

Tables and Figures

Table 1: Clinical diagnostic characteristics and treatment outcomes for 491 patients from 59 centers in 25 American countries

Table 1A. Participating countries and treatment centers by national income level					
	National Income Level				
n (%)	Low	Lower-Middle	Upper-Middle	High	Total
Number of countries	1 (4%)	6 (24%)	12 (48%)	6 (24%)	25
Number of centers	1 (1.7%)	7 (11.9%)	21 (35.6%)	30 (50.8%)	59

Table 1B. Clinical characteristics at diagnosis by national income level					
	National Income Level				
n/N (%)	Low	Lower-Middle	Upper-Middle	High	Total
Age at diagnosis (months)					
Median (IQR)	32.7 (27.6-46.0)	21.7 (10.8-39.0)	21.7 (9.1-32.3)	15.3 (6.1-25.1)	19.4 (8.3-31.9)
Data available ^a	6/8 (75%)	58/58 (100%)	226/235 (96.2%)	152/190 (80%)	442/491 (90%)
Laterality at presentation^b					
Unilateral	6/8 (75%)	40/58 (69%)	174/235 (74%)	111/190 (58.4%)	331/491 (67.4%)
	6/331 (1.8%)	40/331 (12.1%)	174/331 (52.6%)	111/331 (33.5%)	
Bilateral	2/8 (25%)	18/58 (31%)	61/235 (26%)	79/190 (41.6%)	160/491 (32.6%)
	2/160 (1.3%)	18/160 (11.3%)	61/160 (38.1%)	79/160 (49.4%)	
Sex^b					
Female	3/8 (37.5%)	35/58 (60.3%)	119/235 (50.6%)	75/190 (39.5%)	232/491 (47.3%)
	3/232 (1.3%)	35/232 (15.1%)	119/232 (51.3%)	75/232 (32.3%)	
Male	5/8 (62.5%)	23/58 (39.7%)	116/235 (49.4%)	115/190 (60.5%)	259/491 (52.7%)
	5/259 (1.9%)	23/259 (8.9%)	116/259 (44.8%)	115/259 (44.4%)	
Family history of retinoblastoma					
Yes	0	0	12/235 (5.1%)	23/189 (12.2%)	35/490 (7.1%)
	0	0	12/35 (34.3%)	23/35 (65.7%)	
No	8/8 (100%)	58/58 (100%)	223/235 (94.9%)	166/189 (87.8%)	455/490 (92.9%)
	8/455 (1.8%)	58/455 (12.7%)	223/455 (49%)	166/455 (36.5%)	
Data available ^a	8/8 (100%)	58/58 (100%)	235/235 (100%)	189/190 (99.5%)	490/491 (99.8%)

Table 1B (Continued)

