numeric data like age was presented as mean and S.D, whereas the qualitative data like gender was presented in frequency and percentages. A p-value was calculated using the  $\chi^2$  test. Data were stratified for gender, age and age at diagnosis. Post-stratification, Chi-square test was used taking p-value  $\leq 0.05$  as significant.

## RESULTS:

Total 81 children presenting with both unilateral and bilateral retinoblastoma were enrolled in this study. There were 52(64.2%) male and 29(35.8%) female. The mean age of patients was  $3.41 \pm 1.45$  year.

Leukocoria and strabismus were the most common presenting features. According to age at diagnosis distribution, 39(48.1%) patients had ages <3 years, while 42(51.9%) had >3 years.

According to laterality distribution, 28(34.6%) patients had right eye disease, while 33(40.7%) and 20(24.7%) had left eye and both eyes disease respectively.

Among 81 children, 20(24.7%) had recurrence of the disease. Main solid tumor recurrence (n = 2, 10%), subretinal seed recurrence (n = 4, 20%), vitreous seed recurrence (n = 11, 55%), and new tumor (n = 3, 15%) requiring management with focal therapy (transpupillary thermotherapy, cryotherapy) (n = 4, 20%), intra-arterial chemotherapy (n = 3, 15%), intravitreal chemotherapy (n = 12, 60%), or enucleation (n = 1, 5%).

Risk factors for recurrence included younger patient age at presentation, greater International Classification of Retinoblastoma group, shorter tumor distance to optic disc, and presence of subretinal seeds. No side effect, metastasis or death was observed during the course of this study.

**Table-1: Frequency distribution of gender**

| Gender | Frequency | Percentage |
|--------|-----------|------------|
| Male   | 52        | 64.2       |
| Female | 29        | 35.8       |
| Total  | 81        | 100.0      |

**Table-2: Frequency distribution of age at diagnosis**

| Age at diagnosis | Frequency | Percentage |
|------------------|-----------|------------|
| <3 years         | 39        | 48.1       |
| >3 years         | 42        | 51.9       |
| Total            | 81        | 100.0      |

**Table-3: Frequency distribution of laterality**

| Laterality | Frequency | Percentage |
|------------|-----------|------------|
| Right eye  | 28        | 34.6       |

|                  |    |       |
|------------------|----|-------|
| <b>Left eye</b>  | 33 | 40.7  |
| <b>Both eyes</b> | 20 | 24.7  |
| <b>Total</b>     | 81 | 100.0 |

**Table-4: Frequency distribution of recurrence**

| <b>Recurrence</b> | <b>Frequency</b> | <b>Percent</b> |
|-------------------|------------------|----------------|
| <b>Yes</b>        | 20               | 24.7           |
| <b>No</b>         | 61               | 75.3           |
| <b>Total</b>      | 81               | 100.0          |

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**Table-5: Stratification of recurrence with respect to gender**

| Gender | Recurrence |       | Total  | p-value |
|--------|------------|-------|--------|---------|
|        | Yes        | No    |        |         |
| Male   | 13         | 39    | 52     | 0.931   |
|        | 25.0%      | 75.0% | 100.0% |         |
| Female | 7          | 22    | 29     |         |
|        | 24.1%      | 75.9% | 100.0% |         |
| Total  | 20         | 61    | 81     |         |
|        | 24.7%      | 75.3% | 100.0% |         |

**Table-6: Stratification of recurrence with respect to age groups**

| Age groups | Recurrence |       | Total  | p-value |
|------------|------------|-------|--------|---------|
|            | Yes        | No    |        |         |
| <3 years   | 8          | 31    | 39     | 0.401   |
|            | 20.5%      | 79.5% | 100.0% |         |
| >3 years   | 12         | 30    | 42     |         |
|            | 28.6%      | 71.4% | 100.0% |         |
| Total      | 20         | 61    | 81     |         |
|            | 24.7%      | 75.3% | 100.0% |         |

**Table-7: Stratification of recurrence with respect to age at diagnosis**

| Age at diagnosis | Recurrence |       | Total  | p-value |
|------------------|------------|-------|--------|---------|
|                  | Yes        | No    |        |         |
| <3 years         | 8          | 31    | 39     | 0.401   |
|                  | 20.5%      | 79.5% | 100.0% |         |
| >3 years         | 12         | 30    | 42     |         |
|                  | 28.6%      | 71.4% | 100.0% |         |
| Total            | 20         | 61    | 81     |         |
|                  | 24.7%      | 75.3% | 100.0% |         |

**Table-8: Stratification of recurrence with respect to laterality**

| Laterality       | Recurrence |       | Total  | p-value |
|------------------|------------|-------|--------|---------|
|                  | Yes        | No    |        |         |
| <b>Right Eye</b> | 5          | 23    | 28     | 0.397   |
|                  | 17.9%      | 82.1% | 100.0% |         |
| <b>Left Eye</b>  | 8          | 25    | 33     | 0.397   |
|                  | 24.2%      | 75.8% | 100.0% |         |
| <b>Both Eyes</b> | 7          | 13    | 20     | 0.397   |
|                  | 35.0%      | 65.0% | 100.0% |         |
| <b>Total</b>     | 20         | 61    | 81     | 0.397   |
|                  | 24.7%      | 75.3% | 100.0% |         |

