Article published online: 2022-07-02

Challenges in the Management of Retinoblastoma during Nationwide Lockdown: An Observational Study from a Retinoblastoma Center in South India

Janani Arul[1] Suganeswari Ganesan[2] Vikas Khetan[2] Latha M. Sneha[1] Dhaarani Jayaraman[1] Julius Xavier Scott[1]

[1] Division of Pediatric Hemato-Oncology, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India
[2] Department of Ophthalmology (Vitreoretina and Oncology), Sankara Nethralaya, Chennai, India

Address for correspondence Janani Arul, MD, Division of Pediatric Hemato-Oncology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu 600116, India (e-mail: jananiarul@yahoo.in).

Ind J Med Paediatr Oncol 2022;43:250–254.

Abstract

Introduction The nationwide lockdown due to coronavirus disease 2019 led to travel restrictions resulting in a delay in diagnosis, treatment, and follow-up of children with retinoblastoma (RB).

Objectives We audited the impact and challenges of lockdown among RB children over 1-year period (May 2020–2021).

Materials and Methods It is a cross-sectional study of 104 children with RB, who presented within the 1-year study period. The demographic details, clinical presentations, and outcome of treatment due to lockdown were studied.

Results Of the 152 eyes of 104 children, unilateral RB was observed in 52% and bilateral in 48%, in which four children had metastatic disease and one child had trilateral RB. International classification groups D ($n = 64$ eyes, 42%) and E ($n = 38$ eyes, 25%) were in majority. Almost, half of the children ($n = 53$, 51%) underwent enucleation. Overall, the vision was preserved in 32% of the children and globe preservation in 49% of children. Eleven children (10.5%) succumbed due to disease progression. But, only five children were affected with severe acute respiratory syndrome coronavirus 2 infection. The majority of children ($n = 72$, 69%) had to travel more than or equal to 1,000 km for treatment. About 57% ($n = 60$) patients were newly diagnosed during the lockdown period and due to the travel restrictions, they had a mean delay of 2.2 months (range: 0–15 months) in starting treatment and 27% ($n = 29$) of children on treatment had an interruption of treatment.

Conclusion Multidisciplinary team management with strategies to support the RB families during locked down crisis is essential to continue care without interruptions.

Keywords
- COVID-19
- children
- retinoblastoma
- lockdown
- travel restrictions

DOI https://doi.org/10.1055/s-0042-1750204.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has created a significant void in the availability and accessibility of treatment modalities and timely intervention for children with cancer. The lockdown with travel restrictions and financial constraints has been a major cause. Furthermore, in retinoblastoma (RB) already a strong disparity exists between the delay in diagnosis, stage of presentation, abandonment, and survival in the developing and developed countries prior to the COVID-19 pandemic.[1] Despite the development of healthcare in diagnosis and treatment, 50% of children with RB in developing countries present at a more advanced stage and succumb to the disease, whereas in developed countries, it is less than 5%.[2,3] The COVID-19 pandemic has caused an additional strain on the diagnosis and treatment process of RB children. There are multifactorial reasons for treatment delay including hospital resource constraints, affordability of transport, financial constraints along with the fear among parents regarding the implications of COVID-19 rather than RB.[4,5] The major reason is the inability to reach their respective health centers leading to interruption of treatment.[6,7] Our study is to assess the challenges of the COVID-19-related nationwide lockdown on disruption of access to healthcare and its impact on the management of children with RB and the strategies we developed to overcome these challenges.

Materials and Methods

This is a cross-sectional study of 104 children with RB, who presented within the 1-year study period (May 2020–April 2021) to Sankara Nethralaya (SN) tertiary referral eye hospital in Tamil Nadu. These children were collectively managed by both the pediatric oncology unit in Sri Ramachandra Institute of Higher Education and Research (SRIHER), and SN. The demographic details, clinical presentations, initiation delay and interruptions of treatment, and the outcome of treatment during this lockdown period were collected. Initiation delay was defined as time from onset of symptoms to initiation of treatment of more than 4 weeks. Interruptions are defined as a delay of more than 2 weeks during therapy. The examination included comprehensive eye evaluation under anesthesia (EUA), ultrasonography of the eye to measure the tumor dimensions, RetCam imaging, magnetic resonance imaging of the brain and orbit to assess the optic nerve status, and presence of the primary neuroendocrine tumor. Children diagnosed with RB but continued treatment in their native place were excluded from study.

