ANDES PEDIATRICA
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Andes pediatr. 2024;95(4):389-396
DOI: 10.32641/andespediatr.v95i4.5045

ORIGINAL ARTICLE

Health Related Quality of Life in retinoblastoma patients

Calidad de vida de pacientes con retinoblastoma

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Received: November 24, 2023; Approved: March 17, 2024

What do we know about the subject matter of this study?

Retinoblastoma and its treatment can cause monocular vision and cosmetic alterations (facial asymmetry and the need for ocular prostheses), which can profoundly affect the quality of life of survivors.

What does this study contribute to what is already known?

The quality of life of patients aged 2-18 years treated for Rb was evaluated from the perspective of the patient and their parents and it was analyzed which factors of the patient, the disease, or the treatment were associated with worse outcomes. We found impairment of their overall quality of life and in its four dimensions; age at diagnosis >18 months had a statistically significant association with lower quality of life.

Abstract

Retinoblastoma (Rb) is the most common intraocular cancer in children and, along with its treatment, can negatively impact the Quality of Life (QoL). Few studies have explored this subject in these patients; none in Latin America. **Objective:** To evaluate the general, physical, emotional, social, and school quality of life of patients treated for Rb and to analyze which patient, disease, or treatment factors are associated with worse outcomes. **Patients and Method:** Descriptive, cross-sectional, analytical study in 59 cases aged between 2 and 18 years treated between 2007-2021, in remission and at least one year of follow-up. The PedsQL 4.0™ scale, which measures QoL in the pediatric population in four dimensions, was applied to children and one caregiver. Non-parametric (Kruskal-Wallis and median) and parametric (Chi-square) tests were used to study differences. The study was approved by the Institutional Ethics Committee. **Results:** QoL reported by patients was medium for the general and school dimensions (73.8 and 70, respectively), high for physical and social health (83.1 and 80),

Keywords:
Retinoblastoma;
Quality of Life;
Childhood Cancer;
Chemotherapy

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Edited by:
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How to cite this article: Andes pediatr. 2024;95(4):389-396. DOI: 10.32641/andespediatr.v95i4.5045

and low for the emotional dimension (65). The quality of life reported by parents was high for general and physical and social health (78, 87.5, and 80, respectively), and medium for emotional and school dimensions (70 and 75). No significant differences were found regarding sex, disease stage at diagnosis, Rb laterality, or treatment received. Age at diagnosis > 18 months was associated with worse QoL in general and in all dimensions and was significant in parents. **Conclusion:** Children treated for Rb had their QoL affected, particularly in emotional and school dimensions.

Introduction

Retinoblastoma (Rb), a tumor that develops in the growing retina in response to the loss of both alleles of the RB1 tumor suppressor gene on chromosome 13 of germ or somatic cells[1,2], is the most frequent primary intraocular cancer in children with an incidence of 1 per 16,000 live newborns (LNB) worldwide, with a higher frequency in countries with a high birth rate[2]. In Chile, the incidence is estimated at 13 cases per year[3].

The most frequent clinical manifestations are leukocoria and strabismus and, in late cases, visual impairment, eye pain, and proptosis[1]. It can be uni- or bilateral and, in some cases, involve intracranial structures such as the pineal gland and the suprasellar or parasellar regions[1]. Treatment is complex and varies according to the tumor extension. Enucleation, focal laser therapy, external radiotherapy, brachytherapy, and/or systemic, intra-arterial, or intravitreal chemotherapy can be performed[3]. In Chile, the enucleation rate reaches 76.5-81.3%, and between 10-38.9% of patients with bilateral Rb require bilateral enucleation[3].

Sequelae include monocular vision, with a negative effect on movement processing, depth perception, and distance evaluation[4]. In addition, it can be associated with cosmetic alterations, facial asymmetry, and the use of ocular prostheses, which can affect the quality of life[10]. In a study by Sheppard et al, 74% of children have been victims of abuse because of their appearance or prosthesis[5].