## DISCUSSION:

Retinoblastoma is the most common intra ocular malignancy of childhood <sup>16</sup> with incidence of 1 in 18000 live births <sup>17</sup> and is the second most common malignant intraocular tumor after uveal melanoma.<sup>18</sup>“In 1957 retinoblastoma was first described as fungus hematodes and enucleation was considered as the primary mode of management”.<sup>19</sup>Previously “retinoblastoma was considered as a disease, which only leads to death, but in last few decades advances have revolutionized that concept with good anticipated prognosis”.<sup>20</sup>

Our study shows a male predominance (64.2%), which is similar to the gender distribution shown in reports from Mexico <sup>21</sup> (52.4%), Mali <sup>22</sup> (54.5%), Egypt <sup>23</sup>(60.25), and Jordan <sup>24</sup>(70.0%).

“Retinoblastoma was more prevalent in >3 years of age group in our study while in another study it was also more prevalent among >36 months of age group”.<sup>25</sup>“Minimum number of patients were of <36 months of age group. A study conducted in United States showed that greater than 24 months of age group was associated with minimum number of patients associated with retinoblastoma”.<sup>26</sup>

“Over the last three decades, intravenous chemotherapy (IVC) has played a major role in the conservative treatment of RB”.<sup>27,28</sup>“The eventual globe salvage rate has usually been >70% in several previous reports employing IVC and focal treatments”.<sup>27,28-30</sup>However, long-term tumor control and development of recurrence and new tumors are still major concerns after IVC.

Current studies completed by the Retinoblastoma Study Group show the promising use of chemotherapy (carboplatin, vincristine sulfate, and etoposide phosphate) as a primary mode of treatment in reducing tumor bulk, followed by various forms of local approaches (radiotherapy [external beam or plaque], cryotherapy, thermotherapy, and photocoagulation) that can be used for final tumor control.

In our study, systemic chemotherapy was administered for the treatment of disease. Local therapy including cryotherapy and laser photocoagulation was administered. There are studies showing role of local therapy as adjuvant to systemic chemotherapy in reduction of vitreous seeding.<sup>31,32</sup>

Chemotherapy may also be used prior to external beam radiotherapy (EBRT), as completed by Kingston and associates in an attempt to improve local control and visual outcomes, using carboplatin, etoposide, and vincristine, followed by 40-44 Gy of EBRT.<sup>33</sup>

Shields and associates used “carboplatin, etoposide, and vincristine chemotherapy, followed by cryotherapy, photocoagulation, and 125 I plaque treatment in an attempt to improve outcome for eyes with more advanced retinoblastoma commonly treated with enucleation”.<sup>34</sup>

Some reports suggest the addition of cyclosporine in combination with the chemotherapy regimen of carboplatin, etoposide, and vincristine. These reports showed that this addition enhances the efficacy of chemotherapy and eliminates the need for radiation.

In 2018, Usha Singh<sup>1</sup> conducted a study on treatment outcomes of retinoblastoma showed that histopathological high risk features (post laminar optic nerve invasion, massive choroidal invasion, anterior chamber, scleral and extrascleral involvement) were significantly less in the eyes that received chemoreduction (5%) versus primary enucleation (20.8%) with local recurrence in 4.3%, metastasis in 0.4% and death in 2.8%.

In a study conducted by A.K. Gündüz<sup>35</sup> 64/246 (26.0%) eyes treated with frontline IVC developed recurrence at a mean follow-up of 80 months. Bertil Damatoa (2018)<sup>36</sup> reported that recurrences occurred in 29.9% of 61 eyes that had not undergone primary enucleation while in our study, among 81 children, 20 (24.7%) had recurrence of the disease.

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**CONCLUSION:**

Intravenous chemotherapy is efficient but recurrence still can occur. Younger patients with more advanced, posteriorly located tumors and subretinal seeds at presentation are at increased risk, but recurrence can often be managed with globe-sparing therapy.

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## **Ethical Approval:**

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

## **Consent**

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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Appendix

**PERFORMA**

**OUTCOME OF 6 CYCLES OF PRIMARY INTRAVENOUS CHEMOTHERAPY OF  
RETINOBLASTOMA PATIENTS IN TERMS OF RECURRENCE IN A TERTIARY  
HEALTH CARE HOSPITAL**

Reg. No.: \_\_\_\_\_ Date: \_\_\_\_\_

Name: \_\_\_\_\_

Address: \_\_\_\_\_

Age: \_\_\_\_\_ (years)

Gender: Male  Female

Age at diagnosis: \_\_\_\_\_

Laterality: \_\_\_\_\_

Group of Disease: \_\_\_\_\_

Recurrence after intravenous chemotherapy: Yes  No

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