*Original Article*

Ophthalmology and Allied Sciences
Volume 10 Number 2/May - August 2024
DOI: http://dx.doi.org/10.21088/oas.2454.7816.10224.2

# Outcomes of Retinoblastoma Treated as per Protocol based on International Classification of Retinoblastoma

**Sanjiv Kumar Gupta[1], Nishant Verma[2]**

**How to cite this article:**
Sanjiv Kumar Gupta, Nishant Verma. Outcomes of Retinoblastoma treated as per protocol based on International Classification of Retinoblastoma. Ophthalmol Allied Sci. 2024;10(2):45–53.

**Abstract**

***Context:*** There is a lack of universally applicableand updated treatment protocol for retinoblastoma in India, which causes hurdles in the management of this childhood cancer. We have described the outcomes of subjects treated using our protocol (based on the International Classification of Retinoblastoma)that could be adopted for the management of retinoblastoma.

***Aim:*** The international classification of retinoblastoma defines the prognosis-based classification of subjects. The protocol followed at our institute is based on the ICR and the retinoblastoma outcomes for the last 5 years have been analysed and presented.

***Setting & Design:*** Tertiary care centre-based retrospective study.

***Methods and Material:*** Five-year records of the retinoblastoma patients treated using a standard ICR-based protocol were analysed for clinical profile, treatment delivered, and outcomes. Appropriate statistical tests were used for parametric/non-parametric data and categorical variables to compare the groups. Kaplan-Meier survival analysis was used to describe the survival probability. A p-value of 0.05 was considered significant.

***Results:*** There were 209 subjects and 251 retinoblastoma-affected eyes which were included and analysed in the study. The overall survival rate was 90.10% and 1, 2, 3 and, 5-year survival estimates were 96.6%, 94.9%, 92.2%, 88.3% respectively. Forty-two (16.73%) eyes with retinoblastoma were retained after local tumour control and 209 (83.27%) eyes needed enucleation.

***Conclusions:*** The retinoblastoma treatment protocol based on ICR has shown improvement in the outcomes at our centreanddefined the resources needed for the management of retinoblastoma.

**Keywords:** Retinoblastoma; retinoblastoma treatment protocol; IRC based treatment protocol; eye cancer; ICR; classification of retinoblastoma.

**Key Messages:** The described retinoblastoma protocol can be used to initiate and build upon a national SOP for the management of retinoblastoma.

**Author Affiliation:** [1]Professor, Department of Ophthalmology, [2]Additional Professor, Department of Pediatrics, King George's Medical University, Lucknow 226003, Uttar Pradesh, India.

**Corresponding Author: Sanjiv Kumar Gupta,** Professor, Department of Ophthalmology, King George's Medical University, Lucknow 226003, Uttar Pradesh, India.

**Email:** sanjivguptaresearch@gmail.com

**Received on:** 22.08.2024

**Accepted on:** 13.11.2024

## INTRODUCTION

In India, the management of retinoblastoma has a different clinical picture compared to the developed nations due to the socioeconomic conditions, advanced stage at the time of presentation, and limitation of resources and specialized centres for the management of the disease. To reduce the delay in the management of retinoblastoma, a suitable protocol is needed that will not only provide a guideline for standardizing the management of retinoblastoma at apex centres but also delineate the management responsibilities which can be shared by the primary and secondary levels of medical care. This will improve the outcomes by providing early management at the first point of care and reduce the burden of the advanced stages of retinoblastoma which is the main reason for higher mortality in India.

Such a protocol can also help the planning agencies to decide the minimum resources in terms of infrastructure, equipment, and manpower to equip the present tier-based health care system for the management of retinoblastoma. If we look at the present scenario regarding such protocol we find old publications by the ICMR (Indian Council for Medical Research), published in 2010, by Chawla *et al.* in 2017, Singh *et al.* in 2017. However, these publications focus mainly on the review of the literature and outcomes of their patients and not on providing any protocol or algorithm for deciding the treatment modality for various stages of the disease.

Other available treatment protocols have been designed by and for advanced centres worldwide and include advanced treatment modalities like intra-arterial chemotherapy (IAC) and brachytherapy, apart from other options. The advanced treatment modalities may not be available/feasible in less developed centres/ nations. Thus, there is a need for a protocol that is aligned with ICR and includes treatment modalities that are available at less advanced centres. The international classification of Retinoblastoma (ICR) has been developed keeping in mind the spread of the disease and the prognosis after appropriate treatment for the stage of the disease. The success of ICR in defining the treatment protocol has been discussed in the existing literature and is a useful tool for deciding the treatment plan for retinoblastoma subjects.[4-7]

In the above context, we have been managing retinoblastoma subjects for more than 3 decades and have developed and evolved a treatment protocol over that period. The present protocol which is suitable for our group of patients and is aligned with the resources at our centre is based on the ICR. This institutional protocol has been instituted at our centre since 2015. This study was done to analyse the outcomes of the retinoblastoma subjects treated at our institute using this protocol. Being a representative tertiary care centre in central India the treatment protocol used at our institute can be used by other institutes treating retinoblastoma in India and nations with similar socioeconomic structures and can replicate the success we had.

