

Enucleation and Globe Preservation Across Treatment Eras in Unilateral and Bilateral Retinoblastoma: A Retrospective Cohort Study

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Abstract

Background

To evaluate changes in enucleation and globe preservation rates before and after the application of targeted chemotherapy approaches in unilateral and bilateral retinoblastoma (RB).

Methods

In this retrospective cohort study, 491 patients with 719 affected eyes were classified into T1 (2001–2012, inclusive) and T2 (2013–2024) based on the time of enucleation. The primary outcome was any enucleation. Secondary analyses evaluated international classification of retinoblastoma (ICRB)-specific outcomes, final anatomical preservation of the globe, time to enucleation, treatment patterns, and overall survival.

Results

The cohort included 263 patients with unilateral disease (263 eyes) and 228 patients with bilateral disease (456 eyes). In unilateral disease, enucleation decreased from 79 of 97 eyes (81.4%) in T1 to 99 of 166 (59.6%) in T2. In bilateral disease, enucleation decreased from 63 of 144 eyes (43.8%) to 83 of 312 (26.6%). T2 was associated with a 29% lower enucleation risk in unilateral disease (RR, 0.71; 95% CI, 0.63–0.80; $P < 0.001$) and a 45% lower risk in bilateral disease (RR, 0.55; 95% CI, 0.46–0.66; $P < 0.001$). The relative T1-to-T2 reduction was greater in bilateral RB (ratio of RRs, 0.78; 95% CI, 0.62–0.97; $P = 0.026$). The largest stage-specific improvement occurred in ICRB group D, with enucleation decreasing from 82.6% to 12.5% in unilateral RB and from 56.7% to 14.0% in bilateral RB. Eleven deaths occurred, limiting the precision of overall-survival comparisons.

Conclusions

The post-2012 treatment era was associated with substantially greater globe preservation rate in both unilateral and bilateral retinoblastoma, with particularly pronounced improvement in ICRB group D disease.

Clinical trial registration

Not applicable.

Introduction

Retinoblastoma is the most common primary intraocular malignancy of childhood. Its incidence is approximately 1 in 15,000 to 20,000 live births, with reported rates varying widely across populations [1, 2]. Globally, approximately 8,000 new cases are diagnosed each year. Retinoblastoma arises from disruption of the RB1 tumor suppressor pathway on chromosome 13q14 and occurs predominantly in early childhood, with the highest incidence in children younger than 5 years. [3–5]. Despite major advances in diagnosis and treatment, substantial geographic differences remain in presentation, access to specialized care, and clinical outcomes. [6–10].

Retinoblastoma may involve one eye or both eyes, and laterality has important clinical implications. Unilateral disease accounts for approximately 60% to 75% of cases, whereas bilateral disease represents approximately 25% to 40% and is more commonly associated with heritable retinoblastoma. Unilateral disease generally presents at an older age and may

be more advanced at diagnosis. These differences in presentation and disease burden can influence treatment selection and the likelihood of preserving the affected eye [2, 3].

Treatment strategies have changed substantially over the past two decades. Systemic chemotherapy, particularly vincristine, etoposide, and carboplatin, was historically a cornerstone of eye-preserving treatment. The development of targeted ocular chemotherapy introduced a significant advantage in management. Intra-arterial chemotherapy enables direct delivery of chemotherapy through the ophthalmic artery, while intravitreal chemotherapy allows treatment to be delivered directly into the vitreous cavity. These approaches can achieve high intraocular drug concentrations while reducing systemic exposure and have expanded opportunities for conservative treatment, including in selected eyes with advanced disease [11, 12].

Despite this therapeutic shift, the extent to which enucleation risk has changed across treatment eras remains incompletely characterized. In particular, it remains uncertain whether an era-associated change in enucleation persists after accounting for differences in International Classification of Retinoblastoma (ICRB) severity and whether the magnitude of this change differs between unilateral and bilateral retinoblastoma. The primary objective of this study was therefore to compare the risk of any enucleation before 2012 (T1) and after 2012 (T2) in unilateral and bilateral RB and to formally assess whether the era-associated change differed by laterality. Secondary objectives were to evaluate changes according to ICRB group, final anatomical globe preservation, time to globe loss, treatment patterns, and overall survival. Associations between individual targeted-treatment modalities and enucleation were considered exploratory because the observational design does not allow causal attribution of era-related outcome changes to a specific treatment.

Materials and Methods

Study design and setting

This retrospective cohort study included 491 patients younger than 15 years who were diagnosed with retinoblastoma between December 2001 and December 2024. The study was conducted at the Ocular Oncology Service of Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, a tertiary referral center for ocular oncology. Patient care was provided by a multidisciplinary team including ocular and pediatric oncologists, an ophthalmic plastic and reconstructive surgeon, a clinical geneticist, a pathologist, and a neurovascular surgeon. Systemic chemotherapy was coordinated across Rassoul Akram Hospital, Ali-Asghar Children's Hospital, and MAHAK Hospital.

All consecutive patients with a clinical diagnosis of retinoblastoma during the study period were eligible. Patients were excluded only if the diagnosis was not confirmed or if records were insufficient to establish laterality or the primary outcome. No a priori sample-size calculation was performed because the study included all eligible patients treated during the prespecified study period.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies.

Diagnostic evaluation and tumor classification

Patients underwent comprehensive ophthalmic assessment, including examination under anesthesia and fundus imaging with RetCam (Massie Industries, Dublin, CA, USA), performed by a dedicated ocular oncologist (MN). Eyes were initially classified using the Reese-Ellsworth system. Beginning in 2005, the International Classification of Retinoblastoma (ICRB) was adopted for newly diagnosed eyes, and earlier records were retrospectively mapped to the ICRB system to provide a common classification throughout the study period. Each affected eye was assigned an ICRB group from A to E. In patients with bilateral disease, the two eyes were classified separately because ICRB severity could

differ between eyes. For records predating routine ICRB use, retrospective classification was based on documented examination findings and fundus images when available. Ambiguous classifications were reviewed by an experienced ocular oncologist before final assignment.

Treatment

Treatment was individualized according to laterality, ICRB group, patient age and weight, anticipated visual potential, socioeconomic considerations, family preferences, and clinician judgment.

Before the introduction of targeted ocular chemotherapy, management predominantly included systemic chemotherapy with vincristine, etoposide, and carboplatin (VEC), enucleation, and focal treatments including transpupillary thermotherapy, cryotherapy, plaque brachytherapy, and, in selected advanced cases, periocular chemotherapy. The standard systemic regimen consisted of six cycles of VEC using vincristine 0.05 mg/kg, etoposide 5 mg/kg, and carboplatin 18.6 mg/kg and could be extended to nine cycles when clinically indicated. Resistant or recurrent disease could be treated with six cycles of high-dose VEC using vincristine 0.025 mg/kg, etoposide 12 mg/kg, and carboplatin 28 mg/kg, with oral cyclosporine 33 mg/kg/day in selected cases.

Transpupillary thermotherapy and cryotherapy were used as primary or adjunctive treatments for small tumors, generally 3 mm or smaller, when the tumor location permitted treatment without unacceptable risk to the fovea or optic disc. Ruthenium-106 plaque radiotherapy (Eckert & Ziegler BEBIG, Germany) delivering approximately 40 Gy to the tumor apex was used mainly for recurrent medium-sized tumors or localized seeding and, in selected cases, as primary treatment for solitary tumors without seeding.

