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Supplementary appendix

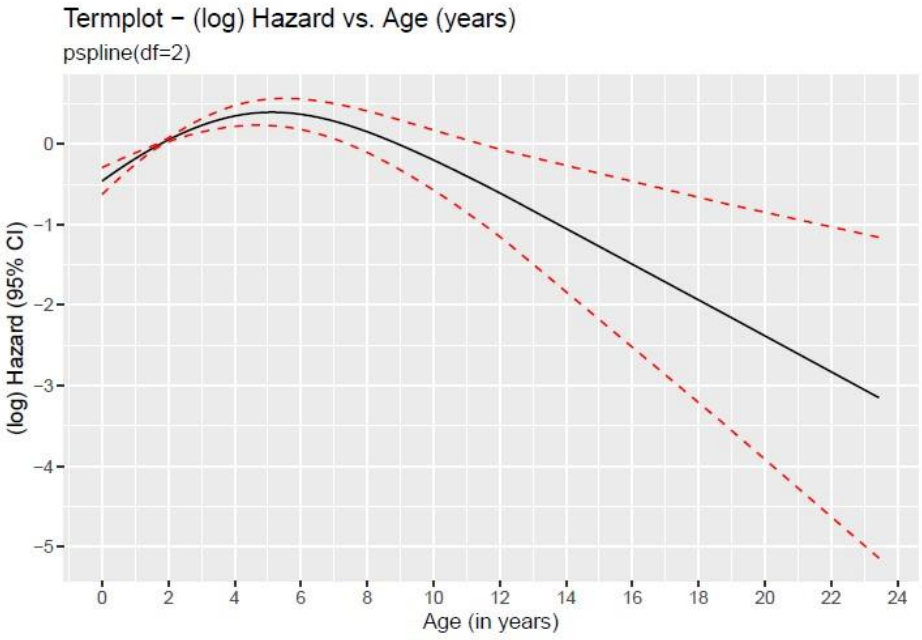
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The Global Retinoblastoma Study Group. The Global Retinoblastoma Outcome Study: a prospective, cluster-based analysis of 4064 patients from 149 countries. *Lancet Glob Health* 2022; **10:** e1128–40.

Relationship between age at diagnosis and hazard

1. Age and survival
    a. Preliminary analysis:
    The linearity of the relationship of log hazard to age at diagnosis was assessed using a pspline (with either 2 or 3 degrees of freedom) for age and all the other specified predictors (income group, laterality, tumor stage, sex, family history of retinoblastoma and hereditary status). The fits were very similar. For age with the 2 df fit, the non-linear component reached a p-value of 4.5*10 to the power -13.

eFigure 1.



    b. Examples of the relationship between age and hazard in our final model:
        i. For two subjects both less than 3 years, they are affected only by the first term (i.e. age), with coefficient 0.027. If they differ in age by one year, the difference in log hazard is 0.027*12 = 0.324. The hazard ratio (HR) is 1.38.
        ii. Two subjects, one less than 3 years, the other above 3 years, for example 30 and 42 months old. For both subjects, the first term plays in just as above. For the first subject, the second term (age>3 years) = 0. For the second subject, the second term = 6. The difference in log hazard is 0.027*12 - 0.028*6 = 0.155. The HR is 1.17.
        iii. Two subjects both older than 3 years but less than 7 years, and one year apart in age. The difference in log hazard is 0.027*12 - 0.028*12 = -0.013 (i.e. the older subject now has very slightly lower log hazard than the younger one, but the difference is small, as these subjects are "on the plateau"). The HR is 0.99.
    c. **eTable 1** shows the calculated HR (and lower and upper 95% confidence interval, CI) in 6 months steps, compared to age = 12 months (HR=1), from our final model. Greener – larger numbers, redder – smaller numbers.

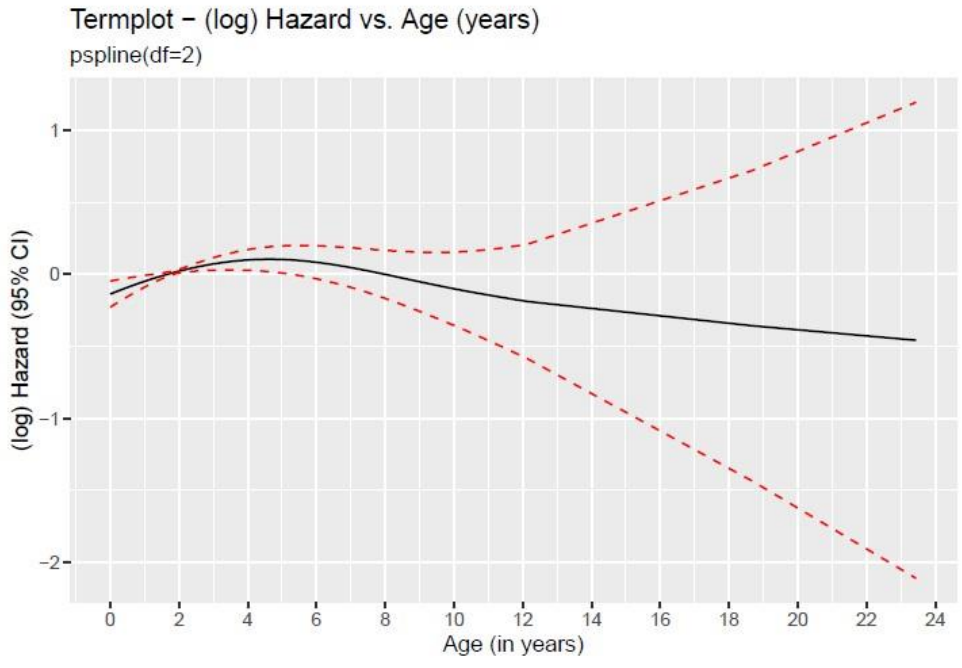
eTable 1

Age (months)	Hazard Ratio	CI Lower	CI upper	
6	0.850912708	0.798350929	0.906935046	
12	1	1	1	
18	1.17520868	1.102614795	1.252581996	
24	1.381115441	1.215759386	1.568961656	
30	1.623098853	1.340514286	1.965253122	
36	1.90747986	1.478070885	2.461640678	
42	1.894596549	1.489535469	2.409809068	
48	1.881800252	1.483431709	2.387148776	
54	1.869090383	1.459415111	2.393766404	
60	1.856466358	1.420203148	2.426742502	
66	1.843927597	1.370118823	2.481586944	
72	1.831473524	1.313372096	2.553956552	
78	1.819103567	1.253232781	2.640481352	
84	1.806817158	1.191964652	2.738829742	
90	1.585047386	1.121141621	2.24090799	↑ significant
96	1.390497763	0.996981728	1.939337478	↓ non significant
102	1.219827272	0.833140411	1.785987758	
108	1.070104975	0.666661329	1.71770074	
114	0.938759678	0.521115496	1.691121721	
120	0.823535778	0.402416118	1.685347947	
126	0.722454526	0.308674444	1.690909477	
132	0.633780044	0.235828472	1.70325975	

2. Age and globe salvage - Preliminary analysis:

   A similar analysis as for “age and survival” was performed. For age, the non-linear component reached a p-value of $1.1e^{-5}$.