The staging was based on International Intraocular Retinoblastoma Classification (IIRC) in SN; patients were referred to the pediatric hemato oncology unit in SRIHER for staging evaluations, intravenous chemotherapy, and radiotherapy.[8] Metastatic work if needed included bone marrow aspiration and lumbar puncture for cerebrospinal fluid analysis. The treatment modalities consisted of focal therapy, intravenous, intra-arterial, intravitreal chemotherapy, radiotherapy, and enucleation as per staging after the discussion in the combined institutional tumor board. The outcome was measured based on vision salvage, globe salvage, and life salvage.

Chemotherapy regimens commonly used are of two types: standard dose VEC (vincristine, etoposide, carboplatin) for intraocular RB and high-dose VEC for extraocular RB. For metastatic and trilateral RB, four drug regimen was used: vincristine (1.5 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by cisplatin (80 mg/m^2) and etoposide (200 mg/m^2). Enucleation was performed when required. The enucleated eyes were analyzed for high-risk features, which were involvement of optic nerve, choroid invasion, anterior segment, scleral, and extrascleral involvement.

The impact of lockdown on delay in diagnosis, interruption of treatment, and outcome was studied. The reasons for treatment interruption like transport restrictions, financial constraints, and accommodation difficulty were analyzed. The residence of the RB children, the distance needed to travel to reach the treating hospital during the lockdown times, financial constraints, difficulty in accommodation during the lockdown, and the challenges faced were obtained. History pertaining to COVID-19 infection in any of the family members was obtained. The treatment outcome was measured in terms of vision salvage, globe salvage, and life salvage.

Statistical Analysis

The data collected was entered in MS Excel and the mean, percentage, and statistical analysis were performed by SPSS version 20.1

Ethics

Ethics clearance was obtained from both the institutional ethics committee (SN and SRIHER- CSP-MED/21/JUN/69/97) in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from either of the parents prior to enrolment.

Results

A total of 104 children were treated during this period from May 2020 to April 2021. This included both newly diagnosed cases and follow-up children already on treatment. The total number of children who underwent EUA was 122 in the previous year (pre-COVID-19 lockdown) and the newly diagnosed was 67 as compared with 60 during the lockdown period (May 2020–April 2021).

Of the 152 eyes of 104 children, 52% were unilateral RB and 48%were bilateral RB in which four children had metastatic disease and one child had trilateral RB. The mean age at diagnosis was 34 months (range: 1–132 months), with 52% males and 48% females. Leukocoria was the most common presenting feature (94%). Family history of RB was positive in only 7.5% ($n = 8$) (►**Table 1**). The cases were classified based on IIRC, and majority were in groups D (42%; $n = 64$ eyes) and E (25%; $n = 38$ eyes). Almost, half of the children 51% ($n = 53$) underwent enucleation. Overall, the vision was preserved in 32% of the children. The globe salvage was achieved in 49% of children, of which 29 children had unilateral and 22 had

Table 1 Demographic and clinical details

Demographics		$n = 104$ children (%)	95% CI
Age at diagnosis		34 months (range: 1–132 months)	
Gender	Male	54 (52)	(42.3, 61.5)
	Female	50 (48)	(38.4, 57.6)
Distance needed to travel	<500 km	26 (25)	(16.7, 33.3)
	500–1,000 km	6 (7)	(1.2, 10.3)
	>1,000 km	72 (68)	(60.3, 78.1)
Family history of RB	Yes	8 (7.5)	(2.57, 12.8)
	No	96 (92.5)	(87.2, 97.4)
Laterality	Unilateral	54 (52)	(42.3, 61.5)
	Bilateral	50 (48)	(38.5, 57.7)
Vision salvage		43 (32)	(31.9, 50.8)
Globe salvage		51 (49)	(39.4, 58.7)
Life salvage		94 (90)	(84.7, 96.1)
Death		10 (10)	(3.9, 15.3)

Abbreviations: CI, confidence interval; RB, retinoblastoma.

bilateral RB. In comparison, globe salvage was achieved in 54% of children in the previous year. Eleven children (10.5%) succumbed to the disease due to disease progression.