This retrospective study evaluated the outcomes of retinoblastoma subjects treated using "The KGMU retinoblastoma treatment protocol".

## SUBJECTS AND METHODS

The records of all the subjects treated for retinoblastoma fromJune 2015 to May 2022 were analysed to evaluate the demographic, clinical features, the status of the disease at the presentation, the treatment provided, and the outcome. The subjects who did not comply with the treatment were excluded from the analysis. Adherence to the declaration of Helsinki was maintained concerning the confidentiality of the subject's identity.

The subjects were subjected to an MRI/CT (Computed Tomogram) scan, and examination under anaesthesia at the time of enrolment for grading the disease as per the International Classification of Retinoblastoma. The treatment was decided as per the protocol developed at our institute for the patients (Fig. 1). The treatment modalities used were LASER photocoagulation, Cryo therapy, enucleation, intravitreal carboplatin injection, systemic chemotherapy (VEC regimen)[1,] and local external radiotherapy, depending on the stage of the disease and our protocol (Fig. 1).

Data were analysed using MedCalc (Version 14.8.1). Descriptive statistics were used as needed. Categorical variables were compared using the Chi Sq/Fisher's exact tests. Kaplan-Meier survival analysis was carried out to study the survival pattern among different groups. A P-value $<0.05$ was considered statistically significant.

## RESULTS

The records of children treated for retinoblastoma from June 2015 to May 2022 at our institute were

reviewed, and we found 216 subjects who were enrolled for retinoblastoma at our tertiary care center. Among those, 209 children completed the treatment as per the KGMU retinoblastoma treatment protocol at our institute.