Following enucleation, eyes with high-risk histopathologic features, including post-laminar optic nerve invasion, extensive choroidal invasion greater than 3 mm, or involved surgical margins, received adjuvant systemic chemotherapy. External-beam radiotherapy (EBRT) was considered when tumor was present at the optic nerve margin or when transscleral extension was identified.

Targeted ocular chemotherapy became an important component of treatment in the later era (T2). Intra-arterial chemotherapy (IAC) was generally administered at 3-week intervals using weight-adjusted melphalan, typically 3.5 to 5 mg, either alone or with topotecan 0.5 to 1 mg and, when indicated, carboplatin 25 mg. IAC was generally avoided in infants younger than 6 months. Intravitreal chemotherapy was used for persistent or recurrent vitreous seeds or as adjunctive treatment after systemic chemotherapy or IAC. Intravitreal melphalan 25 µg/0.1 mL or topotecan 20 µg/0.1 mL was administered initially at 10- to 14-day intervals, with later protocols using 7- to 10-day intervals. Injections were performed under sterile conditions with anterior chamber paracentesis and cryotherapy at the injection site to minimize reflux and extraocular seeding.

Treatment-era and laterality definitions

Patients were categorized as having unilateral disease when only one eye was affected and bilateral disease when both eyes were affected. For eye-level analyses, each affected eye was retained as a separate observation, including both eyes from patients with bilateral disease.

Treatment era was the primary exposure. Patients were classified according to the prespecified database coding as T1, representing treatment before 2012, or T2, representing treatment after 2012. This division was selected to represent the transition from predominantly systemic chemotherapy-based management toward increasing use of targeted ocular chemotherapy, particularly IAC and intravitreal chemotherapy. Treatment eras were defined as T1 (2001 through 2012, inclusive) and T2 (2013 through 2024). Accordingly, all patients diagnosed during calendar year 2012 were assigned to

T1. Because treatment allocation was based on clinical circumstances rather than random assignment, treatment era was analyzed as an observational exposure and treatment-specific comparisons were not interpreted as causal effects.

Data collection and outcome definitions

Demographic, clinical, treatment, and outcome data were obtained retrospectively from medical records and the study databases. Patient-level variables included age at diagnosis, sex, nationality, laterality, follow-up time, and vital status. Eye-level variables included affected-eye side, ICRB group, tumor focality, subretinal fluid, vitreous and subretinal seeding, recurrence, treatment modalities, and enucleation status. Treatment variables included IAC, intravitreal chemotherapy, focal therapy (cryotherapy, thermotherapy, plaque brachytherapy), EBRT, and other available treatment modalities. Clinical data were abstracted using a standardized data-collection process by trained members of the study team, and uncertain entries were resolved by review of the source medical record.

The primary outcome was any enucleation of an affected eye. Primary enucleation referred to enucleation performed as the initial definitive management strategy, whereas secondary enucleation referred to removal of an eye after initial conservative management. Final anatomical globe preservation was defined as retention of the affected eye without any recorded primary or secondary enucleation. EBRT alone was not classified as anatomical globe loss.

Overall survival was evaluated at the patient level using the recorded vital-status indicator and follow-up time. Death was considered the event, and patients without a recorded death were censored at their last recorded follow-up.

Statistical Analysis

Analysis population and study outcomes

Analyses were performed at both the patient and affected-eye levels. Patient-level data were used for demographic characteristics and overall survival. The affected eye was the unit for ICRB group, treatment, enucleation, and globe-preservation analyses. Both affected eyes from patients with bilateral retinoblastoma were retained, and eye-level inferential analyses accounted for correlation between eyes from the same patient. The primary exposure was treatment era, using the source database classification of T1 before 2012 and T2 after 2012. The primary outcome was any enucleation of the affected eye. The primary comparison was the T2 versus T1 enucleation risk within unilateral and bilateral disease. An era-by-laterality interaction formally tested whether the relative change from T1 to T2 differed between unilateral and bilateral disease.

Descriptive and primary analyses

Continuous variables were summarized as medians with interquartile ranges, and categorical variables as counts and percentages using non-missing denominators. Patient-level comparisons between unilateral and bilateral disease used Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables. Observed enucleation risks were calculated for each era and laterality group. Ninety-five percent confidence intervals for observed risks, absolute risk differences, and crude risk ratios were obtained from 2,000 patient-cluster bootstrap replicates, with resampling performed at the patient level so that the two eyes of a bilateral patient remained together.

Adjusted risk ratios were estimated with modified-Poisson generalized estimating equations using an exchangeable working correlation and robust standard errors. The primary model included treatment era, laterality, their interaction, ICRB severity grouped as A-C, D, or E, sex, and age at diagnosis. Age was modeled with a natural cubic spline with 3 degrees of freedom in the primary model. Sparse subgroup models used a linear age term if a valid spline could not be

estimated. The era-by-laterality interaction tested one specific clinical question, namely whether the relative reduction in enucleation from T1 to T2 was different in unilateral and bilateral disease.

Globe preservation and time-to-event analyses

Final anatomical globe preservation was defined as retention of the affected eye without any recorded primary or secondary enucleation. No minimum follow-up duration was imposed on this descriptive endpoint. To account for unequal follow-up, time to globe loss was measured from diagnosis to enucleation and eyes without enucleation were censored at their last recorded follow-up. Kaplan-Meier methods estimated globe-preservation probabilities. The 7-year summaries distinguish the number of eyes entering the survival analysis, the number still under observation and event-free at 7 years, the number of enucleations that had occurred by 7 years, and the total number of enucleations during all recorded follow-up.

Adjusted hazard ratios for enucleation were estimated using Cox proportional-hazards regression with robust standard errors clustered by patient and adjustment for ICRB severity, age, sex, and the era-by-laterality interaction. Proportional-hazards assumptions were assessed using scaled Schoenfeld residuals. Overall survival was analyzed at the patient level from diagnosis to death or last follow-up. Because only 11 deaths occurred, overall-survival regression was deliberately parsimonious and used Firth-penalized Cox regression with era and laterality as predictors. Seven-year overall-survival tables separately report deaths occurring by 7 years and total deaths during complete recorded follow-up.

Stage-specific management and treatment analyses

Secondary analyses described ICRB-group-specific primary management, secondary enucleation after conservative initial management, final globe preservation, and use of validated treatment modalities. Stage-specific T2 versus T1 enucleation risk ratios were estimated with patient-clustered modified-Poisson generalized estimating equations. The Benjamini-Hochberg procedure controlled the false discovery rate across the 10 laterality-by-ICRB comparisons. For comparability with published globe-salvage analyses, a stricter salvage definition was retained only as a supplementary sensitivity analysis. Under that supplementary definition, primary enucleations were excluded, a retained eye required at least 12 months of recorded follow-up, and secondary enucleation or external-beam radiotherapy was considered failure. This stricter definition was not used for the main globe-preservation outcome.

Targeted chemotherapy and its intra-arterial and intravitreal subtypes were reported from the harmonized targeted-treatment fields. Associations between targeted treatment and enucleation were restricted to advanced eyes treated during T2 and were considered exploratory because treatment allocation was not randomized, primary enucleation precluded later globe-preserving therapy, and exact treatment dates were not available.