eFigure 2



Clinical characteristics at the time of diagnosis

eTable 2. Clinical characteristics at the time of diagnosis in 4064 new patients with retinoblastoma in 149 countries in 2017.					
	National income level				
	No. (% within the national income level) [% within the evaluated parameter]				
Parameter	**Low**	**Lower-middle**	**Upper-middle**	**High**	**Total**
Age at diagnosis					
Median (IQR), mo	30.0 (18.2 - 46.1)	24.4 (12.2 - 37.7)	20.9 (10.0 - 34.3)	13.6 (6.0 - 27.1)	23.2 (11.0 - 36.5)
Total, No. (%)[a]	469/480 (97.7)	1751/1791 (97.8)	1120/1151 (97.3)	635/642 (98.9)	3975/4064 (97.8)
Laterality[b]					
Unilateral at presentation	358 (74.6) [12.7]	1221 (68.2) [43.5]	815 (70.8) [29.0]	415 (64.6) [14.8]	2809 (69.1)
Bilateral at presentation	122 (25.4) [9.7]	570 (31.8) [45.4]	336 (29.2) [26.8]	227 (35.4) [18.1]	1255 (30.9)
Sex[b]					
Female	223 (46.5) [12.2]	798 (44.6) [43.7]	527 (45.8) [28.8]	279 (43.5) [15.3]	1827 (45.0)
Male	257 (53.5) [11.5]	993 (55.4) [44.4]	624 (54.2) [27.9]	363 (56.5) [16.2]	2237 (55.0)
Family history of retinoblastoma					
Yes	15 (3.4) [7.7]	73 (4.2) [37.6]	51 (4.5) [26.3]	55 (8.6) [28.4]	194 (4.9)
No	427 (96.6) [11.3]	1661 (95.8) [44.1]	1093 (95.5) [29.0]	583 (91.4) [15.5]	3764 (95.1)
Total, No. (%)[a]	442/480 (92.1)	1734/1791 (96.8)	1144/1151 (99.4)	638/642 (99.4)	3958/4064 (97.4)
Clinical Tumor, Node, Metastasis, Heredity 8th Edition Staging					
Primary tumor					
cT1	4 (0.9) [1.6]	87 (5.0) [33.9]	67 (6.5) [26.1]	99 (15.6) [38.5]	257 (6.7)
cT2	59 (12.9) [5.0]	364 (20.9) [31.0]	436 (42.5) [37.1]	316 (49.7) [26.9]	1175 (30.5)
cT3	198 (43.3) [10.9]	943 (54.3) [51.7]	469 (45.7) [25.7]	214 (33.6) [11.7]	1824 (47.3)
cT4	196 (42.9) [32.8]	342 (19.7) [57.2]	55 (5.4) [9.2]	5 (0.8) [0.8]	598 (15.5)
Retinoma	0	2 (0.1) [50.0]	0	2 (0.3) [50.0]	4 (0.1)
Total, No. (%)[a]	457/480 (95.2)	1738/1791 (97.0)	1027/1151 (89.2)	636/642 (99.1)	3858/4064 (94.9)
Regional lymph node					
NX	78 (16.9) [11.6]	263 (15.0) [39.0]	226 (19.9) [33.5]	108 (16.9) [16.0]	675 (16.9)
N0	340 (73.8) [10.7]	1409 (80.3) [44.5]	884 (78.0) [27.9]	531 (83.1) [16.8]	3164 (79.3)
N1	43 (9.3) [28.9]	82 (4.7) [55.0]	24 (2.1) [16.1]	0	149 (3.7)
Total, No. (%)[a]	461/480 (96.0)	1754/1791 (97.9)	1134/1151 (98.5)	639/642 (99.5)	3988/4064 (98.1)
Distant metastasis					
M0	368 (81.4) [10.0]	1597 (91.1) [43.4]	1082 (95.2) [29.4]	636 (99.5) [17.3]	3683 (92.5)
cM1	56 (12.4) [28.4]	104 (5.9) [52.8]	36 (3.2) [18.3]	1 (0.2) [0.5]	197 (4.9)
pM1	28 (6.2) [27.7]	52 (3.0) [51.5]	19 (1.7) [18.8]	2 (0.3) [2.0]	101 (2.5)
Total, No. (%)[a]	452/480 (94.2)	1753/1791 (97.9)	1137/1151 (98.8)	639/642 (99.5)	3981/4064 (98.0)
Hereditary trait					
HX	320 (70.8) [13.6]	1106 (63.3) [46.9]	708 (62.4) [30.0]	225 (35.2) [9.5]	2359 (59.4)
H0	0	42 (2.4) [17.6]	55 (4.8) [23.1]	141 (22.0) [59.2]	238 (6.0)
H1	132 (29.2) [9.6]	598 (34.2) [43.5]	372 (32.8) [27.0]	274 (42.8) [19.9]	1376 (34.6)
Total, No. (%)[a]	452/480 (94.2)	1746/1791 (97.5)	1135/1151 (98.6)	640/642 (99.7)	3973/4064 (97.8)

[a]The number of individuals for whom data were available.

[b]Inclusion criterion: 100% reporting.

Abbreviations: IQR - interquartile range.

Treatments

eTable 3. Diagnostic and treatment modalities available for 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017					
Parameter	**National income level (n (%))**				
	Low (n=480)	**Lower-middle** (n=1,791)	**Upper-middle** (n=1,151)	**High** (n=642)	**Total** (n=4,064)
Genetic tests	5 (1.0)	369 (20.6)	505 (43.9)	586 (91.3)	1,465 (36.0)
CT	231 (48.1)	1217 (68.0)	860 (74.7)	388 (60.4)	2696 (66.3)
MRI	164 (34.2)	1317 (73.5)	1082 (94.0)	638 (99.4)	3201 (78.8)
CT + MRI	76 (15.8)	805 (44.9)	837 (72.7)	384 (59.8)	2,102 (51.7)
Pathology	462 (96.3)	1,759 (98.2)	1,128 (98.0)	637 (99.2)	3986 (98.1)
Laser therapy	244 (50.8)	1,451 (81.0)	995 (86.4)	634 (98.8)	3,324 (81.8)
Cryotherapy	157 (32.7)	1,243 (69.4)	939 (81.6)	634 (98.8)	2793 (73.2)
Enucleation	Available for all children				
Intravenous chemotherapy	462 (96.3)	1,787 (99.8)	1,124 (97.7)	641 (99.8)	4,014 (98.8)
Intra-ophthalmic artery chemotherapy	9 (1.9)	550 (30.7)	811 (70.5)	538 (83.8)	1908 (46.9)
Intravitreal chemotherapy	148 (30.8)	1,055 (58.9)	980 (85.1)	631 (98.3)	2,814 (69.2)
Plaque brachytherapy	5 (1.0)	410 (22.9)	231 (20.1)	483 (75.2)	1,129 (27.8)
External beam radiotherapy	194 (40.4)	1,403 (78.3)	793 (68.9)	524 (81.6)	2914 (71.7)

