



ORIGINAL RESEARCH PAPER

NEOADJUVANT CHEMOTHERAPY AND ENUCLEATION ACCEPTANCE IN ADVANCED RETINOBLASTOMA: A PROSPECTIVE STUDY IN A LOW-RESOURCE SETTING

Oncology

KEY WORDS:
 Retinoblastoma, Neoadjuvant Chemotherapy, Enucleation, Pediatric Oncology, Low-Resource Settings

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ABSTRACT	Background: In low- and middle-income countries (LMICs), retinoblastoma (RB) frequently presents at advanced stages, with parental refusal of enucleation posing a major treatment challenge. Neoadjuvant chemotherapy (NACT) may reduce tumor burden and improve enucleation acceptance. Methods: This prospective observational study was conducted at a tertiary cancer center in India (Dec 2023–Dec 2024). Eleven children (1 month –5 years old) with unilateral Group E RB (ICRB classification) who initially refused upfront enucleation were included. Patients received three cycles of NACT (Vincristine, Etoposide, Carboplatin). Tumor burden reduction was assessed via MRI-based volume measurements before and after NACT. Statistical tests included Chi-square tests, Mann-Whitney U tests, and t-tests. Results: Mean tumor burden reduction was 76.3% (±12.5%) (range: 52–91%, p < 0.0001). Parental enucleation acceptance increased from 0% to 90.9% following chemotherapy and structured counseling. No significant association was found between gender and eye involvement (p = 0.39) or age differences between genders (p = 0.55). Conclusion: NACT significantly reduced tumor burden and improved parental acceptance of enucleation in unilateral Group E RB. These findings suggest that pre-enucleation chemotherapy, combined with structured counseling, may enhance treatment adherence in LMICs. Larger multi-center studies are needed to validate these results.
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INTRODUCTION	Retinoblastoma (RB) is the most common pediatric intraocular malignancy, accounting for approximately 3% of all childhood cancers(1). While early diagnosis and enucleation can result in survival rates exceeding 95% in high-income countries (HICs), the prognosis remains poor in low- and middle-income countries (LMICs) due to delayed presentation, low socioeconomic status, limited healthcare access, cultural factors, social stigmatization and parental reluctance toward enucleation and treatment(2,3). In LMICs, 50–70% of RB cases present at advanced stages (Group D/E), significantly higher than in HICs, where >90% of cases are detected early(4). Various factors, including lack of awareness, screening protocols, income levels, availability of expertise, and resources, impact the outcomes of children with RB in LMICs(5). Refusal to therapy and poor compliance to the treatment are other major issues that may cause poor outcomes of RB in low-resource setting(6). In low-resource settings, enucleation is often the only available curative treatment, as chemotherapy and focal therapy may not be always available(7). Parental refusal of enucleation is a major factor which leads to delay in treatment, particularly in LMICs, which ultimately results in poor outcomes in these children which is preventable(5). Survival rates of patients who temporarily refused treatment were significantly lower which was associated with progression of tumor stage(3). Delayed presentation and clinical stage are strongly associated with survival (8). Despite upfront enucleation being the standard of care for Group E RB, many parents in LMICs refuse the procedure due to sociocultural beliefs, fear of disfigurement, and lack of awareness about life-saving treatment. Treatment refusal contributes to high abandonment rates (~30–50%), leading to increased mortality (9). Neoadjuvant chemotherapy (NACT) has been proposed as a bridge therapy to reduce tumor burden, potentially increasing parental acceptance of enucleation(10). Studies suggest that NACT leads to 50–85% tumor shrinkage in Group E RB, although its impact on enucleation acceptance remains unclear(5). Additionally, standardized structured parental counseling throughout NACT cycles has shown promise in improving treatment adherence(3).
	This study aims to evaluate the impact of NACT on tumor burden reduction and enucleation acceptance in unilateral Group E RB in a low-resource setting. We hypothesize that NACT will significantly reduce tumor burden and improve enucleation acceptance in a population where upfront enucleation refusal is common.
	METHODS This prospective observational study was conducted at a tertiary cancer hospital in Central Maharashtra, India, from December 2023 to December 2024. Ethical approval was obtained from the institutional ethics committee, and written informed consent was obtained from parents/guardians. Children aged 1 month to 5 years with unilateral Group E intraocular RB (ICRB classification) and whose parents/guardians refused upfront enucleation after initial counseling were included. Children with metastatic disease were excluded. All patients underwent Examination under anesthesia (EUA), Magnetic Resonance Imaging (MRI) of the brain and orbits, Cerebrospinal fluid (CSF) analysis, Bilateral bone marrow aspiration. Genetic counselling and screening of siblings was done in all patients. All patients received three cycles of NACT, consisting of: Vincristine (0.05 mg/kg IV, Day 1), Etoposide (5 mg/kg IV, Days 1–2) and Carboplatin (18.6 mg/kg IV, Day 1). Reassessment was done using MRI and tumor volume and characteristics were noted. Counselling of the parents regarding enucleation was done regularly during each cycle. Primary outcome was tumor burden reduction, calculated using MRI-based volume measurements: Tumor Burden Reduction (%) = [(Pre-NACT Volume – Post-NACT Volume) / Pre-NACT Volume] × 100. Secondary outcome was change in parental acceptance of enucleation.