Sensitivity analyses, missing data, and software

Prespecified sensitivity analyses were restricted to advanced ICRB D/E eyes, group D, group E, eyes without primary enucleation, and data excluding eyes coded as receiving targeted treatment during T1. No statistical imputation was performed. Each analysis used available complete observations for its required variables and all denominators are reported explicitly. All tests were 2-sided. A P value below 0.05 defined statistical significance for primary analyses, and a false-discovery-rate adjusted q value below 0.05 was used for the stage-specific family of tests. Analyses were performed in R 4.5.0 using geepack 1.3–13, survival 3.8-6, coxphf 1.13.4, and related packages. The reproducibility seed for bootstrap analyses was 2532026.

Ethical considerations

The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD. REC.1398.292). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for clinical evaluation and treatment was obtained from parents or legal guardians. Patient data were deidentified before statistical analysis and were accessed only by authorized study personnel.

Results

Cohort and baseline characteristics

The cohort comprised 491 patients with 719 affected eyes, including 263 patients with unilateral disease involving 263 eyes and 228 patients with bilateral disease involving 456 eyes. Median age at diagnosis was 24.0 months (IQR, 13.0–44.0) in unilateral disease and 13.5 months (IQR, 9.0–36.0) in bilateral disease ($P < 0.001$). Advanced patient-level disease, defined by a worst-eye ICRB group of D or E, was present in 82.9% and 87.7%, respectively ($P = 0.162$). Median follow-up was 45.0 months (IQR, 27.0–75.0) for unilateral and 50.0 months (IQR, 36.0–91.0) for bilateral disease ($P = 0.023$). Totally, enucleation was performed in 67% of unilateral tumor involvement and 62.3% of bilateral ones ($P = 0.218$) (Table 1). The data-quality audit and reconciliation checks are summarized in **Table S1**.

Table 1
Patient-level characteristics by retinoblastoma laterality.

Characteristic	Unilateral (n = 263)	Bilateral (n = 228)	P value
Patients, n (%)	263 (53.6%)	228 (46.4%)	
Affected eyes, n	263	456	
Age at diagnosis, median (IQR), mo	24.0 (13.0–44.0)	13.5 (9.0–36.0)	< 0.001
Age ≤ 24 mo, n/N (%)	135/261 (51.7%)	150/228 (65.8%)	0.002
Male sex, n/N (%)	141/263 (53.6%)	127/226 (56.2%)	0.585
Nationality, n/N (%)			0.177
Iranian	248/263 (94.3%)	201/222 (90.5%)	
Iraqi	13/263 (4.9%)	20/222 (9.0%)	
Afghan	2/263 (0.8%)	1/222 (0.5%)	
Worst-eye ICRB group, n (%)			0.118
A	2 (0.8%)	0 (0.0%)	
B	24 (9.1%)	12 (5.3%)	
C	19 (7.2%)	16 (7.0%)	
D	39 (14.8%)	49 (21.5%)	
E	179 (68.1%)	151 (66.2%)	
Advanced worst-eye disease (D/E), n (%)	218 (82.9%)	200 (87.7%)	0.162
Follow-up, median (IQR), mo	45.0 (27.0–75.0)	50.0 (36.0–91.0)	0.023
Died, n (%)	3 (1.1%)	8 (3.5%)	0.123
Any targeted chemotherapy, n (%)	50 (19.0%)	71 (31.1%)	0.002
Enucleation rate, n (%)	178 (67.7%)	142 (62.3%)	0.218

Among patients with unilateral RB, 139 of 263 affected eyes (52.9%) were right eyes (OD) and 124 (47.1%) were left eyes (OS). The era-specific eye-side distribution and detailed affected-eye characteristics are shown in **Table S2**.

Primary outcome and treatment-era change

Among unilateral RB patients, enucleation decreased from 79 of 97 eyes (81.4%; 95% CI, 74.2%–88.7%) in T1 to 99 of 166 (59.6%; 95% CI, 51.8%–67.5%) in T2. This was an absolute reduction of 21.8 percentage points (95% CI, 11.5–33.2 percentage points) and a crude RR of 0.73 (95% CI, 0.62–0.85). Among individuals with bilateral tumor involvement, enucleation decreased from 63 of 144 eyes (43.8%; 95% CI, 38.2%–49.3%) to 83 of 312 (26.6%; 95% CI, 22.8%–30.4%). This was an absolute reduction of 17.1 percentage points (95% CI, 10.8–23.7 percentage points) and a crude RR of 0.61 (95% CI, 0.50–0.73) (Table 2; Fig. 1).

Table 2
Primary enucleation outcome by treatment era and laterality.

Outcome/contrast	T1	T2	Absolute change, pp (95% CI)	Relative effect (95% CI)	P value
Unilateral disease					
Observed enucleation risk	79/97 (81.4%) 95% CI, 74.2%-88.7%	99/166 (59.6%) 95% CI, 51.8%-67.5%	-21.8 (-33.2 to -11.5)	Crude RR, 0.73 (0.62–0.85)	
Adjusted modified-Poisson GEE	Reference	T2 vs T1	-	Adjusted RR, 0.71 (0.63–0.80)	< 0.001
Bilateral disease					
Observed enucleation risk	63/144 (43.8%) 95% CI, 38.2%-49.3%	83/312 (26.6%) 95% CI, 22.8%-30.4%	-17.1 (-23.7 to -10.8)	Crude RR, 0.61 (0.50–0.73)	
Adjusted modified-Poisson GEE	Reference	T2 vs T1	-	Adjusted RR, 0.55 (0.46–0.66)	< 0.001
Era-by-laterality interaction					
Crude ratio of RRs	-	-	-	0.83 (0.65–1.06)	0.142
Adjusted ratio of RRs	-	-	-	0.78 (0.62–0.97)	0.026

After adjustment for ICRB severity, age, and sex, the T2-versus-T1 RR was 0.71 (95% CI, 0.63–0.80; $P < 0.001$) in unilateral disease and 0.55 (95% CI, 0.46–0.66; $P < 0.001$) in bilateral disease. These estimates correspond to relative reductions in enucleation risk of approximately 29% and 45%, respectively. The adjusted ratio of these two era effects was 0.78 (95% CI, 0.62–0.97; $P = 0.026$), indicating that, after adjustment for case mix, the T1-to-T2 relative reduction in the probability of undergoing enucleation at any time during the recorded follow-up was greater in bilateral than unilateral eyes. This interaction tests whether the size of the T1-to-T2 change differs between unilateral and bilateral disease; it does not test whether either group improved on its own (Fig. 2).

ICRB-specific management and final globe preservation

Primary enucleation increased substantially with ICRB severity. In unilateral disease, primary enucleation occurred in 17 of 39 group D eyes (43.6%) and 140 of 179 group E eyes (78.2%); the corresponding frequencies in bilateral disease were 14 of 80 (17.5%) and 100 of 178 (56.2%). In contrast, all 24 unilateral group B eyes received conservative initial management and all 24 remained in situ. Among unilateral group C eyes, 18 of 19 (94.7%) were finally preserved and 1 of 19 underwent secondary enucleation due to recurrent vitreous seeding which was unresponsive to treatment. Final globe preservation was 18 of 39 (46.2%) for unilateral group D, 23 of 179 (12.8%) for unilateral group E, 56 of 80 (70.0%) for bilateral group D, and 62 of 178 (34.8%) for bilateral group E (Table 3).

Table 3
ICRB-group-specific primary management and final globe preservation.

