Journal of Applied Cognitive Neuroscience, Vol. X · Num. X (period, year)
https://revistascientificas.cuc.edu.co/JACN/index
e-ISSN 2745-0031

Is ocular salvage feasible in patients with high-risk intraocular retinoblastoma?

¿Es factible el salvamento ocular en pacientes con retinoblastoma intraocular de alto riesgo?

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Received: 23-10-2025 **Accepted:** XXX **Published**: XXX

KEYWORDS: Retinoblastoma; Eye; Risk; Ophthalmologic Surgical Procedures; Ophthalmology.

PALABRAS CLAVES: Retinoblastoma; Ojo; Riesgo; Procedimientos Quirúrgicos Oftalmológicos; Oftalmología.

The management of high-risk intraocular retinoblastoma (RB) has progressed remarkably over the past two decades [1,2]. Yet, the central clinical question persists: to what extent is ocular salvage feasible in children presenting with advanced intraocular disease, and at what cost (oncologic or functional)? [1,2]. The recently published long-term results from the AIEOP RTB 012 prospective study provide renewed insight into the limits and possibilities of conservative management in this population [3], offering an opportunity for reflection on the evolving balance between tumor control, ocular survival, and visual function in high-risk cases.

EVOLVING CONSERVATIVE STRATEGIES AND THE AIEOP RTB 012 CONTRIBUTION

The AIEOP RTB 012 study evaluated 60 patients (88 eyes) with high-risk RB treated with carboplatin-etoposide-based chemoreduction and focal therapies [3].

At nearly nine years of median follow-up, only 42 of 88 eyes (48%) were preserved, and the 5-year ocular survival was 48.9%. As expected, outcomes varied sharply by International Intraocular Retinoblastoma Classification (IIRC) group: 5-year survival was 73.3% for Group C, 42.5% for Group D, and only 14.3% for Group E. These data reaffirm what decades of clinical experience have taught us, ocular salvage is achievable, but the likelihood diminishes steeply as disease burden increases [3].

Importantly, nearly one-third of all preserved eyes were salvaged through second-line intra-arterial chemotherapy (IAC) or intravitreal chemotherapy (IVTC), underscoring the indispensable role of contemporary ocular-directed treatments [3]. Without these modalities, salvage rates for Groups D and E would have been substantially lower.

THE CHANGING ROLE OF IAC AND IVTC IN HIGH-RISK RETINOBLASTOMA

The results from RTB 012 echo global trends: systemic chemoreduction alone is insufficient for most advanced eyes [3]. Meta-analytic evidence confirms that ocular salvage with systemic chemotherapy declines from >90% in Groups A-C to 40% for Group D and <20% for Group E, even with optimal focal therapy. Contemporary series now demonstrate superior tumor control with IAC, particularly in D and E eyes [3].

Yet, this efficacy introduces new concerns. The RTB 012 cohort showed that 5 of 13 eyes preserved with IAC/IVTC developed ocular toxicities such as salt-and-pepper retinopathy and cataract, complications consistent with reports of choroidal ischemia, vascular injury, and reduced retinal function in eyes treated with IAC [3]. Thus, while IAC has redefined what is oncologically feasible, it has also shifted the conversation toward what is visually meaningful [3].

VISUAL FUNCTION: A CRITICAL BUT OFTEN OVERLOOKED ENDPOINT

The study provides a valuable long-term lens on functional outcomes. Although 42 eyes were ultimately preserved, only 28 had quantifiable vision, and merely 13 achieved 20/40 or better [3]. In bilateral

disease, 12 of 28 patients reached binocular acuity of at least 20/30, reassuring, but largely attributable to preserving at least one early-stage eye [3].

This pattern reinforces a crucial clinical insight: ocular salvage does not necessarily equate to functional preservation. Group D and E eyes, even when anatomically saved, often carry irreversible macular or vascular compromise [3]. For families and clinicians, survival of the eye must be weighed against the likelihood of useful vision, a distinction that becomes central when making shared decisions about salvage attempts versus timely enucleation [3].