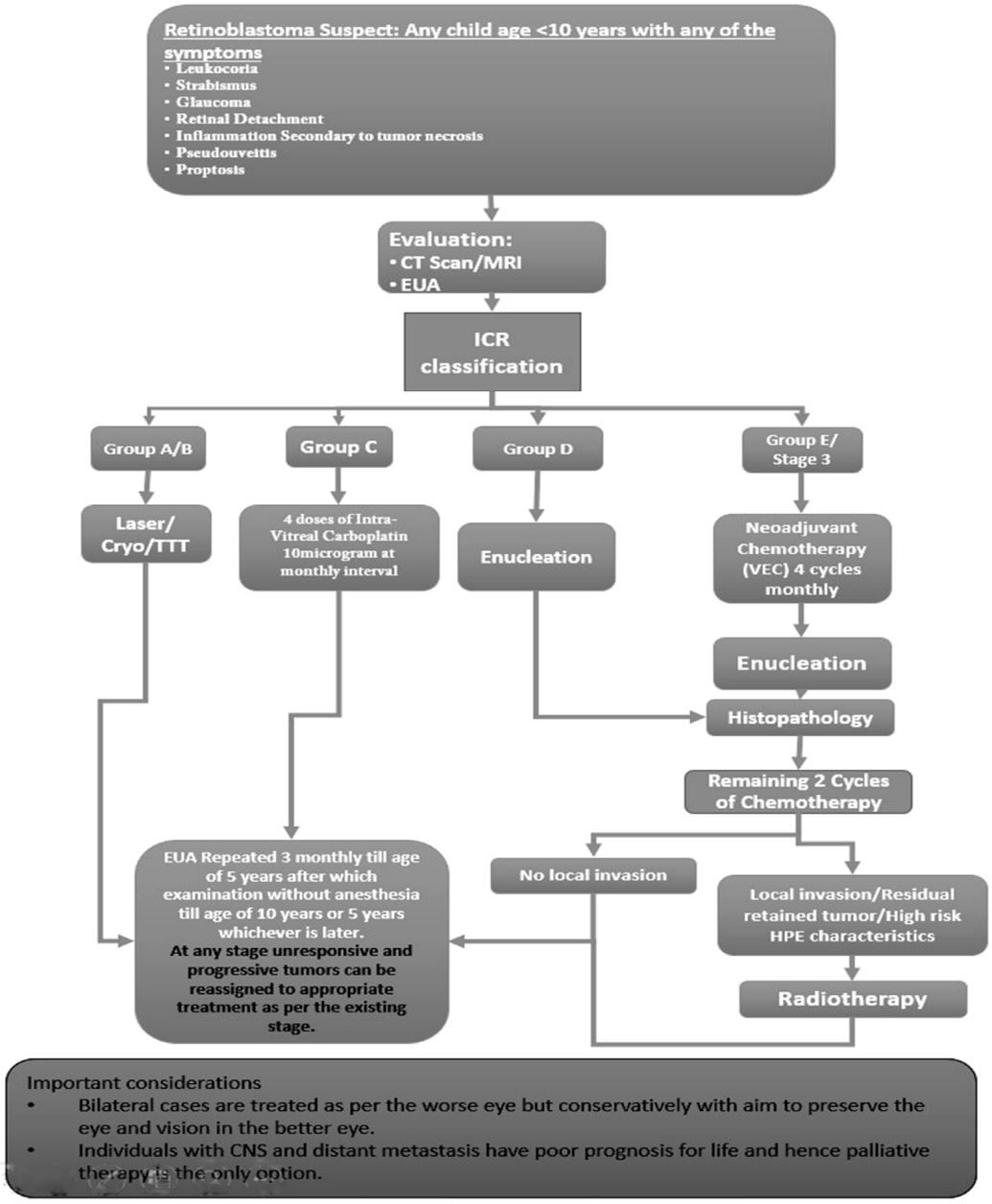



**Fig. 1:** International Classification of Retinoblastoma (ICR) Based Management Protocol for Retinoblastoma Subjects

There were 136 (65.1%) male vs. 73 (34.9%) female subjects. There were 167 (79.9%) cases of unilateral disease and 42 (20.1%) cases of bilateral disease. Table 1.

The average age at the time of first symptoms was 28.76 months (range 0.0-103, SD 21.09). This was statistically similar in both male and female subjects with a p-value of 0.74 (Mann-Whitney test). All subjects' average age at presentation was 34.12 months (Range 1.7-104.8, SD 21.93), and the average age at presentation in males and females was statistically similar (p=0.88). However, unilateral cases presented (35.50 months) later than the bilateral cases (28.90 months) but this difference was not significant (p=0.14). Similarly, the symptoms were also noted earlier in the bilateral patients (23.30 months) than in the unilateral cases (30.24 months) but the difference was statistically insignificant (p=0.07). Table 1.

**Table 1:** Clinical and demographic details of patients included in the study

| | Unilateral (167) | Bilateral (42) | p-value | Average age at enrolment (Months) | p-value | Average age at appearance of first symptom (Months) | p-value | Latency in presentation (Months) | p value |
|---|---|---|---|---|---|---|---|---|---|
| Male (136) | 111 | 25 | 0.5 | 34.25 | 0.88 | 29.33 | 0.74 | 5.41 | 0.77 |
| Female (73) | 56 | 17 | — | 33.89 | — | 27.75 | — | 6.72 | — |
| Unilateral | — | — | — | 35.5 | 0.14 | 30.24 | 0.07 | 5.39 | 0.24 |
| Bilateral | — | — | — | 28.9 | — | 23.3 | — | 7.77 | — |
| | 167 | 42 | — | 34.12 (1.7-104.8, 21.93) | — | 28.76 (0.0-103, 21.09) | — | 5.87 (0.2-64.8, 7.45) | — |

The average latency in presenting at the hospital, from the date of the first symptom, which can be considered a surrogate for the awareness among the public and referral system efficiency was 5.87 months (Range 0.2-64.80 months, SD 7.45). The latency in the presentation was similar across the genders (p=0.77) and whether the disease was unilateral or bilateral (p=0.24). When the latency in the presentation was compared across the ICR groups it was evident that the children with ICR group E and extraocular presentation had a significantly longer duration (Average 6.08 and 16.35 months respectively) with a p-value of <0.001 (ANOVA test). However, the subjects with disease falling in groups A, B, C, and D, albeit in diverse groups, had statistically similar presentation latency.

Only 7 (3.3%) subjects had a family history of retinoblastoma while 6 (2.9%) children had a history of other malignancies in any of the blood relatives.

Out of the total of 209 subjects, there were 167 (79.90%) children with unilateral disease and 42 (20.10%) children had bilateral disease. The total number of eyes with retinoblastoma was 251, only the right eye was involved in 93 subjects (44.5%) vs 74 (35.4%) subjects had only left eye involvement, 42 (84 eyes) subjects had Bilateral involvement. Most of the eyes had group E (ICR) disease [106 (42.23%)] at the time of enrolment followed by 74 (29.48%) in group D, 29 (11.55%) in group C, 20 (7.97%) and 12 (4.78%) eyes in group B & A respectively. There were 10 (3.98%) eyes with orbital metastasis (Stage 3) at the time of enrolment. None of the subjects had CNS or distant metastasis.