Laterality	ICRB	Affected eyes	Primary enucleation n/N (%)	Conservative initial management n/N (%)	Secondary enucleation after conservative management n/N (%)	Final globe preservation n/N (%)	Final preservation after conservative management n/N (%)
Unilateral	A	2	0/2 (0.0%)	2/2 (100.0%)	0/2 (0.0%)	2/2 (100.0%)	2/2 (100.0%)
Unilateral	B	24	0/24 (0.0%)	24/24 (100.0%)	0/24 (0.0%)	24/24 (100.0%)	24/24 (100.0%)
Unilateral	C	19	0/19 (0.0%)	19/19 (100.0%)	1/19 (5.3%)	18/19 (94.7%)	18/19 (94.7%)
Unilateral	D	39	17/39 (43.6%)	22/39 (56.4%)	4/22 (18.2%)	18/39 (46.2%)	18/22 (81.8%)
Unilateral	E	179	140/179 (78.2%)	39/179 (21.8%)	16/39 (41.0%)	23/179 (12.8%)	23/39 (59.0%)
Bilateral	A	27	0/27 (0.0%)	27/27 (100.0%)	0/27 (0.0%)	27/27 (100.0%)	27/27 (100.0%)
Bilateral	B	100	0/100 (0.0%)	100/100 (100.0%)	1/100 (1.0%)	99/100 (99.0%)	99/100 (99.0%)
Bilateral	C	71	1/71 (1.4%)	70/71 (98.6%)	4/70 (5.7%)	66/71 (93.0%)	66/70 (94.3%)
Bilateral	D	80	14/80 (17.5%)	66/80 (82.5%)	10/66 (15.2%)	56/80 (70.0%)	56/66 (84.8%)
Bilateral	E	178	100/178 (56.2%)	78/178 (43.8%)	16/78 (20.5%)	62/178 (34.8%)	62/78 (79.5%)

All 100 bilateral group B eyes were initially managed conservatively; 1 of 100 eyes (1.0%) subsequently underwent secondary enucleation after a period of loss to follow-up and subsequent tumor progression, and 99 of 100 eyes (99.0%) were preserved at final follow-up. All Table 3 rows therefore fully reconcile the number of affected eyes, initial management, and final globe outcome.

The largest stage-specific era changes were seen in group D. Enucleation decreased from 82.6% to 12.5% in unilateral group D eyes (RR, 0.15; 95% CI, 0.04–0.56; $q = 0.006$) and from 56.7% to 14.0% in bilateral group D eyes (RR, 0.25; 95% CI, 0.12–0.52; $q < 0.001$). Group E also improved, from 98.4% to 81.4% in unilateral eyes (RR, 0.83; 95% CI, 0.75–0.91; $q < 0.001$) and from 89.8% to 55.8% in bilateral eyes (RR, 0.62; 95% CI, 0.52–0.74; $q < 0.001$). Lower-stage comparisons were limited by few or no enucleation events (**Table S3**; Fig. 3).

Globe preservation over time

Using the simple anatomical definition of final globe preservation, 18 of 97 unilateral eyes (18.6%) in T1 and 67 of 166 (40.4%) in T2 remained in situ without any recorded enucleation. Among bilateral eyes, the corresponding proportions were 81 of 144 (56.3%) in T1 and 229 of 312 (73.4%) in T2, respectively. The Kaplan-Meier analysis, which additionally accounts for follow-up time and censoring, in unilateral RB, estimated 7-year globe-preservation probabilities of 18.6% (95% CI, 11.6%–26.8%) and 30.4% (95% CI, 16.5%–45.4%) in T1 and T2. In bilateral tumor involvement, these rates were

documented as 55.9% (95% CI, 50.3%-61.1%) and 72.1% (95% CI, 67.4%-76.2%) in T1 and T2, respectively (Table 4; Figs. 4A and 4B).

Table 4
Globe preservation and patient overall-survival outcomes.

Outcome/contrast	Laterality	Era/contrast	KM baseline N	At risk at 7 y	Events by 7 y	Total events	Estimate (95% CI)	P value
Seven-year globe preservation								
Kaplan-Meier estimate	Unilateral	T1	97	8	79	79	18.6% (11.6%-26.8%)	
Kaplan-Meier estimate	Unilateral	T2	166	5	99	99	30.4% (16.5%-45.4%)	
Kaplan-Meier estimate	Bilateral	T1	143	50	62	63	55.9% (50.3%-61.1%)	
Kaplan-Meier estimate	Bilateral	T2	311	26	82	83	72.1% (67.4%-76.2%)	
Adjusted Cox model for enucleation								
T2 vs T1 within unilateral disease	Unilateral	T2 vs T1	-	-	-	-	HR, 0.43 (0.34–0.56)	< 0.001
T2 vs T1 within bilateral disease	Bilateral	T2 vs T1	-	-	-	-	HR, 0.40 (0.29–0.55)	< 0.001
Era-by-laterality interaction	Interaction	Bilateral vs unilateral era effect	-	-	-	-	HR, 0.92 (0.61–1.40)	0.703
Seven-year overall survival								
Kaplan-Meier estimate	Unilateral	T1	90	36	0	1	100.0% (100.0%-100.0%)	
Kaplan-Meier estimate	Unilateral	T2	152	11	2	2	93.4% (67.3%-98.8%)	
Kaplan-Meier estimate	Bilateral	T1	71	43	1	3	98.1% (87.1%-99.7%)	
Kaplan-Meier estimate	Bilateral	T2	156	20	5	5	92.4% (79.4%-97.4%)	
Firth-penalized Cox model for death								
T2 vs T1	Patient level	T2 vs T1	-	-	-	-	HR, 2.33 (0.68–8.71)	0.176
Bilateral vs unilateral	Patient level	Bilateral vs unilateral	-	-	-	-	HR, 1.95 (0.60–7.93)	0.279

Overall survival

Eleven deaths occurred among 491 patients. Crude mortality was 1 of 97 (1.0%) in unilateral T1, 2 of 166 (1.2%) in unilateral T2, 3 of 72 (4.2%) in bilateral T1, and 5 of 156 (3.2%) in bilateral T2. All 11 deaths had valid recorded survival times. Eight deaths occurred by 7 years of follow-up and 3 occurred after 7 years of follow-up; therefore, the 7-year event

column in Eight deaths occurred within 7 years, and three occurred thereafter. The 3 later deaths comprised 1 unilateral T1 death and 2 bilateral T1 deaths.

Seven-year overall-survival estimates were 100% for unilateral T1, 93.4% (95% CI, 67.3%-98.8%) for unilateral T2, 98.1% (95% CI, 87.1%-99.7%) for bilateral T1, and 92.4% (95% CI, 79.4%-97.4%) for bilateral T2. Because deaths were sparse, these estimates were imprecise at later time points. In the Firth-penalized Cox model, the HR was 2.33 for T2 versus T1 (95% CI, 0.68–8.71; $P = 0.176$) and 1.95 for bilateral versus unilateral disease (95% CI, 0.60–7.93; $P = 0.279$). The wide confidence intervals do not support a conclusion of equivalent survival between groups (Table 4).

