

Vision-Targeted Health-Related Quality of Life in Adult Survivors of Retinoblastoma

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 Supplemental content

IMPORTANCE Retinoblastoma survivors are at risk for adverse oculo-visual outcomes. Limited data are available regarding long-term vision-targeted health-related quality of life (HRQoL) of adult retinoblastoma survivors.

OBJECTIVE To examine vision-targeted HRQoL as reported on the 25-item National Eye Institute Visual Field Questionnaire for overall and specific scale scores among adult survivors of retinoblastoma.

DESIGN, SETTING, AND PARTICIPANTS The Retinoblastoma Survivor Study is a retrospective cohort of adult retinoblastoma survivors treated at 3 academic medical centers in New York between 1932 and 1994. Participants completed a comprehensive questionnaire between April 2008 and June 2010. Items were scored in January 2013 and preliminary analyses were performed in July 2015. Models were finalized in May 2017.

MAIN OUTCOMES AND MEASURES Self-reported vision-targeted HRQoL as reported on the 25-item National Eye Institute Visual Field Questionnaire. Items are scored from 0 to 100, with 100 representing the highest quality of life.

RESULTS Among 470 adult retinoblastoma survivors (53.6% with bilateral disease; 52.1% female; 86.4% white and non-Hispanic; mean age at study, 43.3 years; range, 18.0-77.0 years), 86% had at least 1 eye removed (1 eye, 74.5%; both eyes, 11.5%); 56.5% were previously treated with radiotherapy; and 61.3% rated their eyesight as excellent/good while 16.2% reported complete blindness. The overall mean (SD) VFQ composite score for all survivors was 81.1 (17.2) (mean [SD] score for unilateral retinoblastoma survivors, 91.4 [7.7]; bilateral retinoblastoma survivors, 72.3 [18.2]; difference between survivors with unilateral and bilateral disease, 19.1 [95% CI, 16.5-21.7; $P < .001$]). Prior exposure to radiotherapy was not associated with decreased overall VFQ ($\beta = -0.08$; 95% CI, -0.15 to 0.002 ; $P = .06$) but was related to a few specific subdomains of visual functioning.

CONCLUSIONS AND RELEVANCE These findings suggest retinoblastoma-related oculo-visual problems are associated with functional status and vision-targeted HRQoL of adult survivors, particularly among those with bilateral disease.

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Retinoblastoma is the most common intraocular malignancy of childhood, with survival rates exceeding 95% in developed countries.¹ Despite these excellent survival rates, treatment paradigms continue to shift in an effort to maximize ocular salvage and vision preservation, which are thought to positively affect long-term quality of life. Work has begun to clarify the long-term medical, cognitive, and psychosocial functioning of adult retinoblastoma survivors,²⁻⁵ but data are lacking on how visual dysfunction affects vision-targeted health-related quality of life (HRQoL) in a large cohort of long-term survivors in the United States.

The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)⁶ is a validated tool used to evaluate vision-related HRQoL in adults with chronic ocular problems.⁷⁻⁹ This study uses the NEI-VFQ-25 to examine the association of retinoblastoma therapy with vision-targeted HRQoL among 470 adult retinoblastoma survivors.

Methods

Participants

The Retinoblastoma Survivor Study is a cross-sectional, self-report study of adult retinoblastoma survivors; these methods have been previously described.^{2,3} Briefly, eligible participants were individuals 18 years or older who were previously treated for retinoblastoma in the New York, New York, area. Interested participants provided written consent and then completed surveys by mail or telephone between April 2008 and June 2010. Items were scored in January 2013 and preliminary analyses were performed in July 2015. Models were finalized in May 2017. The study was approved by the National Cancer Institute and Memorial Sloan Kettering institutional review boards.

Among 987 identified retinoblastoma survivors, we were unable to locate or contact 290 survivors (29.3%). An additional 46 patients were found to be ineligible. Of the remaining 651 patients, 470 consented and completed the survey; 72.2% of those who were contacted and found to be eligible participated (eFigure in the Supplement).