Out of 251 eyes affected with retinoblastoma, 209 eyes (83.27%) eyes were enucleated. There were 42 (16.73%) retinoblastoma-affected eyes that were retained and out of those, 32 (76.19%) eyes had useful vision (Better than 6/24) at the time of reporting. Bilateral enucleation was done in two children with bilateral advanced disease with no visual potential. Out of the total 209 subjects, 20 (9.57%) eventually died because of Retinoblastoma metastasis and associated complications.

As per the "KGMU Retinoblastoma treatment protocol" Thirty-nine (18.66%) eyes of 39 subjects underwent primary enucleation without local or systemic treatment. Table 2. The rest of the enucleated eyes (170, 81.33%) received neoadjuvant chemotherapy to minimizethe possibility of systemic metastasis. Looking at the local treatment given to Retinoblastoma eyes, 5 eyes received LASER photocoagulation, and 5 received Trans scleral cryo treatment. Thirty-two (12.74%) eyes out of 94 eyes that received intravitreal chemotherapy were retained with some vision; the remaining 62 eyes were later enucleated. None of the eyes were treated with exenteration as stage 3 eyes first underwent neoadjuvant chemotherapy which reduced the tumormass, followed by enucleation, and finally, radiotherapy was delivered as per the histology reports. The histology reports of 14 eyes showed optic nerve involvement and so these subjects along with the 10 stage 3 subjects received post-enucleation radiotherapy.

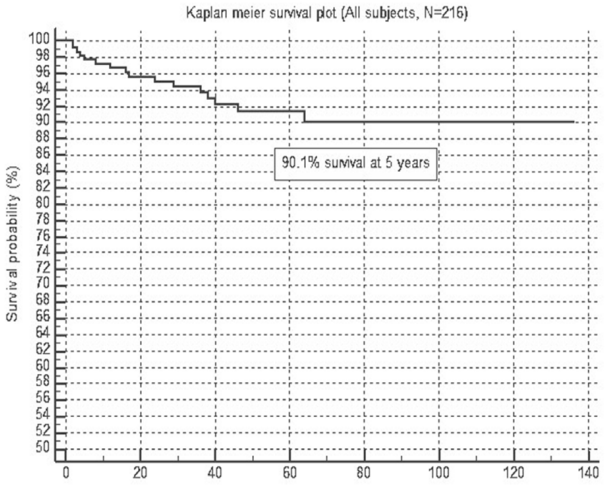
**Table 2:** Distribution of treatment modality used for treating Retinoblastoma patients

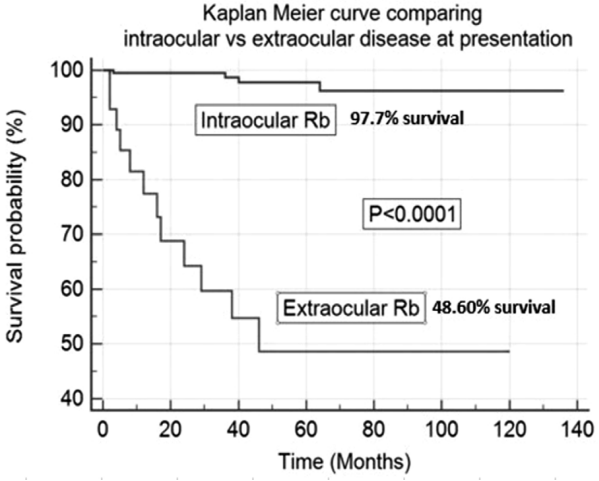
| | Cryo/Laser | Intravitreal chemo with enucleation | Intravitreal chemo with retention of eyeball | Enucleation done without local treatment | Total |
|---|---|---|---|---|---|
| Systemic chemotherapy given | 10 | 62 | 32 | 108 | 212 (84.46%) |
| Systemic chemo not given | 0 | 0 | 0 | 39 | 39 (15.54%) |
| | 10 | 62 | 32 | 147 | 251 |