Targeted treatment and exploratory associations

Patient-level receipt of any targeted chemotherapy increased from 0 of 97 patients (0%) in unilateral T1 to 50 of 166 (30.1%) in unilateral T2, and from 4 of 72 (5.6%) in bilateral T1 to 67 of 156 (42.9%) in bilateral T2. Eye-level targeted-treatment use increased from 0% to 30.1% in unilateral eyes and from 3.5% to 29.8% in bilateral eyes (**Table S4**). Among advanced T2 eyes, targeted therapy was associated with a lower risk of any enucleation (RR, 0.55; 95% CI, 0.42–0.72; $P < 0.001$). Among eyes initially managed conservatively, the association with secondary enucleation was not significant (RR, 1.40; 95% CI, 0.73–2.68; $P = 0.313$) (Table S5). These observational associations should not be interpreted as causal treatment effects.

Sensitivity, diagnostic, and supplementary analyses

Prespecified sensitivity analyses restricted to advanced ICRB D/E eyes and excluding T1 targeted-treatment crossover records yielded results consistent with the primary analysis (**Table S6; Figure S1**). Although the global proportional-hazards test was not significant, the grouped ICRB term showed evidence of nonproportionality; Cox hazard ratios were therefore interpreted as average effects over follow-up (**Table S7**). Additional diagnostic, endpoint-harmonization, safety, treatment-modality, and strict-salvage analyses are reported in Tables **S8–S11** and **Figures S2–S10**.

Discussion

In this retrospective cohort spanning more than two decades, the post-2012 treatment era (T2), was associated with a substantial reduction in enucleation and improved globe preservation in both unilateral and bilateral retinoblastoma. These associations remained evident after accounting for differences in ICRB severity, age at diagnosis, and sex. The adjusted T1-to-T2 relative reduction in the probability of undergoing enucleation at any time during the recorded follow-up was greater in bilateral than unilateral eyes. The improvement was most pronounced in advanced disease, particularly ICRB group D, while meaningful gains were also observed in group E. Time-to-event analyses supported the overall improvement in globe preservation, although they did not show clear evidence that the reduction in enucleation hazard differed by laterality. The later era was also characterized by substantially greater use of targeted chemotherapy; however, because treatment selection was nonrandom, the observed improvement cannot be attributed to any individual treatment modality. Overall-survival comparisons were limited by the small number of deaths.

The differences observed between unilateral and bilateral disease are clinically important. Mohammad et al. [3] similarly reported that unilateral retinoblastoma more often presented with advanced ocular disease and was associated with lower globe preservation than bilateral disease. In our cohort, enucleation remained more frequent in unilateral eyes in both treatment eras, whereas the adjusted relative reduction between eras was greater in bilateral eyes. Several factors may contribute to this pattern, including earlier presentation of bilateral disease, differences in stage distribution between affected eyes, and a greater clinical incentive to pursue conservative management when both eyes are involved. Importantly, laterality should not be viewed as a surrogate for disease severity alone. Our adjusted analyses indicate that the difference in era-associated outcome persisted even after accounting for ICRB severity and other measured clinical characteristics.

The stage-specific findings provide further insight into where the greatest changes in management have occurred. El-Zomor et al. [13] described a stage-directed approach to unilateral retinoblastoma in which conservative treatment was preferentially used for selected lower- and intermediate-stage eyes, whereas primary enucleation remained important for advanced disease, particularly group E. Our findings extend this observation by showing that the largest treatment-era improvement occurred in ICRB group D. This suggests that group D may represent the stage at which contemporary globe-preserving strategies have most clearly shifted the balance away from enucleation. Group E eyes also showed improvement, but enucleation remained common even in the later era. Thus, advances in conservative treatment should not be interpreted as eliminating the role of primary enucleation in eyes with very advanced disease when globe-preserving treatment is unlikely to provide a safe or meaningful benefit.

The time-to-event analyses were consistent with the primary findings. Eyes affected with both unilateral and bilateral tumors experienced substantially lower hazards of enucleation in the later treatment era. An important distinction, however, emerged between the two analytical scales. The primary analysis, which assessed whether an eye underwent enucleation at any time during the recorded follow-up, showed a greater T1-to-T2 relative decrease in bilateral than unilateral disease. In contrast, the Cox model did not show that the relative reduction in the rate of enucleation over time differed by laterality. These findings are not contradictory because the primary analysis considers whether enucleation occurred, regardless of its timing, whereas the Cox model additionally incorporates when enucleation occurred and how long each eye was followed before censoring. Together, the two approaches support a substantial improvement in globe preservation after 2012 while suggesting that the magnitude of laterality-related heterogeneity depends on how the outcome is measured.

A complementary analysis using a stricter, literature-comparable definition of globe salvage yielded a more nuanced pattern. By excluding primary enucleations and defining secondary enucleation or EBRT as treatment failure, this analysis specifically evaluated eyes selected for conservative management. In a recent pathology-focused analysis from our center, high-risk histopathological features were identified in 24.6% of 236 enucleated eyes, with no significant difference in prevalence between primary and secondary enucleation (25.9% vs 19.1%, respectively; $P = 0.334$) [14]. These findings provide complementary histopathological context for interpreting secondary enucleation following globe-preserving treatment; however, given the retrospective design, they should not be interpreted as establishing the oncologic safety of globe-salvage therapy. Advanced ICRB disease remained strongly associated with poorer salvage, consistent with long-term series demonstrating progressively lower globe-salvage rates in groups D and E than in earlier-stage disease [15]. Previous conservative-treatment cohorts have also reported higher globe-preservation rates in bilateral than unilateral retinoblastoma, particularly among eyes with advanced disease [16]. However, substantial improvements in advanced unilateral disease have also been reported with contemporary targeted chemotherapy, including IAC and adjunctive intravitreal chemotherapy [17, 18]. In our cohort, the era-associated improvement under the strict salvage definition was statistically evident in bilateral but not unilateral eyes; however, the era-by-laterality interaction was not significant. Thus, these findings should not be interpreted as evidence of a differential era effect by laterality, but rather as complementary to the primary anatomical globe-preservation analysis and as facilitating comparison with published globe-salvage cohorts.

The observed treatment-era improvement occurred alongside a marked expansion in targeted ocular chemotherapy, consistent with the broader evolution of retinoblastoma management toward increasingly globe-preserving strategies. Previous era-based studies have documented substantial reductions in enucleation following the introduction of Intra-arterial chemotherapy and intravitreal chemotherapy, including advanced unilateral disease, while contemporary bilateral cohorts have likewise reported high ocular salvage with these approaches [17–19]. Similar temporal improvements have been reported in other settings, with increasing adoption of conservative therapies accompanied by declining eye-removal rates and improved preservation of advanced eyes [20, 21]. In our cohort, targeted chemotherapy was associated with a lower risk of any enucleation among advanced eyes in the later era; however, its association with

secondary enucleation among eyes already selected for conservative management was imprecise. This distinction is important because treatment allocation was nonrandom and inherently influenced by disease severity, laterality, visual potential, and clinical judgment, creating substantial potential for confounding by indication and treatment-selection bias. Moreover, treatment era captures concurrent advances in patient selection, focal therapy, imaging, surveillance, and multidisciplinary care. Accordingly, although the increasing use of targeted chemotherapy likely represents an important component of the contemporary shift toward globe preservation, our treatment-specific findings should remain hypothesis-generating and should not be interpreted as evidence that targeted chemotherapy itself caused the observed reduction in enucleation.