ONCOLOGIC SAFETY AND THE BOUNDARIES OF CONSERVATIVE THERAPY

The boundary between reasonable salvage attempt and excessive conservative treatment is not only technical but conceptual [4]. Oncologic safety requires accepting that, beyond a certain point, early enucleation is a neuroprotective intervention: it reduces the risk of extraocular extension, spares the child additional anesthesia exposure, and allows earlier adaptation to monocular vision and rehabilitation [5].

Neuro-ophthalmologically, timely enucleation of a blind or nearly blind eye can be preferable to years of low-probability salvage, especially when the fellow eye is potentially capable of near-normal acuity [5]. In RTB 012, meaningful binocular acuity (≥20/30) in bilateral cases was mostly achieved because at least one eye had low-burden disease (Group A/B) treated successfully without IAC/IVTC [3].

The success story is therefore not high-risk salvage alone, but early detection plus judicious selection of eyes that truly benefit from conservative protocols.

From an evidence-based medicine perspective, the available data are less robust than the technological sophistication of our interventions might suggest. RTB 012 is a single-arm phase II study, with no randomized comparison against primary enucleation or alternative regimens [6]. Outcomes are analyzed per eye, while patients and families experience decisions per child [3]. Selection criteria, institutional expertise, and access to imaging and genetics all shape the apparent success of salvage strategies and limit external validity.

Furthermore, many studies, including RTB 012, prioritize ocular survival and anatomic tumor control as primary endpoints, while visual acuity, neurodevelopmental outcomes, and quality of life are often incomplete or only reported in subsets. This creates a hierarchy of outcomes where globe preservation may overshadow functional and patient-centered measures. Pragmatic trials, prospective registries, and core outcome sets that include binocular vision, visual fields, neurocognitive development, and family-reported burden are urgently needed.

A META-RESEARCH LENS ON OCULAR SALVAGE

Meta-science invites us to ask how the structure of the literature might distort our understanding. Reports from tertiary centers often highlight spectacular salvage of advanced eyes with IAC, while negative or equivocal experiences may remain unpublished. Heterogeneous classifications, evolving protocols, and

variable use of IAC/IVTC complicate pooled analyses and foster salami-sliced evidence that focuses on surrogate endpoints [7-10].

There is also a geography of evidence: high-resource settings generate most data on IAC and IVTC, whereas many children worldwide still present late and are treated in environments where safe ocular-directed techniques are not widely available. Extrapolating high-income country salvage protocols to low-resource contexts without accounting for infrastructure, follow-up capacity, and anesthesia risk may unintentionally increase harm [7-10].

GLOBAL RECOMMENDATIONS

Taking these neurologic, evidence-based, and meta-research considerations together, several principles emerge:

1. Stage and biology first: early diagnosis, genetic profiling, and accurate staging should guide aggressiveness of salvage attempts, especially in Groups D and E.

2. Function, not just form: treatment planning should explicitly consider the probability of useful visual function, not only anatomical globe retention.

3. Oncologic prudence: in eyes with poor response or minimal functional potential, early enucleation should be framed as a proactive, brain-protective decision rather than a failure.

4. Transparent, patient-centered decisions: families need clear communication about absolute risks of central nervous system spread, likelihood of meaningful vision, and the burden of repeated procedures.

5. Stronger evidence infrastructure: international registries, standardized outcome sets, and comparative effectiveness studies are essential to refine indications for ocular salvage and to avoid enthusiasm outpacing data.

In conclusion, ocular salvage in high-risk intraocular retinoblastoma is feasible, but its true value lies at the intersection of neuro-oncologic safety, visual function, and robust evidence. The goal should not simply be to keep eyes in the orbit, but to protect the child’s brain, vision, and future.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

None

Data, Materials, and Code Availability

Not applicable.

Contributor roles

Keiny Maria Medina Pérez: conceptualization, investigation, drafting of the original manuscript, writing, review and editing, approval of the final version.
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María Paz Bolaño Romero: conceptualization, investigation, drafting of the original manuscript, writing, review and editing, approval of the final version.

AI Usage Disclosure

During the preparation of this manuscript, the authors used ChatGPT-5 to improve grammatical style. The authors have reviewed and edited the output and take fully responsible for the content of this publication.

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