Worldwide, few studies evaluate the quality of life in children and adult survivors. Sheppard et al. described that mothers of survivors report a lower quality of life for their children compared with the healthy population, mainly in the psychosocial and physical health domains[5]. This result is similar to that found by Batra et al. who observed that the quality of life, reported by parents of survivors, was significantly lower than that of their siblings without Rb, in all domains[6]. Several disease and treatment factors have been postulated to have a negative impact on quality of life, with contradictory results. According to the type of treatment, Lara reports good quality of life in all groups, being significantly better in the group that received systemic chemotherapy plus local treatment[7]. These results are opposed to those obtained by Weintraub, where both children who received chemotherapy and their parents reported limitation of quality of life, mainly in the social and emotional domains, which was not observed in the other treatment modalities[8]. Regarding enucleation, Zhang reported that the quality of life in survivors of Rb following enucleation is significantly lower than in the control group, mainly in school and social behavior[9]. Banerjee found that 36.9% of adult survivors reported severe impairment of their lives due to enucleation of 1 or both eyes[10], and Friedman reported significantly lower quality of life in adults with complete blindness and bilateral disease[11].

The *Hospital San Juan de Dios* (HSJD), a high-complexity hospital and part of the Chilean public healthcare network, was a national referral center for the treatment of patients from 2012 to 2022, treating people referred from all over the country for intra-arterial chemotherapy (IAC). To date, no study in Chile or Latin America evaluates the impact of Rb and its treatment on the quality of life of survivors. Knowing the quality of life of those treated and knowing what factors could influence it allows us to improve care during treatment and follow-up. The main objective of the study was to evaluate the health-related quality of life (HRQOL) of patients between 2 and 18 years of age treated for Rb at the *Hospital San Juan de Dios* and to analyze which patient, disease, or treatment factors are associated with poor quality of life.

Patients and Method

Descriptive and analytical cross-sectional study including patients with Rb treated between 2007 and 2021 in the HSJD, in remission and with at least one year of follow-up, who agreed to participate, with signed informed consent and assent. Those who refused to participate in the study or whose parents could not be contacted were excluded.

At the time of the study, 73 patients aged between 2 and 18 years were under follow-up. All parents were contacted by telephone to invite them to participate, and the informed consent form was sent via e-mail, which they had to print, sign, and return scanned by the same means. Subsequently, a digital questionnaire was sent via e-mail to be answered by parents and children as appropriate. In case of difficulty in printing and scanning, the possibility of signing the consent via electronic form was added by checking the box "I agree to participate" and signing with full name and RUT[a], in the same link of the survey. For patients under scheduled follow-up in pediatric oncology, consent was signed and the survey was applied in person. In patients older or equal to 7 years old, their informed assent was attached.

Epidemiological and clinical data on age at diagnosis, laterality, inherited disease, treatment received, and complications were obtained from the Clinical Registry for Retinoblastoma (Rb-NET), an electronic database approved by the Hospital's Ethics Committee, which has high standards of computer security.

As a specific objective, it was decided to evaluate the general quality of life and each of its dimensions (physical, emotional, social, and school health), and to compare the children's perception of HRQOL with the parents' opinion of it. For this purpose, the PEDS-QL 4.0 instrument was applied, validated in Chile in a master's thesis in Public Health[12], designed to measure the HRQOL in children and adolescents between 2 and 18 years of age, applicable to healthy and sick children. Parents and/or caregivers were invited to evaluate its 4 dimensions: physical health, emotional, social, and school functioning. The instrument is adapted for different age ranges: 2 to 4 years (for parents only), 5 to 7 years, 8 to 12 years, and 13 to 18 years (for children and parents), which caused a difference in the total number of responses from parents when compared with the survey for children. The instrument uses a five-choice Likert-type scale from 0 to 4. The values obtained from the items were reversed and linearly transformed to a scale of 0-100. A score between 0-68 reflects a low quality of life; between 69-77, intermediate quality; and between 78-100, high quality[12].

In addition, the association of factors such as sex, age at diagnosis, age at remission, and current age with low overall quality of life and its dimensions were studied, as well as the association of disease factors (laterality, inherited disease, and clinical stage at diagnosis) with low overall quality of life and its dimensions, and the association with the type of treatment (focal treatment, enucleation, systemic chemotherapy, IAC, and radiotherapy).

Working hypothesis: In pediatric patients aged 2-18 years treated for Rb, disease- or treatment-related factors have a negative impact on long-term quality of life in all its dimensions (physical, emotional, social, and school), with patients with bilateral disease and those who received a more aggressive treatment modality (systemic chemotherapy or radiotherapy) having a worse quality of life.

To maintain anonymity, identifying data were eliminated and ordered by a sequential number, deleting the original file. The data were classified and organized according to the objectives of the study. The results of the study will be used for scientific purposes, and the research team will keep custody of them for 2 years. The research protocol was approved by the scientific ethics committee of the *Hospital San Juan de Dios*.