Patient survival requires a separate interpretation. Ain-Nasyrah et al. [6] reported high survival among patients with unilateral retinoblastoma in Malaysia and emphasized the importance of timely diagnosis, adherence to treatment, and adequate follow-up. Mohammad et al. [3] likewise found no clear mortality difference between unilateral and bilateral disease despite substantial differences in globe preservation. In our cohort, only 11 deaths occurred during the entire study period. Consequently, survival estimates were imprecise, and neither the era nor laterality comparison provided sufficiently precise evidence to establish a difference in mortality. Importantly, absence of statistical significance should not be interpreted as evidence of equivalent survival. Our data therefore provide substantially stronger evidence regarding globe preservation and enucleation than regarding small differences in patient survival.

Our findings should also be considered within the broader global context. Wong et al. [22] demonstrated substantial international variation in retinoblastoma survival and globe preservation and identified strong associations with socioeconomic conditions and healthcare resources. The improvement observed in our tertiary referral cohort shows that substantial gains in globe preservation are achievable in a middle-income setting with access to multidisciplinary care and contemporary ocular treatment. However, our study did not directly measure healthcare financing, income inequality, referral delay, or population-level access to care. It therefore cannot determine which health-system factors contributed to the treatment-era improvement or whether similar results would be achieved in less specialized settings. This distinction is important when considering the generalizability of our findings beyond a tertiary ocular oncology center.

Long-term survivorship remains another important consideration. Kleinerman et al. [23] highlighted the lifelong risk of subsequent malignant neoplasms and late mortality among retinoblastoma survivors, particularly those with hereditary disease and previous radiotherapy exposure. The increasing availability of local treatment approaches may reduce reliance on some historically used therapies, but our data cannot establish that contemporary treatment reduces the risk of second malignancies or late mortality. Secondary-neoplasm and related long-term safety variables were not uniformly available across the study datasets, and the number of deaths was small. Accordingly, any potential long-term safety advantage of changing treatment patterns requires evaluation in cohorts with substantially longer and more complete survivorship follow-up.

Several sensitivity analyses support the robustness of the primary treatment-era finding. The association between the later era and lower enucleation remained evident when analyses were restricted to advanced ICRB D/E eyes and when eyes recorded as receiving targeted treatment during the earlier era were excluded. Stage-specific analyses also remained most compelling for groups D and E after correction for multiple comparisons. In contrast, analyses restricted to secondary enucleation after conservative management were substantially less precise. Taken together, these findings suggest that the primary result is not driven solely by lower-stage case mix or by the small number of targeted-treatment records in the earlier era, while also showing that conclusions become less certain when the analysis is restricted to smaller treatment-selected subgroups.

This study has several strengths. It includes a relatively large number of affected eyes from a rare childhood malignancy, spans more than two decades of major change in retinoblastoma management, and evaluates unilateral and bilateral

disease separately. Importantly, both eyes of patients with bilateral disease were retained rather than reducing bilateral disease to a single patient-level stage, allowing differences in ICRB severity between eyes to be preserved. The analytical approach also accounted for within-patient correlation, adjusted the primary era comparison for key differences in case mix, evaluated both whether enucleation occurred during the recorded follow-up and when it occurred, and examined the consistency of the findings across stage-specific and sensitivity analyses. These features provide a more detailed assessment of treatment-era changes than a comparison of crude enucleation percentages alone.

Several limitations should be acknowledged. First, the retrospective design makes the study vulnerable to incomplete documentation and residual confounding. Treatment practices changed progressively over the study period, and the division into two eras cannot capture every change in clinical decision-making, supportive care, imaging, focal therapy, or follow-up. Second, treatment allocation was nonrandom and exact treatment dates were not consistently available, preventing causal estimation of the effect of individual targeted-treatment modalities. Earlier cases also required retrospective conversion to the ICRB system, which may have introduced some classification uncertainty. Visual acuity and other standardized functional outcomes were not available, so anatomical globe preservation should not be interpreted as preservation of useful vision. In addition, this was a tertiary referral-center cohort and may include a higher proportion of advanced or complex cases than the general retinoblastoma population. Finally, the small number of deaths limits conclusions regarding overall survival, and evidence of nonproportionality for ICRB severity warrants cautious interpretation of Cox hazard ratios as average time-to-event summaries.

Conclusion

The evolution of retinoblastoma management after 2012 was associated with a clinically meaningful reduction in enucleation and improvement in globe preservation in both unilateral and bilateral disease, with particularly substantial gains among eyes with ICRB group D retinoblastoma. The adjusted T1-to-T2 relative reduction in the probability of undergoing enucleation at any time during the recorded follow-up was greater in bilateral than unilateral eyes. This finding highlights the importance of considering laterality together with eye-specific disease severity when evaluating treatment outcomes. These findings support the continuing shift toward risk-adapted globe-preserving management while maintaining an important role for enucleation in selected eyes with very advanced disease. Because this was an observational study, the observed improvements cannot be attributed to any single treatment modality. Prospective studies with standardized treatment-exposure data, exact treatment timing, visual outcomes, and long-term follow-up are needed to determine which components of contemporary management contribute most to durable globe preservation and patient outcomes.

Abbreviations

BH, Benjamini-Hochberg
CI, confidence interval
EBRT, external-beam radiotherapy
FDR, false discovery rate
GEE, generalized estimating equations
HR, hazard ratio
IAC, intra-arterial chemotherapy
ICRB, International Classification of Retinoblastoma
IQR, interquartile range
KM, Kaplan-Meier
NE, not estimable
OD, oculus dexter (right eye)

OR, odds ratio
OS, oculus sinister (left eye)
pp, percentage points
RB, retinoblastoma
RB1, retinoblastoma 1 tumor suppressor gene
RR, risk ratio
SPSS, IBM SPSS Statistics
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology
T1, earlier treatment era
T2, later treatment era
VEC, vincristine, etoposide, and carboplatin

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD. REC.1398.292) The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for clinical evaluation and treatment was obtained from the parents or legal guardians of all patients.

Consent for publication

Not applicable. The manuscript reports aggregate and deidentified study findings and contains no identifiable individual patient information.

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Conflict of interest interests

The authors declare no financial or nonfinancial competing interests relevant to this work.

Author contributions

[M.F]: Methodology, Investigation, Data curation, Formal analysis, Software, Validation, Visualization, Writing - original draft, and Writing - review and editing.

[R.M]: Investigation, Data curation and Writing - review and editing.

[A.S]: Investigation, Data curation and Writing - review and editing.

[P.F]: Data curation and Writing - review and editing.

[H.G]: Investigation, Data curation and Writing - review and editing.

[M.N]: Conceptualization, Methodology, Investigation, Resources, Data curation, Project administration, Supervision, Writing - original draft, and Writing - review and editing.

All authors reviewed and approved the final manuscript and agree to be accountable for the work. Revise these roles to reflect actual contributions and do not include non-authors in this section.

Data availability

The deidentified data supporting the findings of this study are available from the corresponding author upon reasonable request and subject to approval by the Ethics Committee of Iran University of Medical Sciences and applicable institutional and patient-privacy requirements. The individual-level clinical data are not publicly available because they contain sensitive health information from pediatric patients.

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Patient and public involvement

Patients and members of the public were not involved in the design, conduct, analysis, or reporting of this retrospective studies.

Clinical trial registration

Not applicable.