We developed a protocol to contact the patients telephonically periodically to prevent abandonment. We also made efforts to arrange transport for families to reach the hospital with special permissions and coordinated accommodation with the help of the home-away-home program and coordinated nongovernment organizations (NGO) support for funding for invisible expenses also like food. Financial assistance for EUA, local therapy, chemotherapy, and radiotherapy treatment was completely supported by both hospitals together with NGOs. Whenever required transport and rent allowance for the extended stay during locked down were also supported by NGOs.

Majority of children, 69% ($n = 72$) had to travel more than or equal to 1,000 km for the treatment (►**Table 2**). About 57% ($n = 60$) of children were newly diagnosed during the lockdown period and due to the travel restrictions, they had a mean delay of 2.2 months (range: 0–15 months) in starting treatment and 27% ($n = 29$) of children on treatment had an interruption of treatment. Only three of our children had tested positive for COVID-19 during routine screening. When the children were positive, we withheld treatment for 2 weeks. They were asymptomatic and continued treatment after the resolution of COVID-19 infection.

Table 2 Impact of lockdown on RB follow-up

	(*n*, %)
Loss to follow-up	29, 27
Travel restrictions	18, 62
Financial constraints	8, 28
COVID-19 positivity in family	3, 10

Abbreviations: COVID-19, coronavirus disease 2019; RB, retinoblastoma.

Discussion

COVID-19 was declared a pandemic by the World Health Organization) on March 11, 2020. Following this, many countries went into complete lockdown. India declared lockdown on March 24, 2020, leading to transport restrictions and the inability to reach the healthcare facilities. Children with life-threatening diseases in need of continued hospital care like our oncology patients were affected the most.[9] Children with pediatric solid tumors, transplant recipients, and ocular cancers such as RB faced a major difficulty in continuing their treatment, majorly due to the inability to reach their healthcare providers.[10,11]

Pediatric cancers have also been observed to affect the low (41%) and middle socioeconomic (43%) class more than the upper class (16%), and 90% of the global cancer deaths are from low- and middle-income countries.[12,13] Similarly, RB accounts for 2.5 to 4% of all childhood cancers in most developed countries, and a two- to threefold increase has been reported in India.[14] India accounts for nearly one-third of RB cases in the Asia-Pacific region. The survival of RB is between 95 and 100% in developed countries; however, in parts of Asia and Africa, it is between 30 and 60%.[15] With the already existing social issues prepandemic, the lockdown has caused more strain on the developing counties. Multifactorial reasons have been identified for treatment delay—financial constraints, transport restriction, accommodation issues, and no caregiver to accompany.

Fabien et al in their global RB study from 94 countries have reported approximately 42.3% of families had delays in treatment due to travel restrictions during the current

pandemic as compared with only 10% before the pandemic. They also mentioned that the availability of life-saving treatment modalities such as EUA, enucleation, intravenous chemotherapy, and intraarterial chemotherapy have significantly dropped from 95.9 to 55.2%, 100 to 89.6%, 96.9 to 93.8%, and 49.7 to 37.8%, respectively, before and after the pandemic.[16] Similarly, Gupta et al had reported an average duration of delay in follow-up was 14 days (7–20 days) during pre-COVID-19, as compared with 336 days (56–560 days) during the lockdown period.[17]

This COVID-19 lockdown situation has led many ophthalmic and pediatric oncology centers to revise the policy of examining, treating, and admitting their patients. One such study by Hadjistilianou et al, from Italy, has studied the policies adopted during the COVID-19 pandemic and RB patients. They have observed a wide disparity between various ophthalmology tertiary care centers as to when and who should be tested for COVID-19. Although swab testing was mandatory to ensure the safety of both patients and healthcare workers, only 2 out of 16 institutions they reviewed had ensured mandatory testing in all centers.[18] In our center, mandatory testing was done for both patients and the accompanying attenders and 3 were found to be COVID-19 positive.

During the era of global lockdown and travel restrictions, to help flatten the COVID-19 curve, telemedicine has been fundamental in connecting patients to their healthcare providers. This helped in triaging the patients, hence identifying those requiring immediate medical assistance and others to continue the medical care through teleconsultations.[19]

The COVID-19 pandemic and the nationwide lockdown have created a negative impact on overall healthcare in particular on chronic diseases needing long-term management. Hence, it is imperative to establish a network with necessary support across the hospitals, with the help of government, nongovernment social organizations, shared care with primary practitioners and telemedicine, keeping in mind the psychological impact of the pandemic on the families.