eTable 4. Primary and additional treatments given to 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017					
	National income level				
Treatment[a]	**Low** (n=474)	**Lower-middle** (n=1783)	**Upper-middle** (n=1148)	**High** (n=638)	**Total** (n=4043)
Primary treatment for patient No. (%)[b]					
Intravenous chemotherapy	276 (58.2)	880 (49.4)	502 (43.7)	279 (43.7)	1937 (47.9)
Intra-ophthalmic artery chemotherapy	0	17 (1.0)	181 (15.8)	106 (16.8)	304 (7.5)
Enucleation[c]	129 (27.2)	730 (40.9)	454 (39.5)	258 (40.4)	1571 (38.9)
Exenteration[c]	13 (2.7)	40 (2.2)	1 (0.1)	0	54 (1.3)
Focal laser or cryotherapy	18 (3.8)	110 (6.2)	39 (3.4)	54 (8.5)	221 (5.5)
Plaque brachytherapy	0	0	0	3 (0.5)	3 (0.1)
Vitrectomy	0	0	2 (0.2)	1 (0.2)	3 (0.1)
Palliative therapy	25 (5.3)	23 (1.3)	0	0	48 (1.2)
Observation	0	2 (0.1)	0	2 (0.3)	4 (0.1)
Primary treatment refusal	34 (7.2)	174 (9.8)	37 (3.2)	10 (1.6)	255 (6.3)
Additional treatments for patient No. (%)[d]					
Intravenous chemotherapy	160 (33.8)	634 (35.6)	392 (34.1)	125 (19.6)	1311 (32.4)
Intra-ophthalmic artery chemotherapy	2 (0.4)	45 (2.5)	226 (19.7)	148 (23.2)	421 (10.4)
Enucleation[b]	201 (42.2)	444 (24.9)	252 (22.0)	115 (18.0)	1012 (25.0)
Exenteration[b]	10 (2.1)	20 (1.1)	8 (0.7)	2 (0.3)	40 (1.0)
Focal laser or cryotherapy	52 (11.0)	303 (17.0)	346 (30.1)	294 (46.1)	995 (24.6)

Intravitreal chemotherapy	10 (2.1)	87 (4.9)	145 (12.6)	101 (15.8)	343 (8.5)
Teletherapy[e]	20 (4.2)	112 (6.3)	49 (4.3)	11 (1.7)	192 (4.7)
Plaque brachytherapy	0	22 (1.2)	34 (3.0)	52 (8.2)	108 (2.7)
Vitrectomy	0	14 (0.8)	21 (1.8)	5 (0.8)	40 (1.0)
Palliative therapy	2 (0.4)	16 (0.9)	0	0	18 (0.4)
Treatment refusal after primary treatment	27 (5.7)	88 (4.9)	38 (3.3)	2 (0.3)	155 (3.8)

[a]Per patient.

[b]First and main treatment. In case of combined enucleation/exenteration and chemotherapy, both were counted as primary treatment. In case of enucleation/exenteration/chemotherapy and other listed therapies, the other therapies were not counted as primary treatment.

[c]Primary and secondary enucleation and exenteration numbers do not match the total number in the text, because in this table patients who underwent bilateral surgery could be counted once or twice, depending on the clinical scenario, whereas in the text a patient who underwent enucleation in one or both eyes is counted once.

[d]Additiional treatment for tumor relapse or new tumors. Additional treatments not listed separately: intravitreal anti vascular endothelial growth factor antibody (n=5), cataract surgery (n=2), episcleral topotecan implant (n=1), intracameral chemotherapy (n=1), intrathecal chemotherapy (n=10), intraorbital chemotherapy (n=28), scleral buckle for retinal detachment (n=2), sphincterotomy (n=1), and sub-Tenon chemotherapy (n=6).

[e]External beam radiotherapy, proton beam radiotherapy, or gamma knife radiosurgery.

Survival rate by national income level and by clinical stage

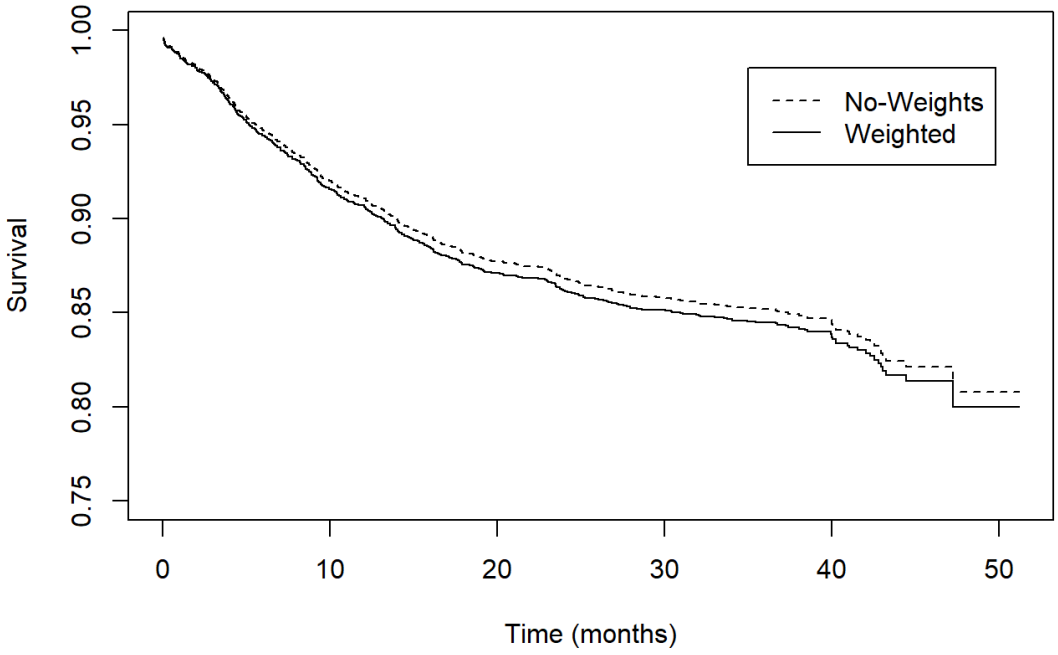
eTable 5. 1, 2, and 3-year survival rate by national income level and by clinical stage in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017.					
	Time (mo)	**Survival Rate (%)**	**SE (%)**	**Lower 95% CI**	**Upper 95% CI**
National Income Level					
Low	**12**	74.4	2.1	70.3	78.8
	24	62.5	2.5	57.8	67.6
	36	57.3	2.8	52.1	63.0
Lower middle	**12**	88.4	0.8	86.8	90.0
	24	82.8	1.0	80.9	84.7
	36	80.3	1.0	78.3	82.3
Upper middle	**12**	95.1	0.7	93.8	96.4
	24	91.9	0.8	90.3	93.6
	36	91.2	0.9	89.5	93.0
High	**12**	99.8	0.2	99.5	100.0
	24	99.7	0.2	99.2	100.0
	36	99.5	0.3	98.8	100.0
Clinical Stage					
cT1	**12**	97.7	0.9	95.9	99.6
	24	97.1	1.1	95.1	99.2
	36	94.4	0.7	93.0	95.8
cT2	**12**	97.6	0.5	96.7	98.5
	24	95.7	0.6	94.5	96.9
	36	94.4	0.7	93.0	95.8
cT3	**12**	95.3	0.5	94.4	96.3
	24	91.3	0.7	90.0	92.7
	36	90.5	0.7	89.1	91.9
cT4	**12**	55.0	2.2	50.8	59.6
	24	39.5	2.3	35.2	44.3
	36	31.9	2.4	27.6	36.9
Abbreviations: SE - Standard error, CI – confidence interval.					