Transparency statement

The guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Generative AI and AI-assisted technologies

Generative AI-assisted tools were used during manuscript preparation for language editing and organizational support. All scientific content, statistical interpretations, references, and final wording were critically reviewed and approved by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

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Figures

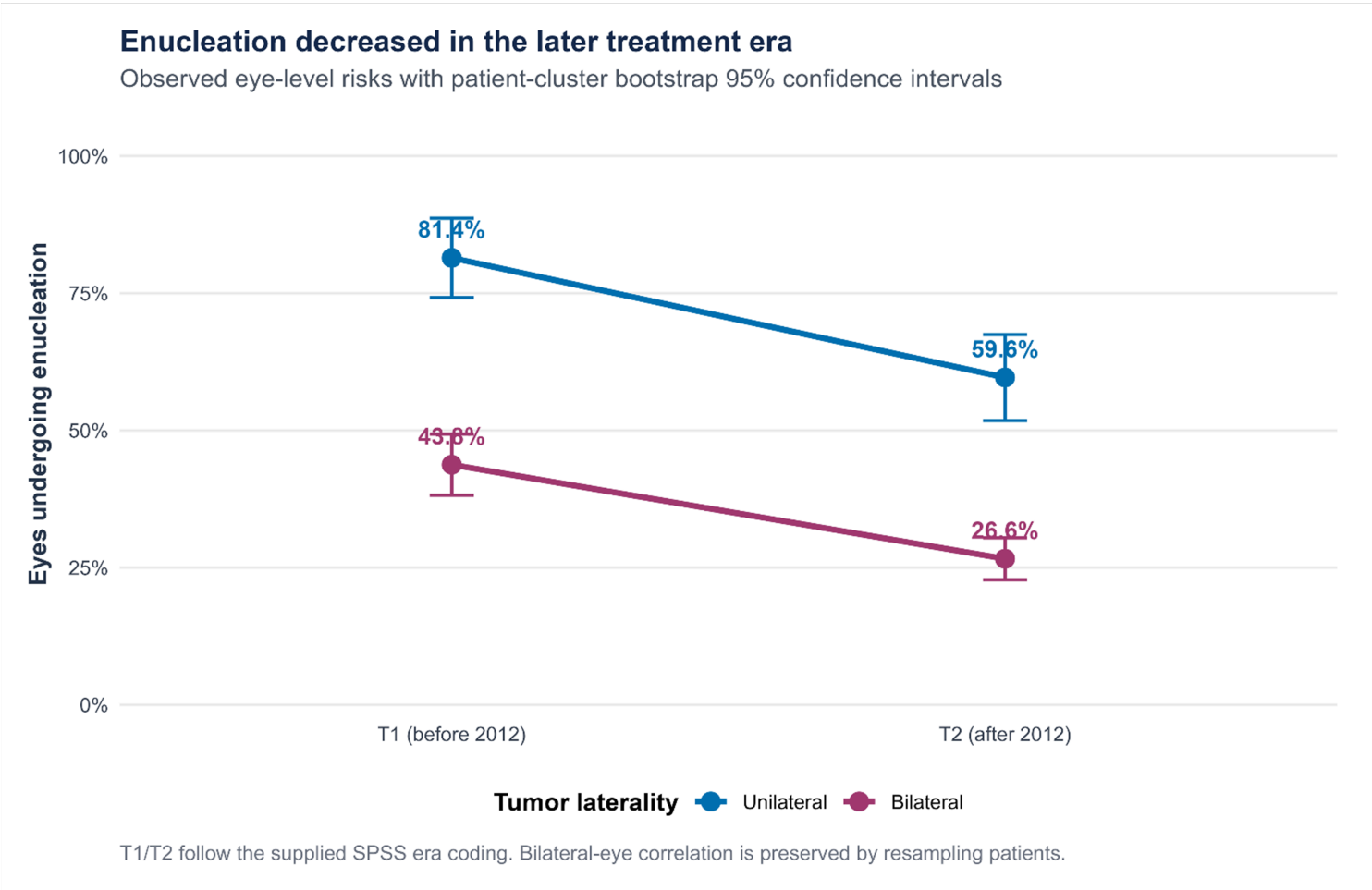


Figure 1

Observed enucleation risk by treatment era and laterality. Points are eye-level risks and error bars are patient-cluster bootstrap 95% CIs; bilateral patients are resampled as clusters.