Survey

Participants completed a comprehensive survey, adapted from the Childhood Cancer Survivor Study questionnaires¹⁰ and supplemented with items from the NEI-VFQ-25,⁶ a validated tool developed by RAND and funded by the National Eye Institute that includes 25 questions measuring self-reported vision-targeted HRQoL on 11 subscales (general vision, difficulty with near vision activities, difficulty with distance vision activities, ocular pain, limitations in social functioning owing to vision, role limitations owing to vision, dependency on others owing to vision, mental health symptoms owing to vision, driving difficulties, limitations with peripheral vision, and color vision) as well as 1 question that assesses the respondent's general health. An overall composite score is calculated by averaging all subscale scores, with the exception of

Key Points

Question How is treatment of retinoblastoma associated with patient-reported vision-focused health-related quality of life during adulthood?

Findings In this cohort study, oculo-visual problems were associated with patient-reported vision-targeted health-related quality of life in adult retinoblastoma survivors, particularly among those with a history of bilateral disease or enucleation. Despite deficits in a few specific domains, overall patient-reported vision-focused HRQoL was largely preserved in this cohort treated for eye tumors at a very young age.

Meaning This study supports the need for continued development of vision-preserving and eye-sparing procedures in the treatment of retinoblastoma, when possible, and suggests long-term survivors should be assessed for specific areas of need to strive for optimization of supportive services.

the general health question. Both the composite and subscale scores range from 0 to 100, where higher scores indicate better quality of life. A copy of the survey is available on request.

Treatment History

Treatment history was abstracted from the National Cancer Institute and Memorial Sloan Kettering databases. Treatment with chemotherapy or radiotherapy was categorized as a yes/no/unknown variable; type of radiotherapy (brachytherapy, external beam radiotherapy, or both) was abstracted as well. All treatment data refer to therapy administered for primary or metastatic retinoblastoma.

Statistical Analysis

Sociodemographic characteristics, treatment modalities, and vision-targeted HRQoL scores by disease laterality were summarized using frequency/percentage for categorical covariates and mean/standard deviation for continuous covariates and were compared using Fisher exact test and the Wilcoxon rank sum test. Overall vision-targeted HRQoL was scored using the NEI-VFQ-25. A linear regression model was used to examine the association between the natural logarithm transformation of the dependent variable (overall VFQ) and the independent variables of interest. Unstandardized β coefficients, which represent the change in the predicted value of the outcome log (overall VFQ) for each 1-unit change in the independent variable of interest, and 95% confidence intervals were reported. A multivariable linear regression model was constructed, which included factors associated with overall VFQ at the P less than .20 level. To evaluate whether radiation modified the association between overall VFQ and disease laterality, we included an interaction term in a separate model. All P values were based on 2-tailed statistical analysis, and P less than .05 indicated significance. Analyses were performed using SAS, version 9.3 (SAS Institute) and R, version 3.3.1 (R Programming).

Results

Participant Characteristics

Table 1 outlines participant demographic and treatment characteristics. Among 470 retinoblastoma survivors (53.6% with bilateral disease) included in the study, 350 (74.5%) had undergone unilateral enucleation, and 54 had bilateral enucleations. When asked about other ocular conditions, 53 (11.5%) reported that they had cataracts (n = 45 with bilateral disease and n = 8 with unilateral disease); 11 (2.4%) reported glaucoma (n = 7 with bilateral disease and n = 4 with unilateral disease); and 5 reported diplopia (n = 3 with bilateral disease and n = 2 with unilateral disease). Sixty-one percent of patients (n = 281) rated their eyesight as excellent/good while 16.2% reported complete blindness (n = 76). Survivors of bilateral disease were more likely than survivors of unilateral disease to have been exposed to radiotherapy (231 [91.7%] of those with bilateral disease vs 34 [15.7%] of those with unilateral disease) and/or chemotherapy (94 [37.3%] of those with bilateral disease vs 25 [11.5%] of those with unilateral disease).