The statistical analysis consisted of the description of variables through summary measures and the evaluation of statistical hypotheses for the comparison of mean scores according to groups or the association of the scale with factors of interest. In general, for quantitative variables, a description was made based on means and standard deviation, and for qualitative variables, absolute and relative frequencies (percentages) were obtained. To determine differences according to sex, age groups, laterality, and other categorical variables in the quantitative scales for parents and children, non-parametric tests such as the Kruskal-Wallis test and the median test were used. The Chi-square test was used to establish the existence of an association between categorical variables. A value of 5% was used to determine statistical significance and the statistical software Stata version 17 was used.

Results

The responses of 59 parents, reporting their perception of their children's quality of life, and those of 49 children (10 children under 5 years of age did not respond to the survey) were studied. Figure 1 shows the flow of cases studied and table 1 shows the characteristics of the population studied.

When comparing the ages at diagnosis, remission, and current age according to sex, the mean was asymmetrically distributed, so the medians were compared. In the female sex, the median at diagnosis was 12.9 months, and for the male sex it reached 9.4 months; lower than in females ($p = 0.299$) but without reaching significance. There was no statistically significant difference when comparing age at remission, current age, and laterality according to sex.

For the stage of the disease at diagnosis, the International Classification for Intraocular Retinoblastoma was used. Stages A, B, and C were merged for analysis and compared with D and E, applying Fischer`s exact test, finding no differences. No statistically significant difference was found in any treatment modality. The number of patients who received sub-

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[a] Chilean ID National Number.

tenon carboplatin chemotherapy (SCC) and intravitreal chemotherapy (IVC) was small and did not show significance.

Table 2 shows the results obtained in the evaluation of the quality of life in both the parents' and the children's survey.

Self-perceived quality of life by patients

The overall quality of life reported was 73.8 (medium quality). In the physical and social health dimensions, they reported high quality (83.1 and 80, respectively); while it was only medium in the school dimension (70) and low in the emotional dimension (65). No significant differences were found between sexes, stage of the disease at diagnosis, or type of treatment received.

Patients with bilateral Rb scored lower in the emotional dimension, with low quality of life, while the group with unilateral Rb reported medium quality. However, they scored higher than them in physical health, with high quality of life. In the rest of the dimensions and the general average, the results were similar, with no significant difference associated with laterality.

When comparing current age, the 8-12-year-old group scored lower in the general average (medium quality) and the emotional and school dimensions with low quality of life, without statistical significance.

When comparing the age at diagnosis, lower quality of life was observed in the group with age at diagnosis >18 months in the general aspect and all dimensions; however, there was statistical significance only in the physical health dimension (p 0.045).

According to the type of treatment, the group that received rescue IAC had a better quality of life in physical health, school, and general average, with high quality of life. The group that received radiotherapy had worse results in physical health, emotional health, and general average, with medium quality, but without statistical significance.

Scores assigned by parents

The overall quality of life reported was 78 (high). In physical and social health, they also reported high (87.5 and 80, respectively), while it only reached medium in emotional and school dimensions (70 and 75), with no significant difference between sexes or stage of the disease at diagnosis.

Regarding laterality, parents of children with bilateral Rb reported a high quality of life when compared with unilateral disease (medium quality). In the different dimensions, the scores of both groups were similar, with no significant difference in laterality.

When comparing according to current age, the group between 8 and 12 years of age reported lower quality of life than the other age groups in the general average and in all dimensions, with low quality in emotional (significant $p = 0.021$) and school health (not significant).

When compared according to age at diagnosis, a lower quality of life was observed in patients with age at diagnosis >18 months, in the general aspect ($p = 0.003$) and the physical ($p = 0.018$), social ($p = 0.007$), and school ($p = 0.052$) health dimensions.

According to the treatment received, the group that received rescue IAC reported better quality of life in the physical, social, and school health dimensions and the general average, with high quality of life. The group with radiotherapy had worse results in physical, emotional, and school health, and the general average with medium-low quality of life, without statistical significance.

Children vs Parents

When comparing the responses of parents and children, the latter reported lower quality of life in the general average and the dimensions of physical, emotional, and school health, with no significant differences. A high correlation was found between parents and children in almost all the dimensions, with statistically significant correlation values being minimum in the physical health dimension (rho Spearman = 0.47; $p < 0.001$) and maximum in the general average (rho Spearman = 0.72; $p < 0.001$).