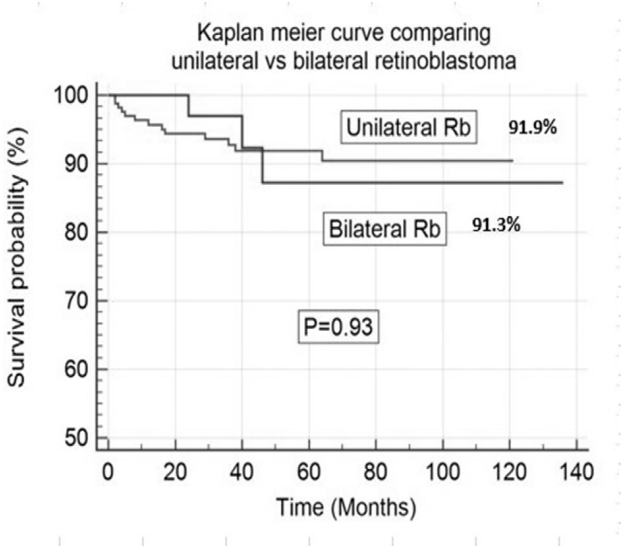
**Survival/mortality**

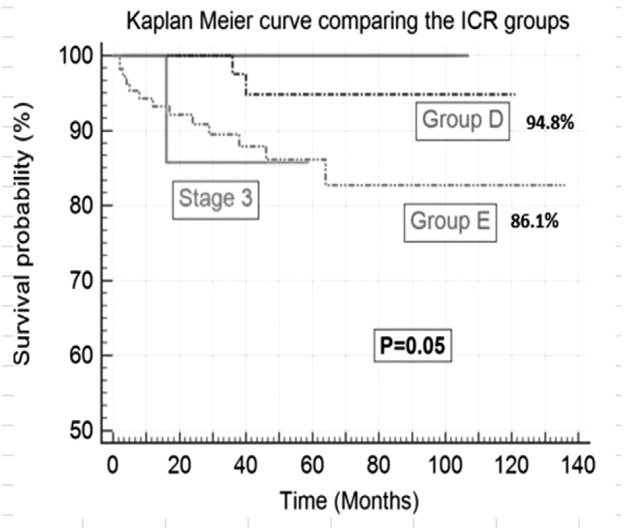
Of 209 subjects, 189 (90.43%) were alive at the time of reporting and two years after treatment had stopped. Survival distribution was 100% among the subjects with unilateral Group A (n=4), and B (n=7) retinoblastoma (ICR). Survival among the groups (ICR) C, D, and E was 94.44% (17 cases) and 95.24% (60 cases), 86.67% (91 cases) respectively. In the patients with stage 3 disease (ICR, orbital metastasis) the mortality was 80% (8cases).

The survival analysis curve (Fig. 2a) depicts 90.1% survival at 5 years (60 Months) for all the subjects combined. The 5-year survival of subjects with extraocular presentation (Stage 3 ICR) was 48.6% in contrast to subjects with the intraocular disease who had 97.7% survival at the same duration (Fig. 2b), (P<0.0001). The 5-year survival of unilateral and bilateral retinoblastoma subjects was statistically similar (P=0.93) being 91.9% and 91.3% respectively (Fig. 2c). The 5-year survival for groups (Worst eye for bilateral cases) A, and B was 100% while for groups C, D, and E it was 93.8%, 92.8%, and 84.0% respectively. The hazard ratio for death due to retinoblastoma was 1.07: 3.49: 5.07 for groups D, E, and stage 3 Retinoblastoma respectively. Thus, the mortality risk increased along with the spread of the disease.



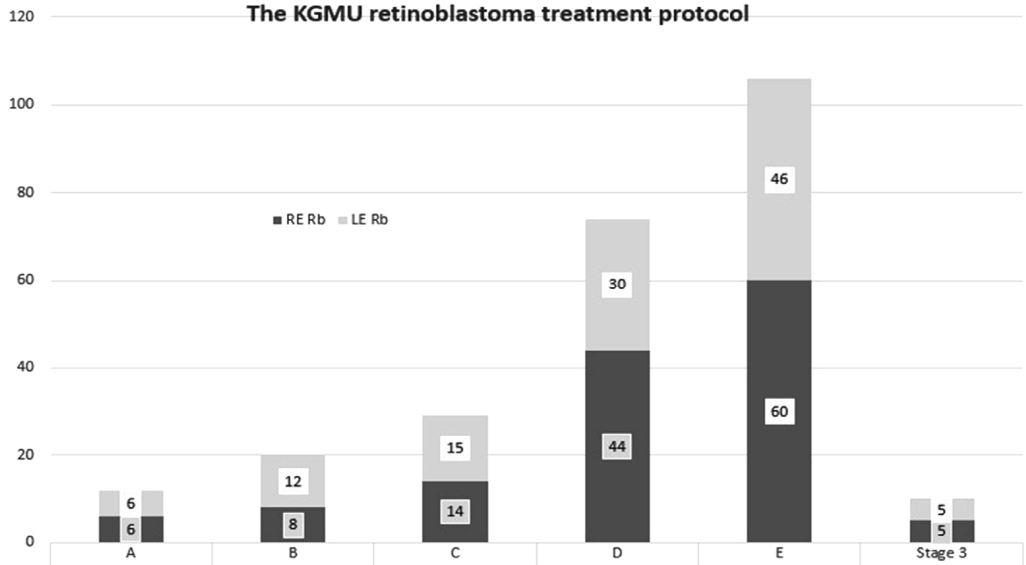




At the time of reporting (follow-up of average 53.22 months, Median 47 months) 189 (90.43%) subjects out of 209 were alive, and out of 251 retinoblastoma-affected eyes 42 (16.73%) were preserved and 32 (12.74% of 251) eyes had a useful vision.