Vision-Targeted HRQoL Among Survivors

Among all survivors, the mean (SD) NEI-VFQ-25 overall score was 81.1 (17.2), with significant differences noted by visual status (mean [SD], 63.1 [12.2] for those with complete blindness vs 84.6 [15.8] for those with excellent, good, or poor eyesight; $P < .001$) and by laterality (mean [SD], 91.4 [7.7] for those with unilateral disease vs 73.2 [18.2] for those with bilateral disease; $P < .001$). Breakdown of subcategories within the NEI-VFQ-25 showed significant differences by laterality for all subscales including general health, general vision, near and distance activities, driving, peripheral vision, color vision, role difficulties, dependency, social functioning, mental health, and ocular pain (**Table 2**).

Effect of Radiation Exposure on Vision-Targeted HRQoL

Overall VFQ score for survivors of either bilateral or unilateral disease did not differ by prior radiotherapy exposure. However, radiotherapy exposure was associated with inferior scores on select subscales (eTable in the [Supplement](#)). Survivors of unilateral disease exposed to radiotherapy had lower mean (SD) scores on the peripheral vision subscale (72.1 [25.9] vs 81.7 [21.2]; $P = .03$) and the dependency subscale (95.3 [9.8] vs 97.9 [9.2]; $P = .01$). Survivors of bilateral disease exposed to radiotherapy had significantly lower mean scores than those without radiotherapy exposure on the near vision subscale (70.4 [25.7] vs 90.7 [16.1]; $P = .001$).

Factors Associated With Overall Vision-Targeted HRQoL

Table 3 summarizes results of the univariate and multivariable analyses. The multivariable analyses indicated that a history of bilateral disease ($\beta = -.16$) and enucleation ($\beta = -.20$ for those with bilateral enucleations and $\beta = -.08$ for those with unilateral enucleation; $P = .002$) were associated with inferior overall vision-targeted HRQoL. Lower level of attained education was not significant ($\beta = -.06$ for completion of high

Table 1. Demographic and Treatment Characteristics of 470 Adult Retinoblastoma Survivors

Characteristic	No. (%)	
	Unilateral Survivors (n = 218)	Bilateral Survivors (n = 252)
Age at study, y		
Mean (SD)	44.4 (11.0)	42.5 (10.8)
Range	19-77	18-69
Sex		
Male	98 (44.9)	127 (50.4)
Female	120 (55.1)	125 (49.6)
Race/ethnicity		
White, non-Hispanic	185 (84.9)	221 (87.7)
Other group	32 (14.7)	30 (11.9)
Do not know/missing	1 (0.4)	1 (0.4)
Health insurance		
Yes or Canadian resident	188 (86.4)	227 (90.5)
No	24 (11.1)	20 (8.0)
Do not know/missing	1 (0.5)	1 (0.4)
Household salary, \$		
<20 000/y	13 (6.5)	32 (13.5)
≥20 000/y	187 (93.5)	205 (86.5)
Do not know/missing	18 (8.3)	15 (5.9)
Education		
Complete high school or less	28 (13.1)	36 (14.5)
High school graduate or some college training	185 (86.5)	209 (83.5)
Missing	5 (2.3)	7 (2.7)
Radiation therapy		
Yes	34 (15.7)	231 (91.7)
No	180 (83.0)	20 (7.9)
Unknown	3 (1.3)	1 (0.4)
Chemotherapy		
Yes	25 (11.5)	94 (37.3)
No	190 (87.6)	157 (62.3)
Unknown	2 (0.9)	1 (0.4)
Surgery		
Unilateral enucleation	190 (87.2)	160 (63.5)
Bilateral enucleation	0 (0.0)	54 (24.1)
None	21 (9.6)	33 (13.1)
Unknown	7 (3.2)	5 (2.0)

school or less; $P = .05$) in predicting inferior overall vision-targeted HRQoL.