n/N (%)	National Income Level				
	Low	Lower-Middle	Upper-Middle	High	Total
Clinical Tumor, Node, Metastasis, Heredity 8th Edition Staging					
Primary tumor					
cT1	1/6 (16.7%)	1/58 (1.7%)	17/231 (7.4%)	32/189 (16.9%)	51/484 (10.5%)
	1/51 (2%)	1/51 (2%)	17/51 (33.3%)	32/51 (62.7%)	
cT2	0	10/58 (17.2%)	59/231 (25.5%)	91/189 (48.1%)	160/484 (33.1%)
	0	10/160 (6.3%)	59/160 (36.9%)	91/160 (56.9%)	
cT3	1/6 (16.7%)	33/58 (56.9%)	134/231 (58%)	64/189 (33.9%)	232/484 (47.9%)
	1/232 (0.4%)	33/232 (14.2%)	134/232 (57.8%)	64/232 (27.6%)	
cT4	4/6 (66.7%)	14/58 (24.1%)	21/231 (9.1%)	1/189 (0.5%)	40/484 (8.3%)
	4/40 (10%)	14/40 (35%)	21/40 (52.5%)	1/40 (2.5%)	
Retinoma	0	0	0	1/189 (0.5%)	1/484 (0.2%)
	0	0	0	1/1 (100%)	
Data available ^a	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	189/190 (99.5%)	484/491 (98.6%)
Regional lymph node					
NX	1/6 (16.7%)	5/58 (8.6%)	22/231 (9.5%)	65/190 (34.2%)	93/485 (19.2%)
	1/93 (1.1%)	5/93 (5.4%)	22/93 (23.7%)	65/93 (69.9%)	
N0	2/6 (33.3%)	48/58 (82.8%)	204/231 (88.3%)	125/190 (65.8%)	379/485 (78.1%)
	48/379 (12.7%)	204/379 (53.8%)	125/379 (33%)	1/93 (1.1%)	
N1	3/6 (50%)	5/58 (8.6%)	5/231 (2.2%)	0	13/485 (2.7%)
	3/13 (23.1%)	5/13 (38.5%)	5/13 (38.5%)	0	
Data available ^a	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	485/491 (98.8%)
Distant metastasis					
M0	3/6 (50%)	50/58 (86.2%)	218/231 (94.4%)	190/190 (100%)	461/485 (95.1%)
	3/461 (0.7%)	50/461 (10.8%)	218/461 (47.3%)	190/461 (41.2%)	
cM1	3/6 (50%)	4/58 (6.9%)	7/231 (3%)	0	14/485 (2.9%)
	3/14 (21.4%)	4/14 (28.6%)	7/14 (50%)	0	
pM1	0	4/58 (6.9%)	6/231 (2.6%)	0	10/485 (2.1%)
	0	4/10 (40%)	6/10 (60%)	0	
Data available ^a	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	485/491 (98.8%)
Heredity trait					
HX	5/7 (71.4%)	40/58 (69%)	163/231 (70.6%)	38/190 (20%)	246/486 (50.6%)
	5/246 (2%)	40/246 (16.3%)	163/246 (66.3%)	38/246 (15.4%)	
H0	0	0	1/231 (0.4%)	54/190 (28.4%)	55/486 (11.3%)
	0	1/55 (1.8%)	54/55 (98.2%)	5/246 (2%)	
H1	2/7 (28.6%)	18/58 (31%)	67/231 (29%)	98/190 (51.6%)	185/486 (38.1%)
	2/185 (1.1%)	18/185 (9.7%)	67/185 (36.2%)	98/185 (53%)	
Data available ^a	7/8 (87.5%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	486/491 (99%)

Table 1C. 3-year outcomes by national income level					
	National Income Level				
n/N (%)	Low	Lower-Middle	Upper-Middle	High	Total
Enucleation *					
Yes	4/8 (50%)	45/58 (77.6%)	184/235 (78.3%)	104/190 (54.7%)	337/491 (68.6%)
	4/337 (1.2%)	45/337 (13.4%)	184/337 (54.6%)	104/337 (30.9%)	
No	4/8 (50%)	13/58 (22.4%)	50/235 (21.3%)	82/190 (43.2%)	149/491 (30.3%)
	4/149 (2.7%)	13/149 (8.7%)	50/149 (33.6%)	82/149 (55.0%)	
Unknown	0	0	1/235 (0.4%)	4/190 (2.1%)	5/491 (1.0%)
	0	0	1/5 (20.0%)	4/5 (80.0%)	
Metastasis *					
Yes	5/8 (62.5%)	12/58 (20.7%)	30/235 (12.8%)	3/190 (1.6%)	50/491 (10.2%)
	5/50 (10%)	12/50 (24%)	30/50 (60%)	3/50 (6%)	
No	2/8 (25%)	39/58 (67.2%)	172/235 (73.2%)	172/190 (90.5%)	385/491 (78.4%)
	2/385 (0.5%)	39/385 (10.1%)	172/385 (44.7%)	172/385 (44.7%)	
Unknown	1/8 (12.5%)	7/58 (12.1%)	33/235 (14%)	15/190 (7.9%)	56/491 (11.4%)
	1/56 (1.8%)	7/56 (12.5%)	33/56 (58.9%)	15/56 (26.8%)	
Survival Status *					
Dead	3/8 (37.5%)	13/58 (22.4%)	24/235 (10.2%)	3/190 (1.6%)	43/491 (8.8%)
	3/43 (7%)	13/43 (30.2%)	24/43 (55.8%)	3/43 (7%)	
Alive	2/8 (25%)	40/58 (69%)	183/235 (77.9%)	178/190 (93.7%)	403/491 (82.1%)
	2/403 (0.5%)	40/403 (9.9%)	183/403 (45.4%)	178/403 (44.2%)	
Unknown	3/8 (37.5%)	5/58 (8.6%)	28/235 (11.9%)	9/190 (4.7%)	45/491 (9.2%)
	3/45 (6.7%)	5/45 (11.1%)	28/45 (62.2%)	9/45 (20%)	
Cause of Death					
Retinoblastoma	3/3 (100%)	13/13 (100%)	18/24 (75%)	3/3 (100%)	37/43 (86%)
	3/37 (8.1%)	13/37 (35.1%)	18/37 (48.6%)	3/37 (8.1%)	
Tx complication	0	0	3/24 (12.5%)	0	3/43 (7%)
	0	0	3/3 (100%)	0	
Other causes	0	0	1/24 (4.2%)	0	1/43 (2.3%)
	0	0	1/1 (100%)	0	
Data missing	0	0	2/24 (8.3%)	0	2/43 (4.7%)
	0	0	2/2 (100%)	0	
Follow-up time (months)					
Median (IQR)	11.0 (2.6-39.8)	30.5 (13.7-34.9)	35.8 (24.5-40.7)	35.2 (30.1-39.9)	34.7 (26.6-39.8)
Data available ^a	6/8 (75%)	55/58 (94.8%)	203/235 (86.4%)	184/190 (96.8%)	448/491 (90.8%)