**Chart 1. Laterality and stage of Rb affected eyes treated using The KGMU retinoblastoma treatment protocol**




| | A | B | C | D | E | Stage 3 |
|---|---|---|---|---|---|---|
| LE Rb | 6 | 12 | 15 | 30 | 46 | 5 |
| RE Rb | 6 | 8 | 14 | 44 | 60 | 5 |

## DISCUSSION

The present retrospective study demonstrates the outcomes of the "KGMU retinoblastoma treatment protocol" developed as per the ICR (International Classification of Retinoblastoma) at a tertiary care centre in India. The treatment modalities used were enucleation, LASER photocoagulation, trans-scleral cryo-destruction, intravitreal chemotherapy (Carboplatin 10microgram), systemic chemotherapy as neoadjuvant chemotherapy, and post-surgical radiotherapy as per the protocol. The study highlights the resources needed, outcomes, and survival of subjects with retinoblastoma in a developing country where relatively advanced disease at presentation is common.

We have compared the results from an earlier report from our centre (2009-2015) to reflect upon the improvements in the management of retinoblastoma at our centre compared to this study extending from 2015 to 2022.[1] The average age at presentation reduced from 42 months to 34.2 months, and the latency in reporting after the appearance of the first symptom reduced from 7.0 months (Range 0-88 months) to 5.8 months. There has been a reduced incidence of extraocular presentation, which has reduced from 41% (2009-15) to 3.81% for reasons that have not yet been studied but can be attributed to better awareness and availability of healthcare services. This improvement can be attributed to an improvement in general awareness, socioeconomic status, prompt referral, and improved availability of healthcare resources in our region.

The changes that can be attributed to "the KGMU retinoblastoma treatment protocol" can be seen in the survival proportion of the cases, eye salvage, and vision preservation as mentioned below. Earlier we had an overall survival of 63% compared to 90.43% at present.[1] The eye salvage rate has remained nearly the same 16.2% to 16.73% after implementing the "KGMU retinoblastoma treatment protocol."However, we were able to salvage 12 group C eyes and 1 group D eye with the help of additional intravitreal chemotherapy which was not practiced earlier. When looking at the survival proportion of patients as per the ICR groups, earlier, too, there was no mortality among the patients in groups B and C, like the present report. However, earlier, there was 33.8% mortality among group D, which is now reduced to 5.0%. Similarly, in group E, the mortality was 42.00% which is now 15.38%. Among the subjects with orbital metastasis,

mortality reduced from 48.78% to 25.00%. Thus, the improvement in survival can be attributed to improved management protocol apart from the relatively early presentation during the present report. Eye retention was 100% for groups A & B, 11.1% for group C, and 0% for group D in the earlier report. This has been maintained at 100% for groups A & B and improved to 38.7% for group C, and one eye (1.25%) out of a total of 80 eyes could be saved from enucleation in group D disease. Thus, there has been a significant improvement in the salvage of eyes with retinoblastoma group C (ICR). All the eyes in group E and stage 3 had to be removed to treat the retinoblastoma and no potential for vision in these eyes. None of the eyes needed exenteration, in contrast to 2.4% of eyes that needed exenteration in our previous study. Overall, the globe salvage was 16.73% in our present study.

**Comparison to studies from the Indian subcontinent**

When we compare this to recent reports from the Indian subcontinent, we find that the median age of retinoblastoma subjects at presentation ranges from 18 to 36 months which is comparable to our median of 32.78 months (Table 2).[3] Although we have included the recent reports from India (2018-2020), still there are differences between the reports from the different geographical areas. Most of the cases were unilateral in the other studies (~60-80% unilateral cases) similar to 78.7% cases with unilateral disease in the present study. One important variable that influences the survival of retinoblastoma subjects is the presence of orbital metastasis of the disease (Stage 3, ICR). In the relevant reports from India, the proportion of orbital metastasis at presentation ranges from 9-58% when compared to our proportion of 3.98%. Another important variable at the presentation that warrants enucleation is advanced retinoblastoma which has destroyed the visual potential of the eye and corresponds to groups D & E (ICR). In our study, this was 71.71% and we enucleated these eyes and a few eyes from group C resulting in enucleation being done in 83.27% of the total eyes affected by retinoblastoma in the present study. In other relevant reports the eyes with advanced intraocular retinoblastoma ranged from 50.1- 85.88% and the eyes which were treated by enucleation ranged from 35-87.5% of eyes affected by retinoblastoma.

