Mémoire de Maîtrise en médecine

IMPACT OF THERAPY ON QUALITY OF LIFE IN PATIENTS TREATED FOR RETINOBLASTOMA

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1. Abstract

Background

Retinoblastoma accounts for 2-4% of childhood cancers and is the most common malignant ocular tumour in childhood. Current treatment modalities allow, in developed countries, a 95% survival rate at 5 years. This is achieved by a combination of local treatments, systemic chemotherapy with focal treatments (CT), external beam radiotherapy (EBR) and/or enucleation. While enucleation causes mainly aesthetic sequelae, EBR increases the risk of secondary radiation induced tumours. This explains why efforts have been made to develop new, more conservative treatment techniques. Since a few years, intraarterial administration of chemotherapy (IAC), and intra-vitreous administration of chemotherapy (IVC), are used as new conservative treatments with the aim of avoiding enucleation and/or EBR.

Limited data is available regarding the impact of these treatments on the health status of survivors and especially on their health-related quality of life (HRQoL).

Objective

To assess HRQoL in children and adolescents who survived retinoblastoma and compare the results between four different treatment modalities: enucleation, EBR, CT and IAC/IVC.

Patients and methods

This is a population-based cross-sectional study. Questionnaires were sent out to all retinoblastoma survivors who were entirely treated at our centre and who had a minimal follow-up of 3 years since end of treatment. The HRQoL was assessed using the KIDSCREEN-52 self-reported and parent proxy version and the total score and the scores of each dimension were compared between the four different treatment modalities.

Results

Our results showed that the perceived global HRQoL of retinoblastoma survivors was very good with a total score and each dimension scores over 4 on a scale of 1 to 5. With regards to the total quality of life score, retinoblastoma survivors who received primary CT (ref group) scored significantly higher than the other groups. Those who were enucleated scored lower (β (p-value) = -2,21 (0,04), followed by those who received IAC/IVC (-2,61 (0,02)) and the group that was treated with EBR (-2,96 (0,03). The CT group reported also better HRQoL on the school environment dimension. They scored significantly higher compared to those who were enucleated in the dimension of psychological well-being, and scored higher than the EBR group in the dimension of self- perception and autonomy. The groups did not differ in physical, moods and emotions, parent relations, social support and social acceptance domains. Factors associated with a lower score were: the older age of the patient at study time, older age at first examination at HOP and HJG, self-reported questionnaires and unilaterality.

Conclusion and perspectives

Our results show that the perceived HRQoL by retinoblastoma survivors was globally good and that the HRQoL differed according to the treatment received. Patients treated with EBR have, as expected, the worst HRQoL. To our surprise, systemic chemotherapy, although related to more general side effects, scored best in almost all domains, even when compared to the newer local chemotherapies (IAC/IVC).

In order to confirm these data, patients who were not yet available will be included and socio-demographic factors such as parents' education, migration background and country of residence, added since they could also affect the HRQoL.

2. Introduction

Retinoblastoma is the most common malignant ocular tumour in childhood. Because of its rareness (3% of all pediatric cancers), treatment is concentrated in highly specialized centres comprising ophthalmologists and oncologists. Current treatment modalities allow, in developed countries, a 95% survival rate at 5 years[1]. This is achieved by a combination of focal treatments (cryoablation, laser photocoagulation, plaque brachytherapy, thermotherapy) with or without systemic chemotherapy (CT) in less advanced disease (International Classification for Intraocular retinoblastoma = IIRC Group B-C; Appendix 1). In the advanced stages (IIRC Group D-E disease), this approach is frequently ineffective leading finally to external beam radiotherapy (EBR) and/or enucleation[2]. While enucleation causes aesthetic and functional sequelae[3], radiotherapy tremendously increases the risk of secondary radiation induced tumours, especially in patients with bilateral, that is, hereditary retinoblastoma presenting a germline mutation of RB1[4,5,6]. This explains why efforts have been made to develop new conservative treatment techniques such as intraarterial administration of chemotherapy (IAC) through the ophthalmic artery by inguinal catheterization[7], and intra-vitreous administration of chemotherapy (IVC) by direct injection into the vitreous[8] with the aim to avoid EBR, and also enucleation, and thus to improve ocular survival.