Discussion

Undoubtedly, good quality of life is one of the goals in the treatment of all oncologic pathologies, regardless of patient survival. This cross-sectional study measured HRQOL using the PEDS-QL 4.0, a tool that seems reliable. Regarding the quality of life of children and adolescents, they scored it at a medium level; an assessment that contrasts with that of their parents or caregivers, who assigned it a high level. Compared with published studies, the quality of life expressed by these children was lower than that of Batra 2015, Zhang 2018, and Dhingra 2021 (medium and high qualities; respectively). The perception of parents in this study was similar to that obtained by Sheppard 2015 and higher than that reported by Batra 2016 and Weintraub 2019. When comparing the responses of parents vs children, the perception of the quality of life perceived by parents was higher than that of their children. Dhingra 2021, Batra 2016, Van Dijk 2007, and Seppard 2005 obtained the opposite result. A study by Yeh 2005 on children with cancer described that parents tend to underestimate the negative impact of the

Table 1. Demographic, clinical and therapeutic characteristics of the patients

Characteristics						
Sex	Female		Male		Total	
	n = 32	54.2%	n = 27	45.8%	n = 59	100%
Age (months):						
At diagnosis						
Average	20.6		17.1		19.0	
SD						
Median	12.5		9		10	
Minimum	0		3		0	
Maximum	115		49		115	
Remission						
Average	33.6		32.0		32.9	
SD						
Median	27.5		31		30	
Minimum	5		4		4	
Maximum	136		64		136	
Actual						
Average	103.2		103.9		103.5	
SD						
Median	108		113		109	
Minimum	34		27		27	
Maximum	214		187		214	
	n	%	n	%	n	%
Laterality						
Unilateral	19	59.4	14	51.9	33	55.9
Bilateral	13	40.6	13	48.1	26	44.1
History of Rb in a 1st degree relative	3	9.4	8	29.6	11	18.6
Stage of the disease at diagnosis						
A + B + C	3	9.3	4	14.8	7	11.8
D	16	50	14	51.9	30	50.8
E	13	40.6	9	33.3	22	37.3
Local treatment	16	50.0	19	70.4	35	59.3
Systemic chemotherapy	20	62.5	21	77.8	41	69.5
IAC*	9	28.1	7	25.9	16	27.1
SCC/IVC**	3	9.4	6	22.2	9	15.3
Enucleation						
Unilateral	23	71.9	22	81.5	45	76.3
Bilateral	1	3.1	1	3.7	2	3.4
No enucleation	8	25.0	4	14.8	12	20.0
Radiotherapy (RT)						
Brachytherapy	4	12.5	1	3.7	5	8.5
External beam	1	3.1	1	3.7	2	3.4
Total	5	15.6	2	7.4	7	11.9

*IAC: intra-arterial chemotherapy; **SCC/IVC: subtenon carboplatin chemotherapy / intravitreal chemotherapy. Rb: Retinoblastoma.

Table 2. Quality of life score assigned by parents and children

Dimension		Children				Parents				
		Total	5-7 years	8-12 years	13-18 years	Total	2-4 years	5-7 years	8-12 years	13-18 years
	n	49	18	22	9	59	10	18	22	9
General average	Median	73.8	75	72	82	78	92	78	70	83
	Interquartile range	10.2	8	14	10	17.9	11	9	22	12
Physical health dimension	Median	81.3	75	82.8	87.5	87.5	96.9	87.5	82.8	93.7
	Interquartile range	25	18.7	19.5	28.1	21.9	15.6	17.2	35.9	12.5
Emotional dimension	Median	65	70	60	65	70.0	77.5	80	65	70
	Interquartile range	30	27.5	25	25	30	22.5	25.6	20	15
Social dimension	Median	80	80	87.5	100	80.0	100	80	80	90
	Interquartile range	30	25	40	15	30	10	17.5	33.7	20
School dimension	Median	70	80	62.5	75	75	87.5	75	57.5	85
	Interquartile range	25	25	18.75	15	30	21.5	20	38.7	25

*Quality of life score: high 78-100, medium 69-77 y low 0-68.