Statistical tests used were Chi-square test (gender vs. eye involvement), One-sample t-test (tumor burden reduction vs. 50% baseline) and Mann-Whitney U test (age differences between genders)

RESULTS

A total of 11 children (mean age 24.64 months ± 13.97 SD) were included. Seven (63.6%) children were males and 4 (36.4%) were female. Male to female ratio was 1.7:1. All children had unocular involvement; Left eye in 5 (45.5%), Right eye in 6 (54.5%) children. Most common presenting features were Leukocoria (n=7, 63.64%), Strabismus (n=7, 63.64%), Redness (n=6, 54.55%), Pain (n=2, 18.18%) and Proptosis (n=1, 9.09%). The mean lag period from the first symptom till presentation was 6.18 ± 4.17 (in months). Reasons for delay included lack of awareness about the disease, lack of access to specialized healthcare, lack of proper referral systems, financial constraints and cultural factors. There was no family history of RB.

Mean tumor reduction was 76.3% ± 12.5% (range: 52–91%). Tumor burden reduction was highly significant (p < 0.0001, t = 51.20, one-sample t-test). After regular counselling during each cycle of chemotherapy, parents of 10 out of 11 children (90.9%) were willing for enucleation and continuation of treatment. Enucleation acceptance increased from 0% to 90.9% following chemotherapy and counseling. There was no significant association between gender and eye involvement (p = 0.39, Chi-square test). No significant age difference between genders (p = 0.55, Mann-Whitney U test) was observed.

Table 1: Patient Characteristics And Demographics

Characteristic	Value
Total Patients (n)	11
Mean Age (Months) ± SD	24.64 ± 13.97
Gender (Male:Female)	7:4 (63.6% Male)
Eye Involvement (Right:Left)	6:5 (54.5% Right, 45.5% Left)
Lag period from the first symptom till presentation (Months) ± SD	6.18 ± 4.17
NACT Cycles Administered	3 (Fixed)
Presenting Symptoms	Leukocoria (n=7, 63.64%) Strabismus (n=7, 63.64%) Redness (n=6, 54.55%) Pain (n=2, 18.18%) Proptosis (n=1, 9.09%)

Abbreviations:
 SD: Standard Deviation
 NACT: Neo-Adjuvant Chemotherapy

Table 2: Statistical Analysis

Statistical Test	Comparison	Test Statistic	p-value
Chi-square Test	Gender vs. Eye Involvement	$\chi^2 = 0.74$	0.39 (NS)
One-sample t-test	Tumor Reduction vs. 50% Baseline	t = 51.20	<0.0001 (Significant)
Mann-Whitney U Test	Age Differences Between Genders	U = 10.50	0.557 (NS)

Abbreviations:
 NS: Not Significant

DISCUSSION

Our study spanning over a time of 1 year included 11 children with Group E RB. There was a preponderance of males, which aligns with reported data in the literature. (11). Mean age at diagnosis was approximately 24 months, which is consistent with other studies from Asia. (12). There was an average lag period of 6 months from the first symptom till presentation at the hospital, which might explain advanced RB in these children. Reasons for this delayed presentation included lack

of awareness about the disease, lack of access to specialized healthcare, lack of proper referral systems, financial constraints and cultural factors. This delay in presentation is comparable to other studies in LMICs(6).

Our study demonstrated that NACT significantly reduced tumor burden (~76%) and increased enucleation acceptance (90.9%) among children with unilateral Group E RB. These findings are consistent with prior studies while highlighting unique challenges in LMICs(13).

Prior studies on NACT in RB report tumor reductions of 35 to 50%, aligning with our findings(14). NACT can lead to a tumor size reduction, improving the feasibility of subsequent enucleation, especially in advanced RB with severe buphthalmia(2). Our observed 76.3% mean reduction (range: 52–91%) is within this reported range, although slightly higher, possibly due to strict chemotherapy adherence and MRI-based tumor assessment.

However, our tumor burden reduction rate is lower than that reported in HIC studies, where multimodal therapy (NACT + intra-arterial chemotherapy) achieves high cure rates in select cases (15). This difference underscores the limitations of systemic chemotherapy in resource-limited settings and the need for accessible advanced treatments.

A key finding of our study was the dramatic increase in enucleation acceptance from 0% to 90.9% following NACT and structured counseling. In contrast, previous studies report post-NACT enucleation acceptance rates of only 40–70% in LMICs (16)

Reason for this higher acceptance rate might be structured Counseling. Parents were educated at each NACT cycle about the disease progression, emphasizing life-saving treatment over cosmetic concerns. Studies suggest that continuous counseling increases adherence rates in LMICs. (17). NACT might provide time for the family and the treating group to discuss and accept the concept of enucleation(2)

Our findings highlight that NACT alone is not enough and structured counseling during chemotherapy cycles is crucial for increasing enucleation acceptance. NACT should be limited so as to avoid further delay in treatment. In LMICs where upfront enucleation refusal is common, NACT may serve as a transition strategy to increase treatment adherence. Despite NACT's benefits, early-stage RB detection should remain the priority to reduce the need for enucleation altogether, which can be achieved by creating awareness and strengthening referral systems.

Our study included only 11 patients, limiting statistical generalizability. Larger multi-center trials are needed. Long-term outcomes of post-NACT enucleation patients were not assessed. Future research should explore overall survival rates. A control group receiving immediate enucleation would provide a better comparison of survival outcomes.

Further research should explore cost-effective drug delivery methods in LMICs. Behavioral Studies on Parental Decision-Making are necessary to understand why some parents still refuse enucleation which might help in improving treatment acceptance.

CONCLUSION

This study highlights that NACT significantly reduces tumor burden (~76%) and improves enucleation acceptance (~90%) in unilateral Group E RB. The combination of chemotherapy and structured parental counseling can enhance treatment adherence in LMICs. Future multi-center trials are necessary to validate these findings and optimize retinoblastoma management in resource-limited settings.

Conflict Of Interest

The authors declare no conflicts of interest.

Author Contributions:

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Statement:

The ethics clearance was obtained from the Institutional Ethics Committee. Signed informed consent was taken from the parent/ legally authorized representative.

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