The care of a child treated for retinoblastoma is very complex. Each case is unique and needs a treatment adapted to its particular situation. The purpose of the treatment is to preserve life, vision and to provide a good quality of life by avoiding EBR and enucleation. Although the number of survivors is increasing, literature on Health-related quality of life (HRQoL) in cured retinoblastoma patients remains scarce. Measurements of HRQoL allow the assessment of a patient's perception of the impact of his disease treatment on daily life and late effects by means of validated questionnaires. In pediatric patients, these questionnaires are, depending on age, either self-reported, or parent proxy questionnaires. Among the studies that reported on HRQoL in retinoblastoma patients, Batra et al (India) [9-10] evaluated quality of life using the PedsQL™ 4.0 generic score scale in retinoblastoma survivors and compared the results to healthy siblings. In 2018, Zhang et al (China)[11] evaluated HRQoL using the same questionnaire in retinoblastoma survivors after enucleation and compared this specific group with healthy children. In Switzerland, a study reported on survivors of childhood cancer in general, including retinoblastoma patients, and compared to healthy siblings using a Short Form-36 (SF-36) questionnaire[12]. Sheppard et al (UK) used the same two questionnaires to evaluate mothers' perception of HRQoL of retinoblastoma survivors compared to the normal population[13]. Alessi et al conducted a study in Northern Italy using a 15-item Health Utilities Index that was specifically created to perform a population-based study of childhood cancer[14]. Finally, between 2006 and 2010, Van Dijk[15,16,17] et al reported several times on HRQoL results of retinoblastoma survivors compared to the Dutch population using either KIDSCREEN self-reported and proxy-reported questionnaire, Short-Form-36 disease specific questionnaire or PedsQL™ 4.0 questionnaire.

However, none of the studies compared HRQoL between the different types of treatment within a group of retinoblastoma survivors. As the development of treatments over the last 25 years has moved from aggressive approach to obtain cure to conservative treatments aiming at cure, but avoiding sequelae and improving thus the quality of life, it would be relevant to know if the HRQoL of the retinoblastoma survivors differs according to the treatment the patients have received. This also raises the question whether more conservative treatments increase the treatment burden and how this burden impacts on HRQoL. Thus, our trial focuses on the comparison of four different treatment types used during four different time periods: enucleation, EBR, CT and IAC/IVC.

3. Methods

3.1 Patient recruitment and study procedures

The present study had a cross-sectional design and was performed between May and September 2018. It was approved by the ethical committee of Vaud, Switzerland (authorization #2018-00460), and is compliant with the Declaration of Helsinki.

Patients treated for retinoblastoma at the Jules Gonin Ophtalmic Hospital (HJG) and the pediatric Hematology Oncology Unit (HOP) between 1998 and 2015 were eligible, if they had all their treatment performed in Lausanne and presented a follow-up of at least 3 years after completion of the treatment. Characteristics of these patients were extracted from the medical charts at HJG and HOP and a specific data base was created. Disease-related information included date of birth, age at diagnosis, gender, laterality (unilateral/bilateral), date of the last control and treatment received. Type of treatment was categorized as (1) primary enucleation, (2) primary systemic chemotherapy with focal treatment, (3) secondary chemotherapy and/or EBR, (4) intraarterial and/or intra-vitreous chemotherapy.

Eligibility criteria for inclusion were: (1) all patients with uni/bilateral retinoblastoma treated and followed at our institution between 1998 and 2015, (2) all disease stages described either as Group I-V according to Reese-Ellsworth score, or Group A-E according to the Murphree IICR, (3) no extraocular or metastatic disease, (4) at least three years of follow-up since the end of the treatment and definite tumour control, (5) all treatment performed in Lausanne, (6) availability to answer the questionnaire.

Patients and/or parents/legal guardians were invited to participate by a letter sent by mail. This letter included an explicative cover letter, a study information document, the Informed Consent Form, the KIDSCREEN-52 questionnaire and a return envelope. Two months were given to answer the questionnaire. Participants could either send back the documents or return them at their annual routine control check for retinoblastoma at HJG or at HOP. Non-responders were sent a reminder letter one month later.
To those patients who had their annual routine control for retinoblastoma planned at HOP during the study time, the study was presented by the retinoblastoma nurse. Written informed consent was obtained after the explanation and the questionnaire was filled out at the end of the medical visit. One hour was given to the participant and his family to read the information, sign the consent and complete the questionnaire after the initial explanation.

The cover letter and the Informed Consent Form were translated into four languages (French, German, Italian and English) and handed or sent out in the most appropriate language according to the patient's and the parents/legal guardians' origin. Patients of pediatric age received an age adapted information/consent form and age-adapted questionnaire (> age 13, age 11-13, < 11 parents' information/consent), and could either sign the consent by themselves or be represented by their parents/legal guardians.

3.2 Health Related Quality of Life (HRQoL) measures

The KIDSCREEN-52 child/adolescent self-report instrument is a generic HRQoL questionnaire, developed within a European project[18-19]. The HRQoL questionnaire has been designed to assess children's (8–11 years) and adolescents' (12–18 years) own perceptions of their subjective health and well-being.

The KIDSCREEN-52 proxy research instrument is derived from the above-mentioned self-report version and is designed to assess parental perceptions of their child's health and well-being. It is used for children under the age of 8 years.

We used the KIDSCREEN-52 self-report version for retinoblastoma survivors over 8 years old and the KIDSCREEN-52 proxy-version for retinoblastoma survivors under 8 years old. All families answered only one version.