Sensitivity analysis for survival

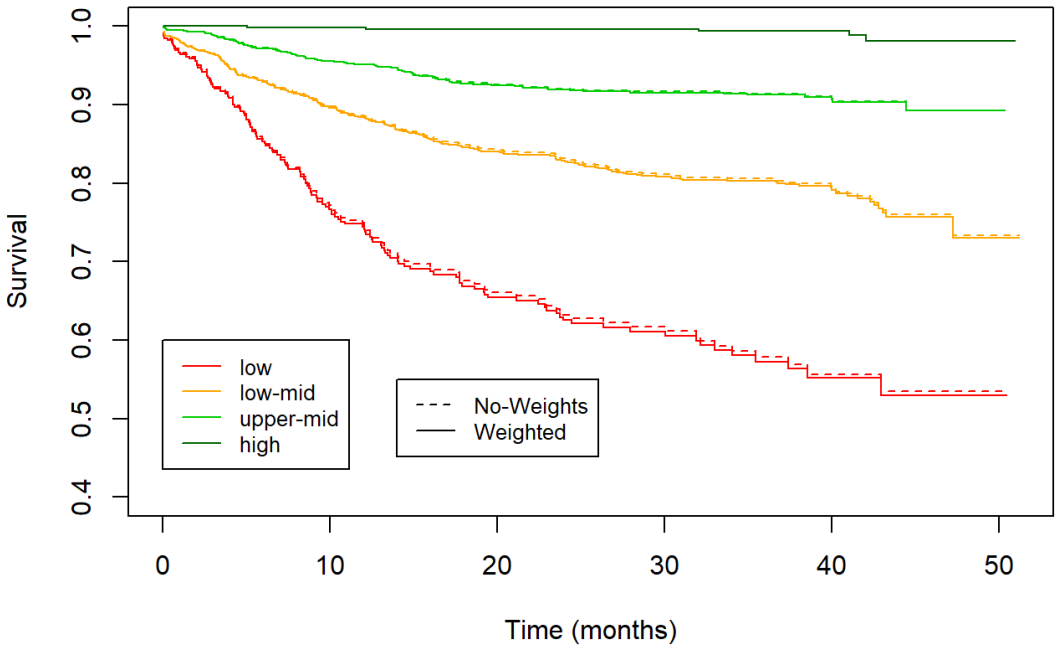
In these sensitivity analyses, we test the effect of weighting, test whether dropping patients with missing values of predictor variables, rather than imputing the missing values, is of significance, test the impact of extending the declaration of missing survival outcomes to participants with follow-up times of 1 month or less, and test whether the relationship of log hazard to age at diagnosis differs by hereditary status.

Weighted vs. no-weights

eFigure 3. Whole cohort survival analysis by Kaplan-Meier method: weighted vs. no-weights



eFigure 4. Survival Kaplan-Meier model by income group: weighted vs. no-weights



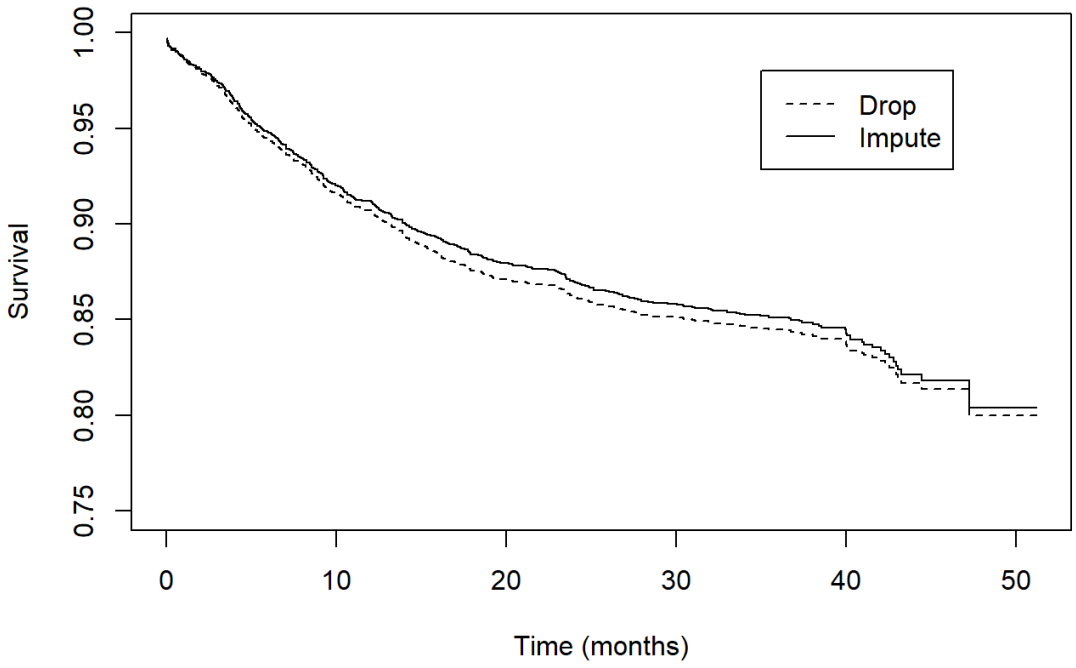
eTable 6. Non-weighted Cox proportional hazards model for survival in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a].

	Coefficient	Robust SE	Z value	P-value (corrected[b])	Hazard ratio	Lower 95% CI	Upper 95% CI
Country of residence income							
Low	Reference				1.00		
Lower-middle	-0.293	0.210	-1.395	0.16 (0.99)	0.75	0.49	1.13
Upper-middle	-0.603	0.263	-2.292	0.022 (0.29)	0.55	0.33	0.92
High	-2.787	0.654	-4.258	<0.001 (<0.001)	0.06	0.02	0.22
Age[c]							
Age HR/mo	0.027	0.006	4.862	<0.001 (<0.001)	1.03	1.02	1.04
Age>3yr HR/mo	-0.028	0.008	-3.281	0.001 (0.013)	0.97	0.96	0.99
Age>7yr HR/mo	-0.022	0.016	-1.367	0.17 (0.99)	0.98	0.95	1.01
Bilaterality							
Unilateral	Reference				1.00		
Bilateral	0.451	0.565	0.798	0.42 (0.99)	1.57	0.52	4.76
Primary tumor							
cT1	Reference				1.00		
cT2	0.080	0.293	0.274	0.78 (0.99)	1.08	0.61	1.9
cT3	0.174	0.335	0.520	0.60 (0.99)	1.19	0.62	2.2
cT4	2.236	0.364	6.149	<0.001 (<0.001)	9.35	4.59	19.07
Sex							
Male	Reference				1.00		
Female	0.126	0.078	1.611	0.11 (0.99)	1.13	0.97	1.32
Family history of retinoblastoma							
Yes	Reference				1.00		
No	0.170	0.334	0.509	0.61 (0.99)	1.19	0.62	2.28
Hereditary retinoblastoma							
Non-hereditary	Reference				1.00		
Hereditary[d]	-0.233	0.582	-0.400	0.69 (0.99)	0.79	0.25	2.48

[a]N=3564, number of events (i.e. death) = 484. 500 observations deleted due to missing observation time.
[b]Multiplied by 13, according to Bonferroni's model.
[c]Age included in the analysis as a continuous parameter. The relation of log hazard to age at diagnosis is estimated by three coefficients, which point to increasing hazard through age 3, then stable hazard until age 7, and then decreasing hazard at older ages. For further details, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.
[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).
Abbreviations: SE - Standard error, CI – confidence interval, yr – years, mo – months.