Future Research Directions

A multicentric study, comparing the RB children during the COVID-19 lockdown period with the non-COVID-19 period in various countries, would help us understand the support system across the centers that can help in preparedness future pandemics.

Limitations of the Study

It is a single-center experience with a limited study population.

Conclusion

Our study has shown that providing collaborative care has enabled 73% of patients to receive emergent care and continue their treatment. Through our study, we advocate that with the involvement of NGOs and meticulous planning of funding support we can provide a structured management strategy during global pandemics. In conclusion, there is a delicate balance of risk assessment and management of RB patients during the pandemic. The decision-makers should make bold new policies weighing the risks and benefits of the situation.

Funding
None.

Conflict of Interest
None declared.

References

1 Sullivan M, Bouffet E, Rodriguez-Galindo C, et al; Contributing Authors. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. Pediatr Blood Cancer 2020;67(07):e28409
2 Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. Lancet Oncol 2008;9(08):721–729
3 Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol 2019;20(01):e42–e53
4 Peter N, Bandyopadhyay S, Lakhoo KGlobal Health Research Group on Children's Non-Communicable Diseases Collaborative. Impact of the COVID-19 pandemic on paediatric patients with cancer in low-income, middle-income and high-income countries: protocol for a multicentre, international, observational cohort study. BMJ Open 2021;11(06):e045679
5 Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. Cancer 2008;112(03):461–472
6 Dvori M, Elitzur S, Barg A, et al. Delayed diagnosis and treatment of children with cancer during the COVID-19 pandemic. Int J Clin Oncol 2021;26(08):1569–1574
7 Cox JA, Karlson CW, Dillard BC, Collier AB III. Impact of COVID-19 pandemic on timing of childhood cancer diagnoses. J Pediatr Hematol Oncol 2021;43(08):e1244–e1246
8 Meel R, Radhakrishnan V, Bakhshi S. Current therapy and recent advances in the management of retinoblastoma. Indian J Med Paediatr Oncol 2012;33(02):80–88
9 Bansal R, Aishwarya A, Rao R, et al. Impact of COVID-19 nationwide lockdown on retinoblastoma treatment and outcome: a study of 476 eyes of 326 children. Indian J Ophthalmol 2021;69 (10):2617–2624
10 Wang H, Elsheikh M, Gilmour K, et al. Impact of COVID-19 pandemic on eye cancer care in United Kingdom. Br J Cancer 2021;124(08):1357–1360
11 Parasole R, Stellato P, Conter V, et al. Collateral effects of COVID-19 pandemic in pediatric hematooncology: fatalities caused by diagnostic delay. Pediatr Blood Cancer 2020;67(08):e28482
12 Magrath I, Steliarova-Foucher E, Epelman S, et al. Paediatric cancer in low-income and middle-income countries. Lancet Oncol 2013;14(03):e104–e116
13 Totadri S, Trehan A, Kaur A, Bansal D. Effect of socio-economic status & proximity of patient residence to hospital on survival in childhood acute lymphoblastic leukaemia. Indian J Med Res 2019; 149(01):26–33
14 Fabian DI, Stacey WA, Foster A, Kivelä TT, et al. Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43 African countries and 518 patients from 40 European countries. Br J Ophthalmol 2021;105(10):1435–1443
15 Fabian ID, Stacey AW, Foster A, et al. Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43

African countries and 518 patients from 40 European countries. Br J Ophthalmol 2021;105(10):1435–1443
16 Fabian ID, Stacey AW, Bowman R, et al; Global Retinoblastoma Study Group. Retinoblastoma management during the COVID-19 pandemic: a report by the Global Retinoblastoma Study Group including 194 centers from 94 countries. Pediatr Blood Cancer 2021;68(01):e28584
17 Gupta AK, Meena JP, Seth R. Reasons for missed chemotherapy appointments in retinoblastoma patients undergoing chemotherapy: a report from a tertiary care hospital from India. Cancer Rep (Hoboken) 2020;3(06):e1279
18 Hadjistilianou D, Barchitta M, Defrancesco S. Covid-19 and retinoblastoma: how we manage it. Eur J Ophthalmol 2020;30(05): NP6–NP10
19 Skalet AH, Allen RC, Shields CL, Wilson MW, Mruthyunjaya P, Gombos DS. Considerations for the management and triage of ocular oncology cases during the COVID-19 Pandemic. Ocul Oncol Pathol 2020;6(03):1–4