The survival in our report is 90.43% and is comparable to Indian reports by Kaliki *et al.* (92%)[9] and Singh *et al.* (97.2%)[11] is better than the reports by Chawla *et al.* (75.7%),[12] and Gupta *et al.* (63%).[1] The survival analysis from the relevant studies is mentioned in only three of the above studies from India. Our survival proportion at 1, 2, 3, and 5 years is 96.6%, 94.9%, 92.2%, and 88.3% respectively, which is better than the reports by Chawla *et al.*.and Gupta *et al.*, and at par with Kaliki *et al.* [1,8,9,12]

The report by Kaliki *et al.* has an overall survival rate of 91% among retinoblastoma patients in south India, and globe salvage was 69%.The globe salvage rate of 69% is higher than our observation of 17.04% however, a globe salvage rate of 69% does not appear feasible as they have reported 68% of the eyes with ICR group D and E disease. The ICR classification defines groups D and E eyes with no visual potential and a high risk of orbital metastasis. Thus, it appears that they have retained 37% of eyes with no visual potential, which is not a logical and safe approach. The study by Bhawna *et al.* published in 2016 reported an overall survival rate of 75.7% and globe retention of 28.2% in north India in retinoblastoma subjects being treated at their centre. These figures though different from our survival rate of 92.5% and globe salvage of 17.04% but are comparable keeping in mind that they had a higher proportion of subjects with orbital metastasis (27.7%) compared to our subjects with orbital metastasis (3.84%), which can explain the higher mortality in their study.

**Comparison to countries with similar socioeconomic status**

If we compare the present report with the reports from contemporary regions of the world, there are few mentionable recent reports from Pakistan, Tehran, Thailand, Brazil, and China The median age at presentation was lower than in our report (except in Pakistan, 30 months), especially in Thailand where it was 8 months compared to 32 months in our report. The proportion of cases with orbital metastasis was higher than our report (3.84%) in all the studies but reports from Thailand (7.3%) and China (8.7%) were comparable. The globe salvage rate ranged from 4.3%-62.5% compared to our report of 17.04%. The survival of retinoblastoma subjects ranges from 64.5% - 93.8% when compared to our report of 88.4%. Thus, in the Asia pacific geographical area, the presentation and outcomes of our retinoblastoma subjects are comparable to other recent published reports.

There is a relevant publication by the Global retinoblastoma group, which reported a large cohort of retinoblastoma subjects from 149 countries. They have segregated the reports from countries based on per capita income. They have reported the extraocular presentation, globe salvage, and survival from the lower middle-income group countries as 19.7%, 32.9%, and 84.6% respectively. In comparison, we have a favourable incidence of extraocular presentation (3.84%), globe salvage rate (17.04%), and survival proportion (88.4%), which is better than that reported for the bracket in which India falls. Treatment using primary intra-arterial chemotherapy was reported for only 7.5% of all the subjects (Only from higher-income group countries) reported in the study, which points out the paucity and its non-availability in middle-income group countries like India. Intra-arterial chemotherapy is not available at our institute and hence is not included in our protocol either.

Though the outcomes of our treatment protocol are not at par with the developed world, the main reason for this can be attributed to the differences in the epidemiology of retinoblastoma in our region. However, "The KGMU retinoblastoma treatment protocol" has resulted in improvement in the outcomes of retinoblastoma at our centre and is now comparable to the top-tier countries in the middle-income group. The study delineates the requisite resources and the protocol, which can be implemented across the regions with a common healthcare structure. This may provide a basis for the protocol-based management of retinoblastoma in India with designated resources needed to establish centres for prompt treatment and optimum outcomes.

**Contribution:**

Mr. Syed Meesam Abbas Rizvi, Department of Ophthalmology, KGMU, Lucknow 226003, Uttar Pradesh.