Impute vs. drop missing x values

eFigure 5. Whole cohort survival analysis by Kaplan-Meier model: impute vs. delete cases with missing predictors



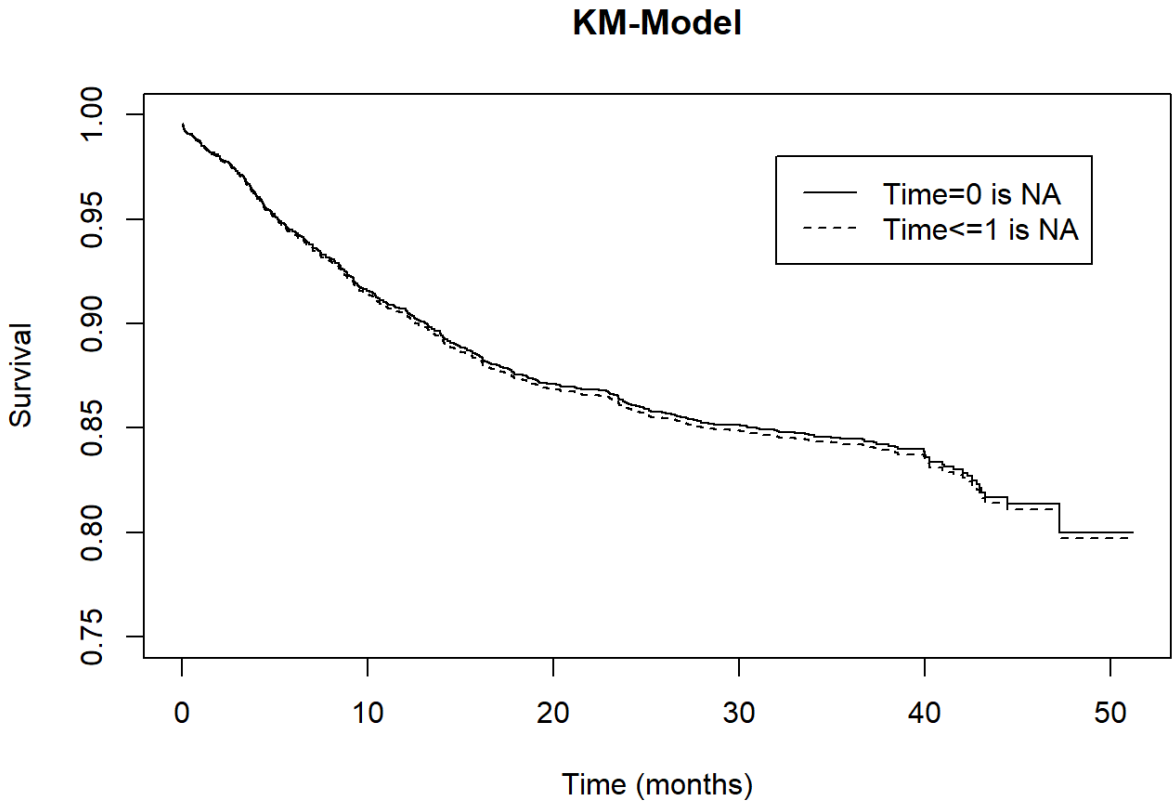
eTable 7. Weighted Cox proportional hazard model for survival in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a]: d**ropped missing x.**							
	Coefficient	**Robust SE**	**Z value**	**P-value (corrected**[b]**)**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**
Country of residence income							
Low	reference				1.00		
Lower-middle	-0.264	0.223	-1.183	0.24 (0.99)	0.77	0.50	1.19
Upper-middle	-0.462	0.284	-1.625	0.10 (0.99)	0.63	0.36	1.10
High	-2.671	0.661	-4.042	<0.001 (<0.001)	0.07	0.02	0.25
Age[c]							
Age HR/mo	0.026	0.006	4.445	<0.001 (<0.001)	1.03	1.01	1.04
Age>3yr HR/mo	-0.027	0.009	-3.011	0.003 (0.034)	0.97	0.96	0.99
Age>7yr HR/mo	-0.021	0.018	-1.221	0.22 (0.99)	0.98	0.95	1.01
Bilaterality							
Unilateral	reference				1.00		
Bilateral	0.302	0.549	0.550	0.58 (0.99)	1.35	0.46	3.97
Primary tumor							
cT1	reference				1.00		
cT2	0.120	0.300	0.402	0.69 (0.99)	1.13	0.63	2.03
cT3	0.206	0.363	0.568	0.57 (0.99)	1.23	0.60	2.50
cT4	2.344	0.404	5.796	<0.001 (<0.001)	10.43	4.72	23.04
Sex							
Male	reference				1.00		
Female	0.126	0.086	1.466	0.14 (0.99)	1.13	0.96	1.34
Family history of retinoblastoma							
Yes	reference				1.00		
No	0.233	0.324	0.720	0.47 (0.99)	1.26	0.67	2.80

Hereditary retinoblastoma							
Non-hereditary	Reference				1.00		
Hereditary[d]	-0.072	0.562	-0.127	0.90 (0.99)	0.93	0.31	2.80

[a]N=3303, number of events (i.e. death) = 438. 404 observations deleted due to missing observation time.
[b]Multiplied by 13, according to Bonferroni's model.
[c]Age included in the analysis as a continuous parameter. The relation of log hazard to age at diagnosis is estimated by three coefficients, which point to increasing hazard through age 3, then stable hazard until age 7, and then decreasing hazard at older ages. For examples, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.
[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).
Abbreviations: SE - Standard error, CI – confidence interval, yr – years, mo – months.

Treating no-death with last follow-up≤1 month as missing

eFigure 6. Whole cohort survival analysis by Kaplan-Meier model: time=0 vs. time≤1 month as no follow-up (NA)



eTable 8. Weighted Cox proportional hazard model for survival in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a]: time≤1 month treated as no follow-up.							
	Coefficient	**Robust SE**	**Z value**	**P-value (corrected[b])**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**
Country of residence income							
Low	reference				1.00		
Lower-middle	-0.304	0.208	-1.466	0.14 (0.99)	0.74	0.49	1.11
Upper-middle	-0.629	0.260	-2.418	0.016 (0.20)	0.53	0.32	0.89
High	-2.825	0.651	-4.339	<0.001 (<0.001)	0.06	0.02	0.21

Age[c]							
Age HR/mo	0.027	0.005	4.947	<0.001 (<0.001)	1.03	1.02	1.04
Age>3yr HR/mo	-0.028	0.008	-3.379	0<0.001 (0.009)	0.97	0.96	0.99
Age>7yr HR/mo	-0.020	0.015	-1.290	0.197 (0.99)	0.98	0.95	1.01
Bilaterality							
Unilateral	reference				1.00		
Bilateral	0.427	0.572	0.747	0.455 (0.99)	1.53	0.50	4.70
Primary tumor							
cT1	reference				1.00		
cT2	0.073	0.294	0.248	0.80 (0.99)	1.08	0.60	1.91
cT3	0.183	0.335	0.545	0.59 (0.99)	1.20	0.62	2.31
cT4	2.200	0.359	6.120	<0.001 (<0.001)	9.02	4.46	18.25
Sex							
Male	reference				1.00		
Female	0.126	0.077	1.639	0.10 (0.99)	1.13	0.98	1.32
Family history of retinoblastoma							
Yes	reference				1.00		
No	0.188	0.337	0.558	0.58 (0.99)	1.21	0.62	2.34
Hereditary retinoblastoma							
Non-hereditary	Reference				1.00		
Hereditary[d]	-0.234	0.590	-0.396	0.69 (0.99)	0.79	0.25	2.51

[a]N=3465, number of events (i.e. death) = 484. 599 observations deleted due to missing observation time.
[b]Multiplied by 13, according to Bonferroni's model.
[c]Age included in the analysis as a continuous parameter. The relation of log hazard to age at diagnosis is estimated by three coefficients, which point to increasing hazard through age 3, then stable hazard until age 7, and then decreasing hazard at older ages. For examples, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.
[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).
Abbreviations: SE - Standard error, CI – confidence interval, yr – years, mo – months.