Data are n/N (%), except where indicated otherwise. Percentages within the national income level and within the evaluated variable are shown.

*Entire cohort has data available

^aThe number of individuals for whom data were available.

^bInclusion criterion: 100% reporting.

Abbreviations: IQR - interquartile range; Tx – Retinoblastoma Treatment

Table 2. Summary of the clustered and weighted Cox proportional hazard model for survival*

	Coefficient	Robust standard error	Z score	P value Unadjusted (Corrected†)	HR (95% CI)
Income level of residence					
Low	Ref	–	–	–	1.00
Lower-middle	-0.18	0.22	-0.82	0.41 (1.00)	0.83 (0.54 – 1.29)
Upper-middle	-0.69	0.62	-1.11	0.27 (1.00)	0.50 (0.15 – 1.69)
High	-1.25	0.76	-1.64	0.10 (1.00)	0.29 (0.06 – 1.27)
All ages‡					
HR per month	0.03	0.02	1.81	0.07 (0.56)	1.03 (1.00 – 1.07)
HR per year	0.41	0.23	1.81	0.07 (0.56)	1.51 (0.96 – 2.35)
Age > 4 years					
HR per month	-0.07	0.02	-2.89	0.004 (0.048)	0.94 (0.90 – 0.98)
HR per year	-0.79	0.27	-2.89	0.004 (0.048)	0.45 (0.27 – 0.78)
Laterality					
Unilateral	Ref	–	–	–	1.00
Bilateral	0.52	0.36	1.46	0.14 (1.00)	1.68 (0.84 – 3.38)
Primary tumor					
cT1	Ref	–	–	–	1.00
cT2	20.8	1.03	20.2	<0.001 (<0.001)	1.10x10 ⁹ (1.46x10 ⁸ – 8.26x10 ⁹)
cT3	22.3	0.67	33.3	<0.001 (<0.001)	4.65x10 ⁹ (1.25x10 ⁹ – 1.72 x 10 ¹⁰)
cT4	24.8	–	–	–	5.98x10 ¹⁰ (No CI)
Sex					
Male	Ref	–	–	–	1.00
Female	0.69	0.23	3.02	0.003 (0.04)	1.98 (1.27 – 3.10)
Family history of retinoblastoma					
Negative	Ref	–	–	–	1.00
Positive	2.41	0.97	2.48	0.01 (0.16)	11.10 (1.66 – 74.8)
Hereditary retinoblastoma§					
H0	Ref	–	–	–	1.00
H1	0.26	0.45	0.58	0.56 (1.00)	1.30 (0.54 – 3.13)