## REFERENCES

1. Pant G, Verma N, Kumar A, *et al.*. Outcome of extraocular retinoblastoma in a resource limited center from low middle income country. Pediatr Hematol Oncol [Internet]. 2017 Nov 17 [cited 2021 Jan 1]; 34(8):419–24.
2. Chawla, Bhavna; Singh, Rashmi. Recent advances and challenges in the management of retinoblastoma. Indian Journal of Ophthalmology 65(2):p 133-139, February 2017. | DOI: 10.4103/ijo.IJO_883_16
3. Singh U, Katoch D, Kaur S, *et al.*. Retinoblastoma: A Sixteen-Year Review of the Presentation, Treatment, and Outcome from a Tertiary Care Institute in Northern India. Ocul Oncol Pathol. 2017 Dec;4(1):23-32. doi: 10.1159/000477408. Epub 2017 Jul 5. PMID: 29344495; PMCID: PMC5757564.
4. Shields, C. L. & Shields, J. A. Basic understanding of current classification and management of retinoblastoma. *Curr. Opin. Ophthalmol*.17, 228–234 (2006).
5. Scelfo C., Francis J. H., Khetan V., *et al.*. (2017). An international survey of classification and treatment choices for group D retinoblastoma. International Journal of Ophthalmology. https://doi.org/10.18240/ijo.2017.06.20
6. Abramson DH, Shields CL, Munier FL,*et al.*. Treatment of Retinoblastoma in 2015. JAMA Ophthalmol [Internet]. 2015 Nov 1;133(11):1341.
7. Abramson DH, Shields CL, Munier FL & Chantada GL(2015):Treatment of retinoblastoma in 2015: agreement and disagreement. JAMA Ophthalmol 133: 1341–1347.
8. Ancona-Lezama D, Dalvin LA, Shields CL, *et al.*. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020 Nov;68(11):2356-2365. doi: 10.4103/ijo.IJO_721_20. PMID: 33120616; PMCID: PMC7774148.
9. Gupta N, Pandey A, Dimri K, *et al.*. Epidemiological profile of retinoblastoma in North India: Implications for primary care and family physicians. J Family Med Prim Care. 2020 Jun 30; 9(6):2843-2848. doi: 10.4103/jfmpc.jfmpc_265_20. PMID: 32984136; PMCID: PMC7491789.
10. Kaliki S, Patel A, Iram S, *et al.*. Retinoblastoma in India: Clinical Presentation and Outcome in 1,457 Patients (2,074 Eyes). Retina. 2019 Feb; 39(2):379-391. doi: 10.1097/IAE.0000000000001962. PMID: 29210937.
11. Padma M, Kumar N, Nesargi PS, *et al.*. Epidemiology and clinical features of retinoblastoma: A tertiary care center's experience in India. South Asian J Cancer. 2020 Jan-Mar;9(1):56-58. doi: 10.4103/sajc.sajc_89_19. PMID: 31956625; PMCID: PMC6956589.
12. Singh U, Katoch D, Kaur S, *et al.*. Retinoblastoma: A Sixteen-Year Review of the Presentation, Treatment, and Outcome from a Tertiary Care Institute in Northern India. Ocul Oncol Pathol. 2017 Dec; 4(1):23-32. doi: 10.1159/000477408. Epub 2017 Jul 5. PMID: 29344495; PMCID: PMC5757564.
13. Chawla B, Hasan F, Azad R, *et al.*. Clinical presentation and survival of retinoblastoma in Indian children. British Journal of

Ophthalmology 2016; 100:172-178.

14. Zia N, Hamid A, Iftikhar S, *et al*.. Retinoblastoma Presentation and Survival: A four-year analysis from a tertiary care hospital. Pak J Med Sci. 2020 Jan; 36(1):S61-S66. doi: 10.12669/pjms.36.ICON-Suppl.1720. PMID: 31933609; PMCID: PMC6943119.
15. Faranoush M, Mehrvar N, Tashvighi M, *et al*.. Retinoblastoma presentation, treatment and outcome in a large referral centre in Tehran: a 10-year retrospective analysis. Eye (Lond). 2021 Feb; 35(2):575-583. doi: 10.1038/s41433-020-0907-z. Epub 2020 May 4. PMID: 32367000; PMCID: PMC8027402.
16. Rojanaporn D, Attaseth T, Dieosuthichat W, *et al*.. Clinical Presentations and Outcomes of Retinoblastoma Patients in relation to the Advent of New Multimodal Treatments: A 12-Year Report from Single Tertiary Referral Institute in Thailand. J Ophthalmol. 2020 Sep 10;2020:4231841. doi: 10.1155/2020/4231841. PMID: 33005446; PMCID: PMC7508219.
17. Selistre SGA, Maestri MK, Santos-Silva P, *et al*.. Retinoblastoma in a pediatric oncology reference center in Southern Brazil. BMC Pediatr. 2016 Apr 3;16:48. doi: 10.1186/s12887-016-0579-9. PMID: 27038613; PMCID: PMC4818960.
18. Gao J, Zeng J, Guo B, He W, *et al*.. Clinical presentation and treatment outcome of retinoblastoma in children of South Western China. Medicine (Baltimore). 2016 Oct; 95(42):e5204. doi: 10.1097/MD.0000000000005204. PMID: 27759657; PMCID: PMC5079341.
19. Global Retinoblastoma Study Group. The Global Retinoblastoma Outcome Study: a prospective, cluster-based analysis of 4064 patients from 149 countries. Lancet Glob Health. 2022 Aug; 10(8):e1128-e1140. doi: 10.1016/S2214-109X(22)00250-9. PMID: 35839812; PMCID: PMC9397647.