Analysis of age at diagnosis by hereditary status

eTable 9. Weighted Cox proportional hazard model for survival in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a]: relation of hazard to age dependent on hereditary status.

	Coefficient	**Robust SE**	**Z value**	**P-value (corrected[b])**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**
Country of residence income							
Low	reference				1.00		
Lower-middle	-0.300	0.209	-1.431	0.15 (0.99)	0.74	0.49	1.12
Upper-middle	-0.633	0.261	-2.421	0.015 (0.20)	0.53	0.32	0.89
High	-2.830	0.652	-4.340	<0.001 (<0.001)	0.06	0.02	0.21
Age[c]							
Age HR/mo	0.030	0.006	4.610	<0.001 (<0.001)	1.03	1.02	1.04
Age>3yr HR/mo	-0.030	0.009	-3.480	<0.001 (0.007)	0.97	0.95	0.99
Age>7yr HR/mo	-0.020	0.015	-1.375	0.17 (0.99)	0.98	0.95	1.01
Bilaterality							
Unilateral	reference				1.00		
Bilateral	0.406	0.569	0.713	0.48 (0.99)	1.50	0.49	4.58
Primary tumor							

cT1	reference				1.00		
cT2	0.061	0.297	0.206	0.84 (0.99)	1.06	0.59	1.90
cT3	0.167	0.336	0.496	0.62 (0.99)	1.18	0.61	2.28
cT4	2.180	0.360	6.063	<0.001 (<0.001)	8.85	4.37	17.90
Sex							
Male	reference				1.00		
Female	0.132	0.077	1.702	0.09 (0.99)	1.14	0.98	1.33
Family history of retinoblastoma							
Yes	reference				1.00		
No	0.213	0.338	0.629	0.53 (0.99)	1.24	0.64	2.40
Hereditary retinoblastoma							
Non-hereditary	Reference				1.00		
Hereditary[d]	-0.064	0.628	-0.102	0.92 (0.99)	0.94	0.27	3.21
Age – hereditary interaction[e]							
Age:hereditary	-0.003	0.010	-0.332	0.74 (0.99)	1.00	0.98	1.02
Age>3yr:hereditary	-0.014	0.020	-0.694	0.49 (0.99)	0.99	0.95	1.03

[a]N=3564, number of events (i.e. death) = 484. 500 observations deleted due to missing observation time.
[b]Multiplied by 13, according to Bonferroni's model.
[c]Age included in the analysis as a continuous parameter. The relation of log hazard to age at diagnosis is estimated by three coefficients, which point to increasing hazard through age 3, then stable hazard until age 7, and then decreasing hazard at older ages. For examples, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.
[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).
[e]Estimation of the difference between hereditary and non-hereditary patients in the relation of log hazard to age. Age>7 years not shown because there were only few patients in this age category.
Abbreviations: SE - Standard error, CI – confidence interval, yr – years, mo – months.

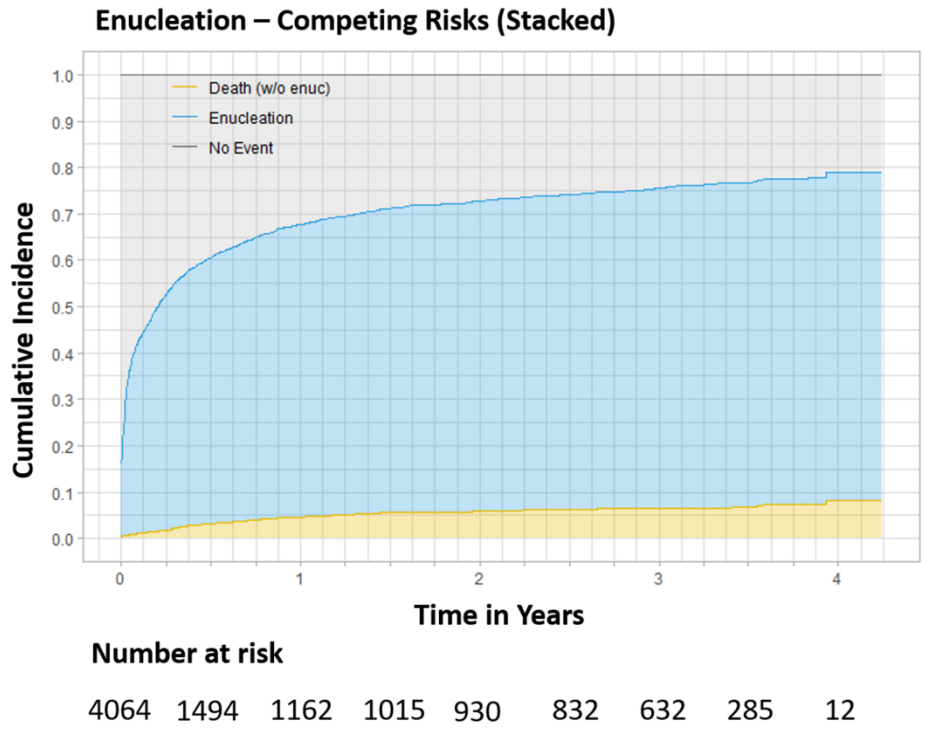
Survival - Multisample Imputation – Death

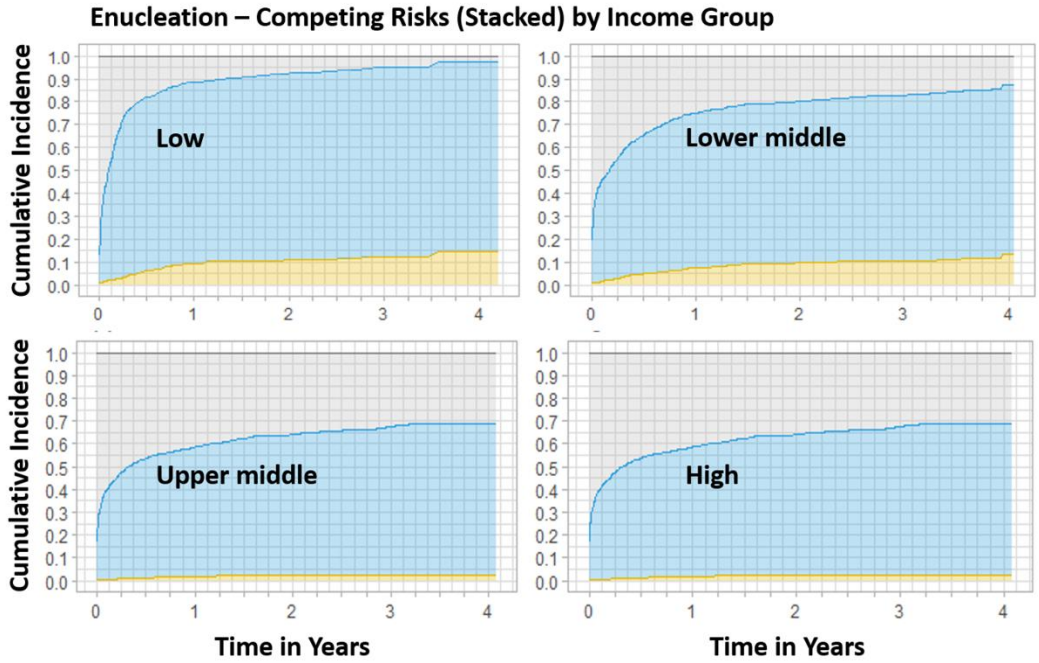
eTable 10. Multisample imputation for survival in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017.