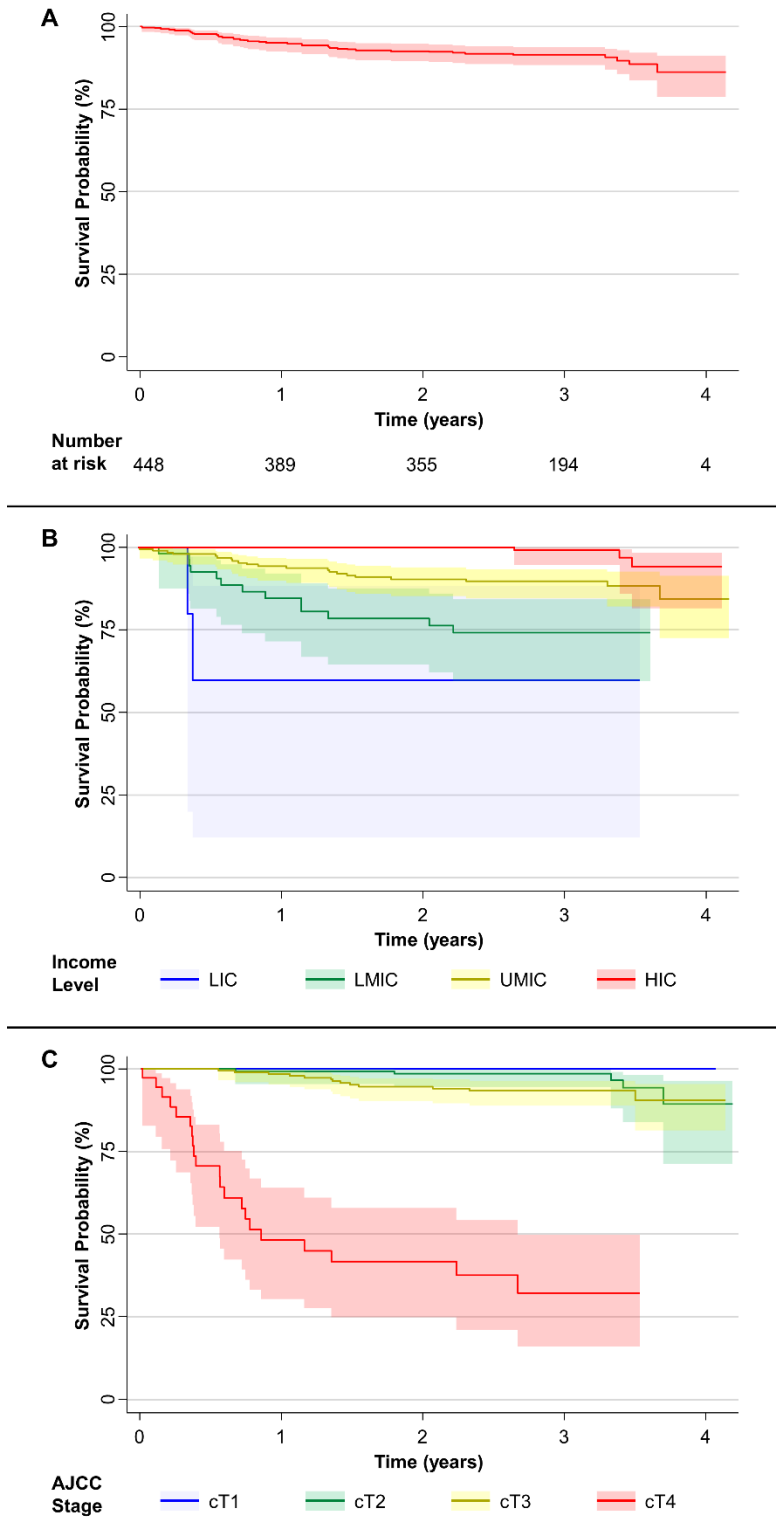
HR= hazard ratio *Overall, 43 observations were dropped from survival analysis because of missing observation time. †Corrected using Bonferroni method (multiplied by 12 for each model term). ‡Age included in analysis as a continuous variable. §Hereditary refers to bilateral or trilateral retinoblastoma, positive family history, or positive blood *RB1* mutation. H0= non-hereditary, H1= hereditary