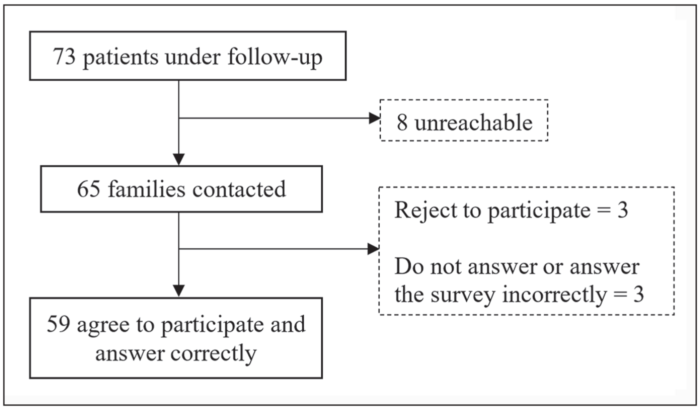

Figure 1. Family inclusion flowchart.

disease on their children's quality of life, which may have occurred in our study.

The children in this study reported worse quality of life in emotional (low) and school (medium) health; dimensions with great variability when compared with other studies. In Batra 2015, the lowest dimension was social health (medium quality); in Zhang 2018 was school (low); and in Dhingra 2021 was physical health.

The dimensions in which parents in this study expressed worse quality of life for their child were also emotional and school (medium quality); similar to what was obtained by Batra 2016 and Weintraub 2019.

In the emotional health dimension, the question with the worst score in the children's survey was "being worried", while the parents assigned the worst scores to "feeling angry" and "being afraid". This could be explained by concern for the future (relapse, second malignancy), in addition to the damage to body image secondary to enucleation. These results suggest the importance of an active role in detecting emotional problems in the follow-up of these patients in order to provide early psychological support and develop coping skills for quality-of-life problems.

Regarding the school dimension, parents and children assigned lower scores for having to miss school to go to the doctor's office, which is in line with other published studies.

It is worth noting that being in the age group >18 months at the time of diagnosis is associated with a poorer general quality of life in all dimensions. This occurred in both children and parents and reached statistical significance in the latter. It is worth recalling that Batra 2016 and Zhang 2018 obtained similar results. This could be explained by the fact that those who received treatment at a younger age already forgot the fear and pain experienced during the diagnosis and treatment phases which is naturally lower in those who were older than 18 months.

Those who received IAC reported better quality of life, in contrast to those who underwent radiotherapy, who felt it worse, both in the survey of parents and children, without reaching statistical significance and with a very small number of patients in both groups. Rescue IAC is the most recent treatment modality; it allows for limiting the systemic toxicity of the chemotherapy and in most cases avoiding the administration of radiotherapy. In these patients, it allowed preserving the vision of several children with bilateral Rb, unilaterally enucleated (13).

As in all other published studies, no association was found between sex, current age, or laterality with quality of life, although it is worth noting that children with bilateral affectation scored lower in the emotional dimension, but without reaching significance.

A more accurate assessment of our findings requires a review of the limitations of this study. We believe it is important to remember that its population was small and that it was impossible to contact several families. This hospital is a referral center for Rb, treating cases from all over Chile; many were followed up in their hospitals of origin and it was not possible to survey them in person. Likewise, it was not possible to monitor whether parents and children answered their surveys individually as they were instructed to do when entering the study. Additionally, others did not participate since the parent affected with Rb with blindness was not able to sign the consent or answer the survey due to physical limitations or lack of a good support network. Furthermore, quality of life is affected by socio-demographic factors that were not evaluated: rurality and socioeconomic or educational level of the child and her/his family. Likewise, there is no population of healthy children in the country to whom the PEDS-QL has been applied to serve as a reference. This does exist in other publications, and it would have been interesting to compare the quality of life of the children studied with their peers without Rb.

Another important aspect is to remember that it is difficult to compare these results with those of other countries given the heterogeneity of assessment tools and the important cultural differences. There are also no similar studies in Latin America whose countries may be more similar to Chile. Finally, this work was carried out close to the COVID-19 pandemic and its consecutive confinement, which could also have impacted the quality of life of these children and adolescents.

In conclusion, children and adolescents treated had their quality of life affected, both in general and in its four dimensions, with emotional and school quality of life being more affected. Among the factors that could influence these results, age at diagnosis > 18 months had a statistically significant association with a lower quality of life. Further research is needed to delve into factors that impact the disease and to implement and evaluate measures that guarantee a better quality of life.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Study partially funded by the 2022 *Concurso Semilla* of the Chilean Society of Pediatrics.

Acknowledgments

Thanks to the patients and their families for participating in this study.

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