Parameter		**Estimated coefficients**	**Standard errors**
Age	Age	0.026	0.006
	Age>3yr	-0.026	0.009
	Age>7yr	-0.023	0.016
Country of residence income	Lower-middle	-0.313	0.205
	Upper-middle	-0.674	0.269
	High	-2.853	0.651
Laterality	Bilateral	0.503	0.561
Primary tumor	cT2	0.036	0.322
	cT3	0.096	0.345
	cT4	2.115	0.361
Sex	Female	0.127	0.078
Family history of retinoblastoma	Yes	0.118	0.337
Hereditary retinoblastoma	Yes	-0.305	0.581

Globe Salvage Analysis by Competing Risks

eFigure 7. Globe salvage analysis by competing risks.



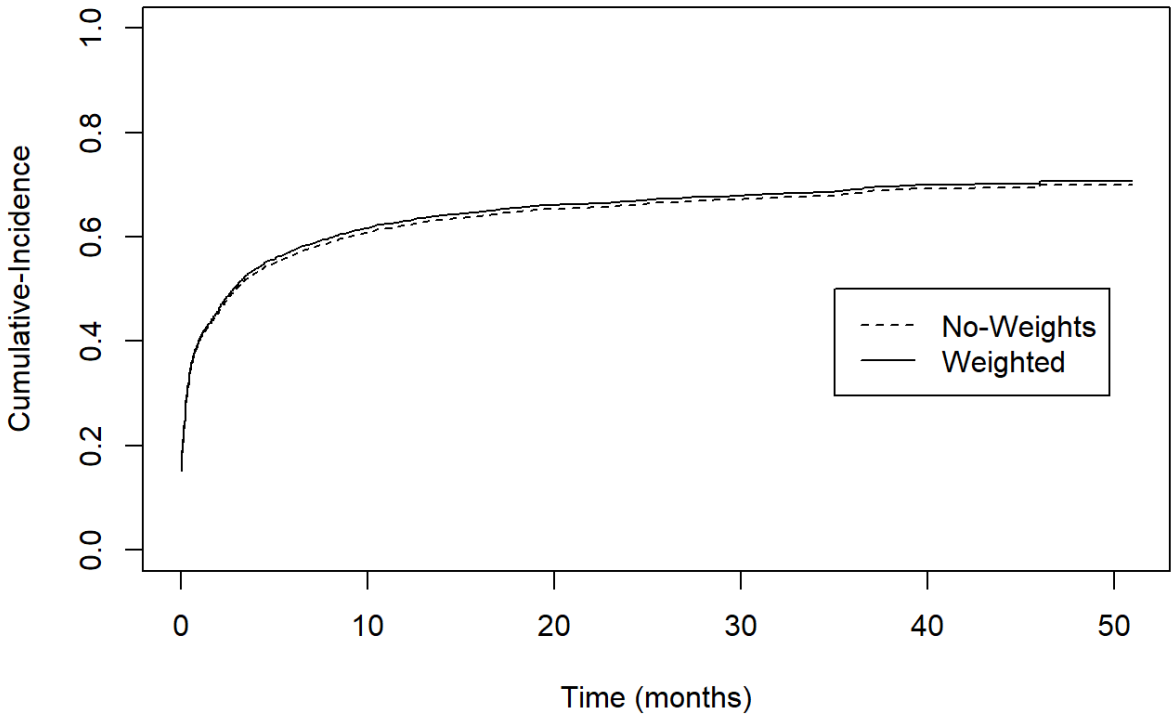


Upper panel: Competing risks plot (stacked), whole cohort analysis. **Lower panel**: Competing risks plot (stacked) by income group.

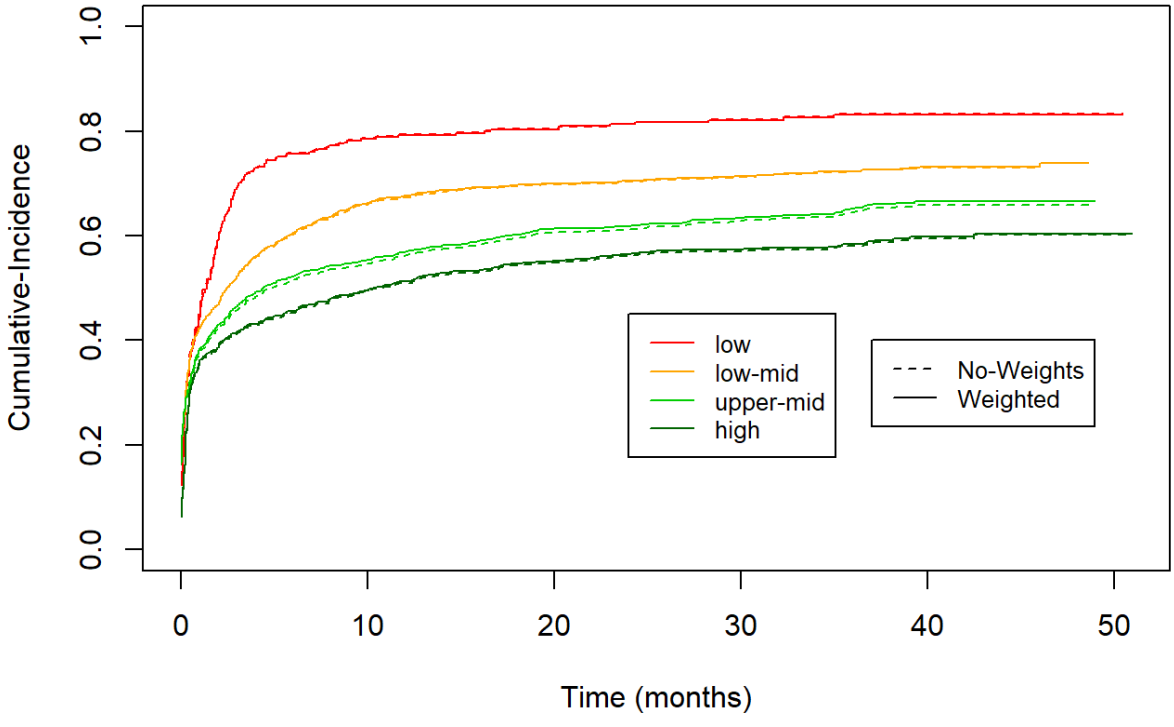
Sensitivity Analysis for Globe Salvage

In these sensitivity analyses, we test the weighting effect, and test whether dropping patients with missing values of predictor variables, rather than imputing the missing values, is of significance.

eFigure 8. Competing risks for globe salvage, whole cohort analysis: weighted vs. no-weights



eFigure 9. Competing risks for globe salvage by income group: weighted vs. no-weights



eTable 11. Non-weighted Cox proportional hazard model for globe salvage in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a].