Table 3: Summary of the clustered and weighted Fine and Gray proportional subhazard model for enucleation*

	Coefficient	Robust standard error	Z score	P value Unadjusted (Corrected[†])	SHR (95% CI)
Income level of residence					
Low	Ref	–	–	–	1.00
Lower-middle	-0.27	0.26	-1.04	0.30 (1.00)	0.76 (0.46-1.27)
Upper-middle	-0.31	0.17	-1.85	0.06 (0.77)	0.73 (0.53-1.02)
High	-0.98	0.36	-2.71	0.007 (0.08)	0.37 (0.18-0.76)
All ages‡					
HR per month	-0.27	0.26	-1.04	0.66 (1.00)	1.00 (0.99-1.01)
HR per year	0.03	0.06	0.44	0.66 (1.00)	1.03 (0.91-1.17)
Age > 4 years					
HR per month	-0.01	0.01	-1.34	0.18 (1.00)	0.99 (0.97-1.01)
HR per year	-0.15	0.11	-1.34	0.18 (1.00)	0.86 (0.69-1.07)
Laterality					
Unilateral	Ref	–	–	–	1.00
Bilateral	-0.48	0.15	-3.08	0.002 (0.02)	0.62 (0.46-0.84)
Primary tumor					
cT1	Ref	–	–	–	1.00
cT2	0.94	0.39	2.42	0.02 (0.19)	2.57 (1.20-5.51)
cT3	1.60	0.38	4.22	<0.001 (<0.001)	4.98 (2.36-10.5)
cT4	0.76	0.39	1.95	0.05 (0.61)	2.14 (1.00-4.58)
Sex					
Male	Ref	–	–	–	1.00
Female	-0.09	0.15	-0.56	0.58 (1.00)	0.92 (0.68-1.24)
Family history of retinoblastoma					
Negative	Ref	–	–	–	1.00
Positive	-0.92	0.36	-2.57	0.01 (0.12)	0.40 (0.20-0.80)
Hereditary retinoblastoma§					
H0	Ref	–	–	–	1.00
H1	-0.18	0.32	-0.57	0.57 (1.00)	0.83 (0.45-1.56)