Era effect on enucleation risk

Risk ratios below 1 favor T2

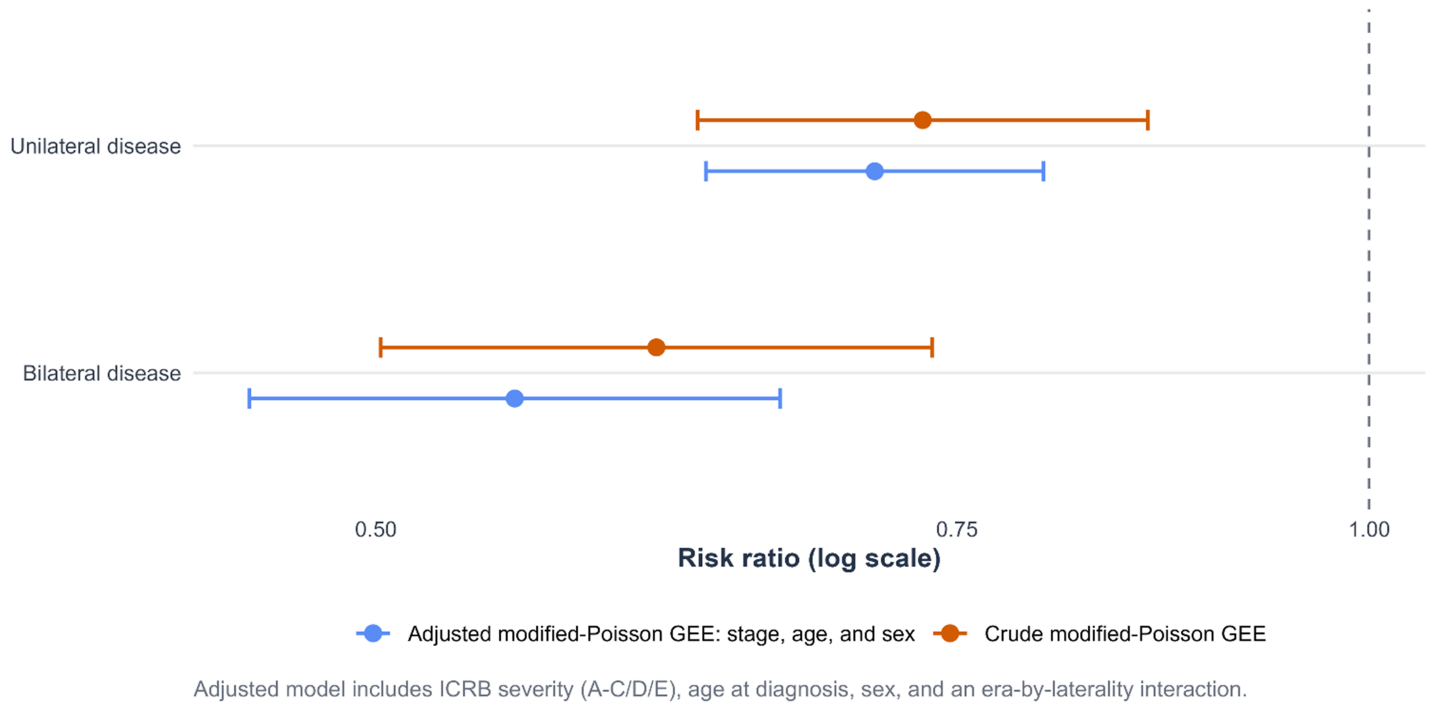
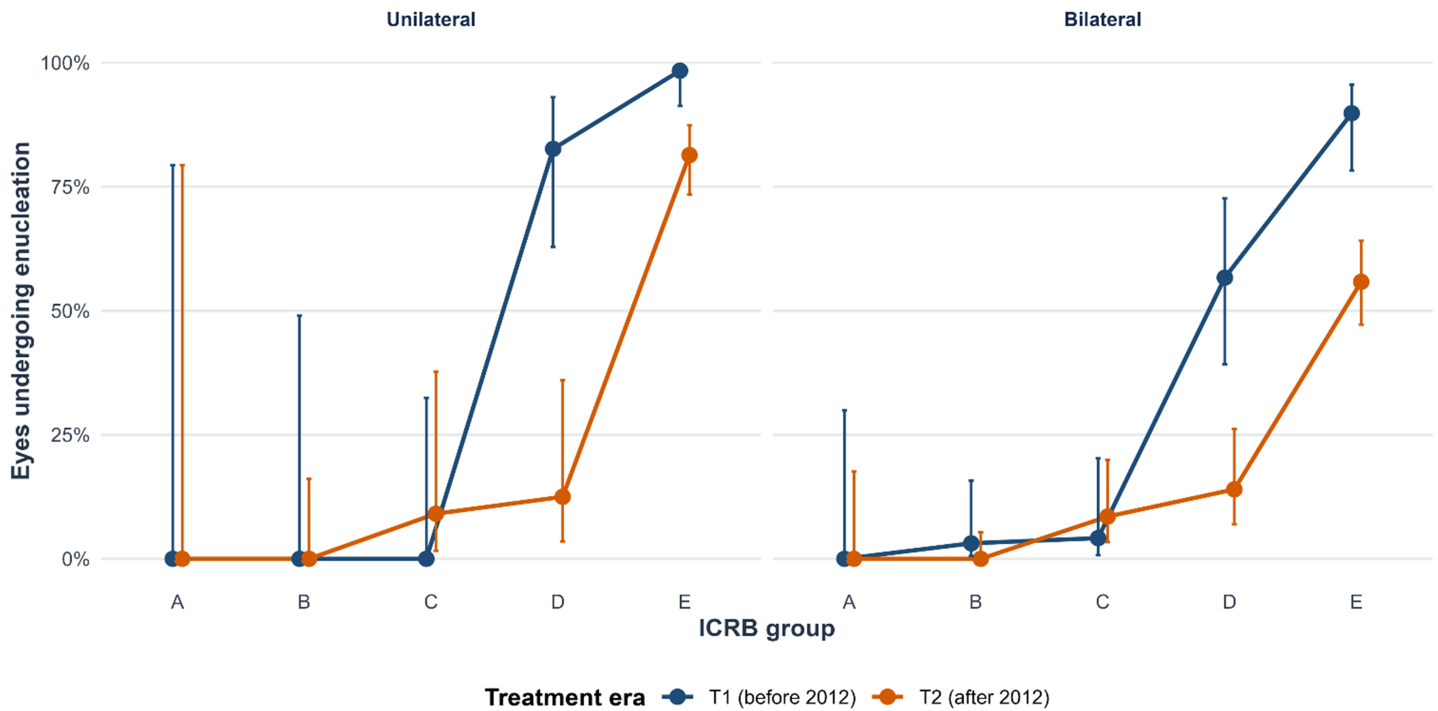


Figure 2

Crude and adjusted T2-versus-T1 enucleation risk ratios. Adjusted modified-Poisson GEE includes ICRB severity, nonlinear age, sex, and era-by-laterality interaction. Values below 1 favor T2.

Enucleation risk by ICRB group

Stage-specific descriptive estimates with Wilson 95% confidence intervals



Formal stage-specific era effects use patient-clustered modified-Poisson GEE; BH-FDR is applied across the 10 stage/laterality tests.

Figure 3

ICRB-group-specific enucleation risks by era and laterality. Error bars are Wilson 95% CIs. Formal stage-specific comparisons use patient-clustered modified-Poisson GEE with Benjamini-Hochberg FDR control.

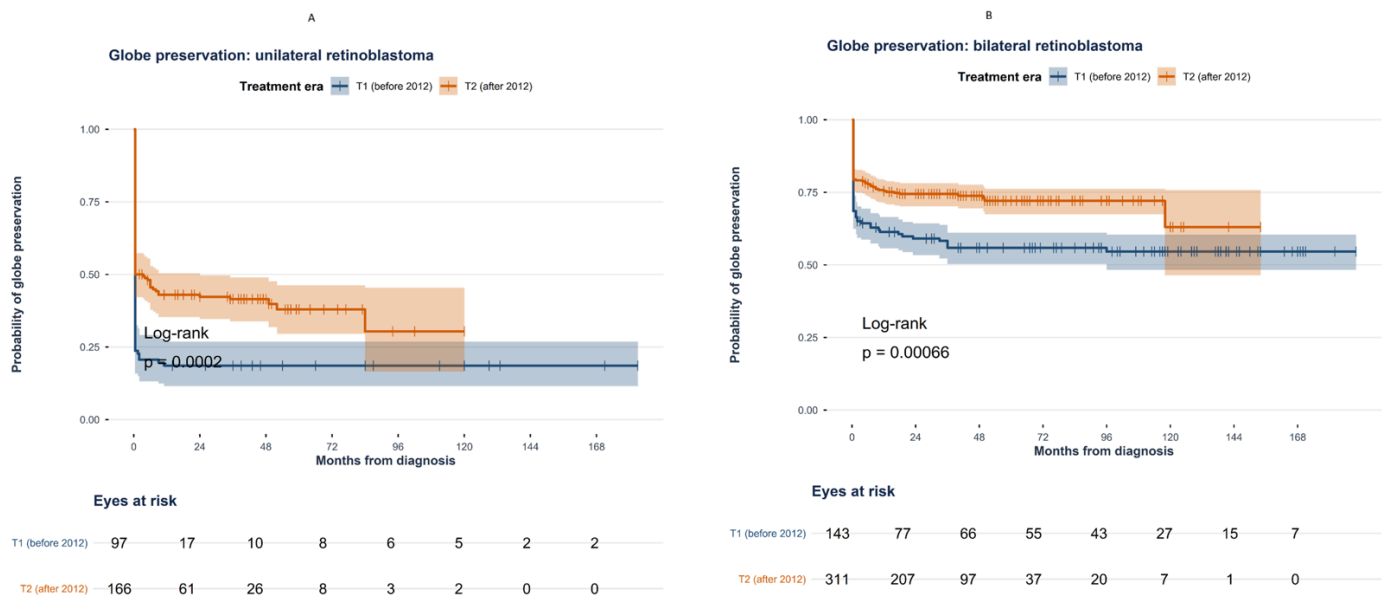


Figure 4

A. Globe-preservation probability in unilateral retinoblastoma. Kaplan-Meier curves compare T1 and T2; shaded bands are 95% CIs and tick marks indicate censoring. **B.** Globe-preservation probability in bilateral retinoblastoma. Both affected eyes were retained; the adjusted Cox analysis uses patient-clustered robust standard errors.

Supplementary Files

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