	Coefficient	Robust SE	Z value	P-value[b]	Hazard ratio	Lower 95% CI	Upper 95% CI
Country of residence income							
Low	Reference				1.00		
Lower-middle	-0.171	0.117	-1.462	0.14 (0.99)	0.84	0.67	1.06
Upper-middle	-0.356	0.204	-1.744	0.08 (0.99)	0.70	0.47	1.05
High	-0.161	0.168	-0.959	0.34 (0.99)	0.85	0.61	1.18
Age[c]							
Age HR/mo	0.007	0.002	3.466	<0.001 (0.007)	1.01	1.00	1.01
Age>4yr HR/mo	-0.013	0.003	-3.796	<0.001 (0.002)	0.99	0.98	0.99
Bilaterality							
Unilateral	Reference				1.00		
Bilateral	-0.471	0.140	-3.370	<0.001 (0.001)	0.62	0.47	0.82
Primary tumor							
cT1	Reference				1.00		
cT2	1.067	0.218	4.883	<0.001 (<0.001)	2.91	1.89	4.46
cT3	2.079	0.243	8.546	<0.001 (<0.001)	8.00	4.96	12.88
cT4	1.562	0.310	5.042	<0.001 (<0.001)	4.77	2.60	8.75
Sex							
Male	Reference				1.00		
Female	0.074	0.058	1.282	0.20 (0.99)	1.08	0.96	1.21
Family history of retinoblastoma							
Yes	Reference				1.00		
No	0.322	0.175	1.839	0.07 (0.99)	1.38	0.98	1.94
Hereditary retinoblastoma							
Non-hereditary	Reference				1.0		
Hereditary[d]	-0.078	0.117	-0.663	0.51 (0.99)	0.93	0.74	1.16

[a]N=3267, number of events (i.e. enucleation) = 2177. 797 observations deleted due to missing observation time. Per patient, enucleation or exenteraion, primary or secondary, one or both eyes.

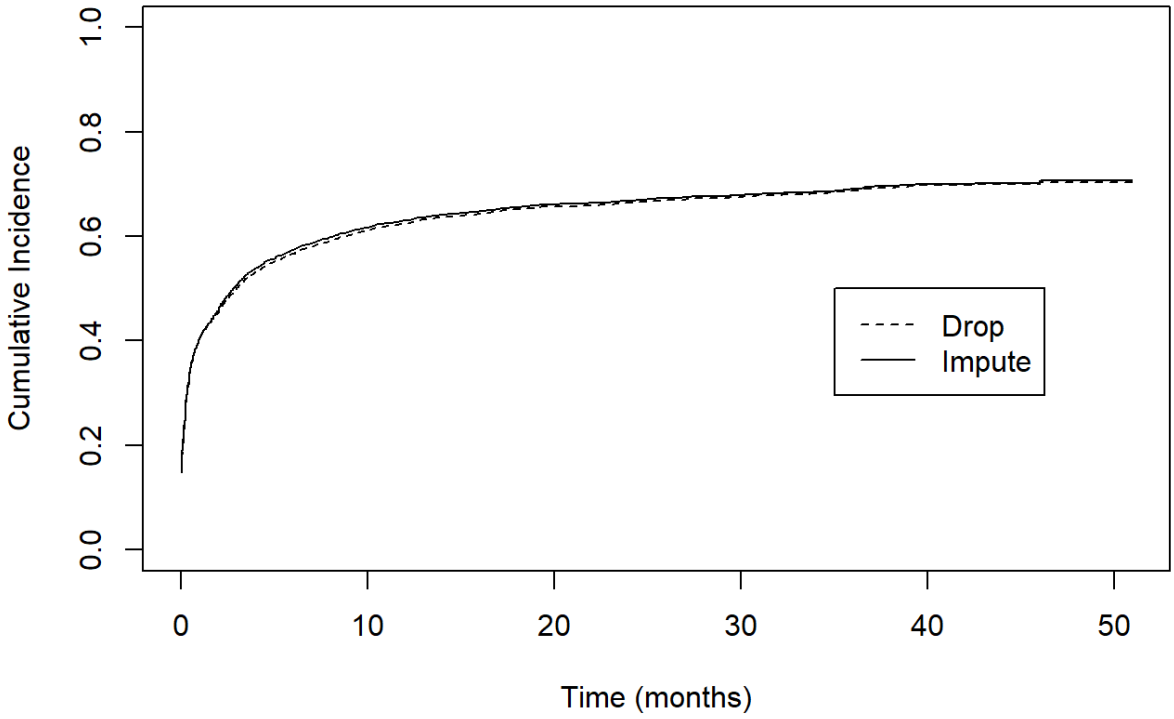
[b]Multiplied by 13, according to Bonferroni's model.

[c]Age included in the analysis as a continuous parameter. For further details on the relationship between age and log hazard for both survival and globe salvage, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.

[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).

Abbreviations: SE - Standard error, CI – confidence interval, mo – months, yr – years.

eFigure 10. Competing risks for globe salvage: impute vs. delete cases with missing predictors



eTable 12. Weighted Cox proportional hazard model for globe salvage in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017[a]: **dropped missing x.**

	Coefficient	Robust SE	Z value	P-value[b]	Hazard ratio	Lower 95% CI	Upper 95% CI
Country of residence income							
Low	Reference				1.00		
Lower-middle	-0.169	0.127	-1.332	0.18 (0.99)	0.84	0.66	1.08
Upper-middle	-0.292	0.229	-1.273	0.20 (0.99)	0.75	0.48	1.17
High	-0.130	0.173	-0.749	0.45 (0.99)	0.88	0.63	1.23
Age[c]							
Age HR/mo	0.007	0.002	3.108	0.002 (0.025)	1.01	1.00	1.01
Age>4yr HR/mo	-0.013	0.004	-3.528	<0.001 (0.005)	0.99	0.98	0.99
Bilaterality							
Unilateral	Reference				1.00		
Bilateral	-0.528	0.143	-3.695	<0.001 (0.003)	0.59	0.45	0.78
Primary tumor							
cT1	Reference				1.00		
cT2	1.149	0.225	5.100	<0.001 (<0.001)	3.16	2.03	4.91
cT3	2.239	0.246	9.105	<0.001 (<0.001)	9.38	5.79	15.19
cT4	1.688	0.320	5.274	<0.001 (<0.001)	5.41	2.89	10.12
Sex							
Male	Reference				1.00		
Female	0.051	0.053	0.976	0.329 (0.99)	1.05	0.95	1.17
Family history of retinoblastoma							
Yes	Reference				1.00		
No	0.212	0.154	1.376	0.17 (0.99)	1.24	0.91	1.67
Hereditary retinoblastoma							
Non-hereditary	Reference				1.00		
Hereditary[d]	-0.037	0.118	-0.316	0.75 (0.99)	0.96	0.76	1.21

[a]N=3051, number of events (i.e. enucleation) = 2027. 656 observations deleted due to missing observation time. Per patient, enucleation or exenteraion, primary or secondary, one or both eyes.
[b]P-values are presented before correction by Bonferroni's model.
[c]Age included in the analysis as a continuous parameter. For further details on the relationship between age and log hazard for both survival and globe salvage, see "Relationship between age at time of diagnosis and log hazard" in the **Supplement**.
[d]Hereditary - bilateral/trilateral retinoblastoma, positive family history or positive blood *RB1* mutation (H1 in cTNMH).
Abbreviations: SE - Standard error, CI – confidence interval, mo – months, yr – years.

Survival - Multisample Imputation - Enucleation

eTable 13. Multisample imputation for globe salvage in 4064 new patients with retinoblastoma diagnosed in 149 countries in 2017.

Parameter		**Estimated coefficients**	**Standard errors**
Age	Age	0.007	0.002
	Age>4yr	-0.012	0.004
Country of residence income	Lower-middle	-0.172	0.118
	Upper-middle	-0.295	0.200
	High	-0.183	0.172
Laterality	Bilateral	-0.442	0.153
Primary tumor	cT2	0.963	0.227
	cT3	1.950	0.262
	cT4	1.437	0.319
Sex	Female	0.068	0.058
Family history of retinoblastoma	Yes	0.268	0.171
Hereditary retinoblastoma	Yes	-0.112	0.133