Discussion

To our knowledge, this is the first report to use a vision-specific HRQoL questionnaire to assess vision-targeted HRQoL in a large cohort of adult retinoblastoma survivors. In this study, we demonstrate that retinoblastoma-related oculo-visual problems are associated with survivors' functional status in adulthood, particularly among those with bilateral disease.

Prior reports on HRQoL in retinoblastoma survivors, which have largely used general HRQoL questionnaires in children

Table 2. Vision-Targeted HRQoL in Adult Retinoblastoma Survivors, Overall and by Laterality, as Reported on the NEI-VFQ-25

NEI-VFQ-25	Mean (SD)		Difference Between Unilateral and Bilateral Survivors (95% CI)	P Value
	Unilateral Survivors (n = 218)	Bilateral Survivors (n = 252)		
Overall VFQ score	91.4 (7.7)	72.3 (18.2)	19.1 (16.5-21.7)	<.001
Subscale score				
General health	78.1 (20.4)	69.0 (22.9)	9.1 (5.2-13.2)	<.001
General vision	84.3 (14.4)	46.1 (22.9)	38.2 (33.0-43.4)	<.001
Near vision	94.5 (10.5)	72.1 (25.6)	22.4 (18.7-26.1)	<.001
Distant vision	94.3 (10.4)	70.9 (25.2)	23.3 (19.7-27.0)	<.001
Driving	89.6 (13.0)	81.3 (19.8)	8.3 (4.6-11.8)	<.001
Peripheral vision	80.1 (22.5)	59.0 (32.8)	21.1 (15.8-26.5)	<.001
Color vision	99.2 (5.1)	87.0 (23.8)	12.2 (8.9-15.1)	<.001
Ocular pain	90.3 (13.1)	84.0 (19.5)	6.3 (3.2-9.4)	.002
Role difficulty	91.1 (18.2)	75.9 (25.8)	15.2 (11.1-19.3)	<.001
Dependency	97.5 (9.3)	81.6 (22.8)	15.9 (12.7-19.2)	<.001
Social functioning	96.9 (8.7)	80.0 (24.5)	16.9 (13.2-20.2)	<.001
Mental health	88.2 (14.1)	75.0 (23.1)	13.2 (9.9-17.0)	<.001

Abbreviations: HRQoL, health-related quality of life; NEI-VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire.

Table 3. Risk Factor Analysis for Overall Vision-Targeted HRQoL in 470 Adult Survivors of Retinoblastoma as Measured by the NEI-VFQ-25^a

Characteristic	Univariate Analysis		Multivariable Analysis	
	β (95% CI)	P Value	β (95% CI)	P value
Age at study, per 10-y increase in age	-0.02 (-0.04 to 0.006)	.15	-0.01 (-0.03 to 0.01)	.43
Race/ethnicity, minorities vs white/non-Hispanic	0.04 (-0.03 to 0.12)	.24	NA	NA
Sex, male vs female	-0.02 (-0.07 to 0.04)	.54	NA	NA
Laterality, bilateral disease vs unilateral disease	-0.27 (-0.32 to -0.22)	<.001	-0.16 (-0.24 to -0.08)	<.001
Radiation exposure, yes vs no	-0.24 (-0.28 to -0.18)	<.001	-0.08 (-0.15 to 0.002)	.06
Chemotherapy, yes vs no	-0.17 (-0.23 to -0.11)	<.001	-0.05 (-0.11 to 0.009)	.10
Enucleation				
Bilateral vs none	-0.31 (-0.41 to -0.19)		-0.20 (-0.31 to -0.08)	
Unilateral vs none	-0.03 (-0.11 to 0.04)	<.001	-0.08 (-0.15 to 0.001)	.002
Any severe or life-threatening chronic medical condition, yes vs no	-0.13 (-0.20 to -0.05)	<.001	-0.03 (-0.10 to 0.04)	.39
Insurance status, yes vs no	0.04 (-0.05 to 0.12)	.49	NA	NA
Highest level of education, graduated high school with some college training vs high school or less	0.08 (-0.002 to 0.15)	.06	0.06 (0.0 to 0.14)	.05

Abbreviations: HRQoL, health-related quality of life; NA, not applicable; NEI-VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire.