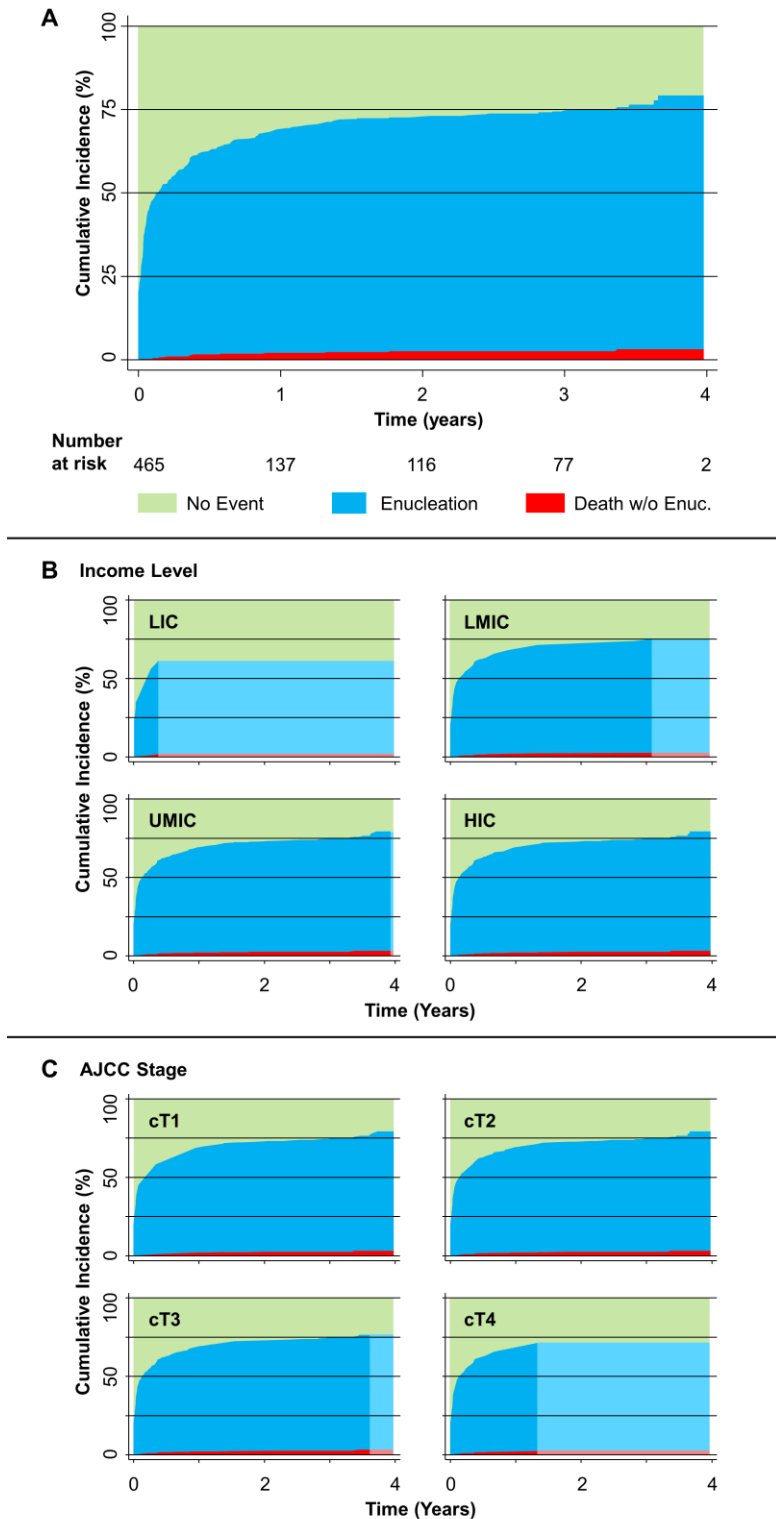
SHR= Subhazard ratio *Overall, 26 observations were dropped from survival analysis because of missing observation time. †Corrected using Bonferroni method (multiplied by 12 for each model term). ‡Age included in analysis as a continuous variable. §Hereditary refers to bilateral or trilateral retinoblastoma, positive family history, or positive blood *RB1* mutation. H0= non-hereditary, H1= hereditary

Figure 1:



Survival analysis for the full study cohort, by national income level, and by clinical stage. (A) Kaplan-Meier survival plot for the entire cohort. (B) Kaplan-Meier survival plot by income group. Income Groups: LIC (Low Income Country); LMIC (Lower-Middle Income Country); UMIC (Upper-Middle Income Country); HIC (High Income Country). (C) Kaplan-Meier survival plot by AJCC tumor stage (cT1-cT4). 95% confidence intervals indicated by shaded regions.

Figure 2:



Cumulative incidence of enucleation and competing risk of death for the full cohort, by income level, and by clinical stage. (A) Stacked cumulative incidence plot for entire cohort. (B) Stacked cumulative incidence plots by income group. Income Groups: LIC (Low Income Country); LMIC (Lower-Middle Income Country); UMIC (Upper-Middle Income Country); HIC (High Income Country). (C) Stacked cumulative incidence plots by AJCC tumor stage (cT1-cT4). Note: Lighter color regions (e.g., LIC incidence in 2B before 1 year; cT4 incidence in 2C after 1 year) denote rates that are estimated using the last known values per group, reflecting limited follow-up data.

Supplemental Figures:

eTable 1. Treatments available by national income level

Treatment n (%)	National Income Level				
	Low (n=8)	Lower-Middle (n=58)	Upper-Middle (n=235)	High (n=190)	Total (N=491)
Genetic Testing	0	0	89 (37.9%)	177 (93.2%)	266 (54.2%)
CT	8 (100%)	13 (22.4%)	2 (0.9%)	4 (2.1%)	27 (5.5%)
MRI	0	0	113 (48.1%)	83 (43.7%)	196 (39.9%)
CT + MRI	0	45 (77.6%)	120 (51.1%)	103 (54.2%)	268 (54.6%)
Pathology	8 (100%)	58 (100%)	235 (100%)	185 (97.4%)	486 (99.0%)
Laser therapy	0	52 (89.7%)	218 (92.8%)	188 (98.9%)	458 (93.3%)
Cryotherapy	0	52 (89.7%)	197 (83.8%)	187 (98.4%)	436 (88.8%)
Enucleation/ Exenteration	Available for all patients				
Intravenous chemotherapy	8 (100%)	58 (100%)	232 (98.7%)	189 (99.5%)	487 (99.2%)
Intra-ophthalmic artery chemotherapy	0	9 (15.5%)	189 (80.4%)	164 (86.3%)	362 (73.7%)
Intravitreal chemotherapy	0	9 (15.5%)	190 (80.6%)	188 (98.9%)	387 (78.8%)
Plaque brachytherapy	0	9 (15.5%)	43 (18.3%)	156 (82.1%)	208 (42.4%)
External beam radiotherapy	0	58 (100%)	219 (93.2%)	178 (93.7%)	455 (92.7%)

eTable 2. Treatments given by national income level

Treatment ^a n (%)	National Income Level				
	Low (n=8)	Lower-Middle (n=58)	Upper-Middle (n=234)	High (n=186)	Total (n=486)
Primary treatment for patient^b					
Intravenous chemotherapy	2 (25%)	22 (37.9%)	81 (34.6%)	70 (37.6%)	175 (36%)
Intra-ophthalmic artery chemotherapy	0	0	24 (10.3%)	42 (22.6%)	66 (13.6%)
Enucleation ^c	3 (37.5%)	34 (58.6%)	125 (53.4%)	75 (40.3%)	237 (48.8%)
Focal laser or cryotherapy	0	3 (5.2%)	10 (4.3%)	20 (10.8%)	33 (6.8%)
Plaque brachytherapy	1 (12.5%)	0	0	0	1 (0.2%)
External beam radiotherapy	0	0	1 (0.4%)	0	1 (0.2%)
Vitrectomy	0	0	0	1 (0.5%)	1 (0.2%)
Palliative therapy ^d	2 (25%)	1 (1.7%)	2 (0.9%)	0	5 (1%)
Observation	0	0	0	1 (86.3%)	1 (0.2%)
Primary treatment refusal	2 (25%)	6 (10.3%)	12 (5.1%)	3 (1.6%)	23 (4.7%)
Additional treatment for patient^e					
Intravenous chemotherapy	2 (25%)	20 (34.5%)	75 (32.1%)	47 (25.3%)	144 (29.6%)
Intra-ophthalmic artery chemotherapy	0	2 (3.4%)	29 (12.4%)	41 (22%)	72 (14.8%)
Intravitreal chemotherapy	0	0	24 (10.3%)	31 (16.7%)	55 (11.3%)
Enucleation/Exenteration ^c	2 (25%)	12 (20.7%)	61 (26.1%)	31 (16.1%)	106 (21.8%)
Focal laser or cryotherapy	0	10 (17.2%)	54 (23.1%)	95 (51.1%)	159 (32.7%)
Plaque brachytherapy	0	0	8 (3.4%)	8 (4.3%)	16 (3.3%)
External beam radiotherapy	1 (12.5%)	8 (13.8%)	19 (8.1%)	2 (1.1%)	30 (6.2%)
Vitrectomy	0	0	1 (0.4%)	3 (1.6%)	4 (0.8%)
Palliative therapy	0	1 (1.7%)	0	1 (0.5%)	2 (0.4%)
Treatment refusal after primary	0	0	5 (2.1%)	2 (1.1%)	7 (1.4%)

^a Per patient; bilateral cases are counted twice if the eyes were treated differently.

^b First and main treatment. If both enucleation and chemotherapy were combined, both were counted as primary. If enucleation/chemotherapy was combined with an additional therapy, the other therapies were not counted.

^c Primary and secondary enucleation or exenteration do not match totals in text, because bilateral cases are counted twice on this table (per eye), and once in the text (per patient).

^d Palliative therapy, including oral chemotherapy.

^e Additional treatment for tumor relapse or new tumors.