^a A linear regression model was used to examine the association between the natural logarithm transformation of the dependent variable, log (overall VFQ), and the independent variables of interest. β, the regression coefficient,

represents the change in the predicted value of the outcome for each 1-unit change in the continuous or categorical independent variable of interest. Items with P > .20 in univariate analysis were not included in the multivariate model and are indicated by NA in the table.

or adolescent retinoblastoma survivors, have demonstrated that survivors' overall HRQoL is generally comparable with age-matched control individuals.^{4,11-14} One study of 65 children and adolescents with a history of retinoblastoma in the Netherlands demonstrated that survivors reported very good perceived HRQoL when compared with a healthy Dutch reference group.¹² While vision-targeted HRQoL was not specifically assessed, the authors note that most of the impairments mentioned by survivors were associated with activities related to visual acuity. Another study of 87 adult retinoblastoma survivors in the Netherlands similarly showed that adult survivors experienced a relatively good overall quality of life, with the exception of mental health outcomes, which were slightly worse among survivors when compared with a Dutch popu-

lation reference group.⁴ Factors associated with inferior quality of life included a history of bullying, usually related to appearance of the eye or ocular prosthesis, and feelings of disease-related impairment.⁴

In this study, which specifically assesses self-reported vision-targeted HRQoL, we found that a history of bilateral disease, which is often associated with more intensive retinoblastoma-directed therapies and hereditary risk of subsequent malignancies, and history of enucleation were associated with inferior overall vision-targeted HRQoL. It is possible that these factors were proxies for increased bullying and feelings of impairment, which were noted to be associated with inferior quality of life in existing studies,⁴ but these aspects were not assessed in our questionnaire.

Interestingly, prior radiotherapy exposure was not associated with inferior overall VFQ as measured by the NEI-VFQ-25 in the overall cohort of 470 retinoblastoma survivors enrolled in this study. However, patients with unilateral disease with prior radiotherapy exposure reported lower scores on the dependency and peripheral vision subscales; radiotherapy may thus serve as a proxy for other treatment or demographic factors in this small cohort (n = 34). Among patients with bilateral disease, radiotherapy was associated with lower near activity scores (reading print, sewing, and cooking), which is expected.

However, despite these impairments, overall VFQ scores in this cohort indicate preserved quality of life, particularly among those with a history of unilateral disease. Future study is needed to determine how changing treatment paradigms influence vision-related HRQoL in retinoblastoma survivors.

Limitations

Comparison data from healthy control individuals and/or normative data are lacking, which limits our ability to make unbiased estimates of effect. Additionally, visual acuity data are not available in this self-report, survey-based study. It is also possible that some vision loss in this adult cohort was unre-

lated to prior retinoblastoma-directed therapy and/or related to tumor location/disease stage, which are not modifiable. Finally, radiotherapy is no longer used routinely in patients with retinoblastoma, and contemporary therapy involves far fewer enucleations and more systemic, intra-arterial, and intravitreal chemotherapy; in our center, for instance, primary enucleation rates among patients with advanced unilateral retinoblastoma have decreased from more than 95% prior to the introduction of ophthalmic artery chemosurgery to 7.4% in 2015.¹⁵ Results of this historical cohort may thus not be generalizable to contemporarily treated patients.

Conclusions

This study provides data about vision-related HRQoL in adult retinoblastoma survivors, which could be used by clinicians to inform long-term follow-up, oculo-visual outcomes, and rehabilitative measures to optimize outcomes in this growing cohort. These findings suggest vision-targeted quality of life should be assessed in adult survivors of retinoblastoma at long-term follow-up visits, particularly among those with a history of bilateral disease or enucleation.

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