Both versions of the KIDSCREEN-52 measure 10 HRQoL dimensions: Physical- (5 items), Psychological Well-being (6 items), Moods and Emotions (7 items), Self-Perception (5 items), Autonomy (5 items), Parent Relations and Home Life (6 items), Financial Resources (3 items), Social Support and Peers (6 items), School Environment (6 items) and Social Acceptance (Bullying) (3 items). The recall period for most items was one week. Each item could be scored between 1 (worst) and 5 (best). The score of each dimension was calculated as the sum of the answers to the questions of the dimension, divided by the number of questions. The 10 scores obtained therefore had a similar range between 1 and 5. One represents the worst score and 5 the best score. The total quality of life score was calculated as the sum of these 10 scores, so its range varied between 10 and 50.

The KIDSCREEN-52 was constructed and piloted in more than 3,000 European children and adolescents. In addition to common psychometric analyses, Item-Response-Theory Analysis and Structural Equation Modelling were performed to determine the optimal items and scale characteristics of the questionnaire. One focus of analyses was to identify items showing differential item functioning (DIF). The control of DIF enables comparable measurement of the identified quality of life dimensions across the 13 European countries. The KIDSCREEN-52 was used in representative mail surveys of HRQoL in approximately 1800 children and their parents per country (total n = 22296) and normative data were produced. The final analysis involving national and cross-cultural analysis of the instruments confirmed the results of the pilot test. The sub-scales enable true cross-cultural measurement at an interval scale level by fulfilling the assumption of the Rasch-model and displaying no DIF.

Both versions are available in 8 languages (French, German, Greek, Italian, Portuguese, Russian, Serbian, Spanish and English) and all eligible families received the questionnaire in their mother language or in English if it wasn't available.

3.3 Statistical analysis

Data analysis was performed using the STATA software (StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The socio-demographic data and the scores were summarized by the median and the interquartile range (iqr) for continuous variables and by the number and the percentage for category variables. The 10 scores measuring the quality of life were standardized: For each dimension, the score was calculated as the sum of the answers to the questions of the dimension, divided by the number of questions. The 10 scores obtained have therefore a similar range from 1 to 5. The total quality of life score was calculated as the sum of these 10 scores, so its range varied between 10 and 50. The distribution of the different scores was clearly asymmetric and did not follow a normal distribution. For this, a robust linear regression model was used to compare the level of the scores between the four treatment groups but also to test the association between the different sociodemographic variables and the level of the scores.

4. Results

4.1 Characteristics of the study population

Between 1998 and 2015, 426 patients were treated at HJG and HOP. One-hundred and ninety retinoblastoma survivors were eligible for the study according to the above mentioned criteria. One hundred and sixty-five patients could be contacted, whereas 25 were lost to FU or had an incorrect address (Fig. 1). Eighty-one out of 165 (49 %) returned the questionnaire; 78 participants sent it back by mail and 3 participants filled out the questionnaire during their annual routine control for retinoblastoma at HOP. We included 78 participants in the current

analysis, after dropping 3 (3.85 %) who returned an incomplete questionnaire (Figure 1). Eighty-four participants (51%) didn't return the questionnaire.

Table 1 shows the socio-demographic data. Median age at the time of the survey of the study population was 12.00 (iqr=9.00) years and median age at diagnosis was 15.00 (iqr= 22.00) months (Figure 2). Most of the responders, 57 (73%), were over 8 years old and completed the questionnaire by themselves, whereas only 21 (27%) of the questionnaires were completed by the parents/legal guardians. Within the self-reporting group, 31 were adolescents ≥ 14 years old, 13 patients were between 11-13 years old and 13 were children between 8 and 11. The study group included 50 (64.1%) participants with unilateral and 28 (35.9 %) participants with bilateral disease. The proportion of male to female was 0.9.

Table 2 shows the characteristics of each study group. The first group was composed of 16 patients, 7 males and 9 females, who had had primary enucleation. All of them had had only one eye enucleated and received no further treatment. Fifteen presented a unilateral and one a bilateral disease. Mean age at evaluation was 16 (SD=3.6) years (range 9-22 years).

The second group with 38 participants, had received primary systematic chemotherapy combined with focal treatment. It was composed of 19 males and 19 females. Eleven out of the 38 (29%) underwent a secondary enucleation. Twenty participants suffered from a unilateral and 18 from a bilateral disease. Mean age at evaluation was 11 (SD=4.6) years. Twenty-four patients were over the age of 8 years and responded to the questionnaire by themselves, and 14 children were younger, with parents completing the proxy-questionnaire.

In the third group, 9 cured patients, composed of 5 males and 4 females, had received a secondary chemotherapy and/or an EBR. Three out of 9 underwent secondary chemotherapy after primary enucleation for histological risk factors. A further three had EBR directly, and the last three had EBR after primary chemotherapy. Three of them had a unilateral disease and 6 a bilateral disease. Mean age at evaluation was 15 (SD= 2.4) years, all were more than 12 years old and completed the questionnaire themselves.

The fourth group was composed of 15 participants, 6 males and 9 females, who received an intra-arterial and/or intra-vitreous chemotherapy. This group was the youngest one by age, corresponding to the most recent treatment period, with a mean age, at evaluation, of 7.5 (SD=2.4) years. Eight children were ≥ 8 years old and completed the self-report questionnaire; 7 were younger and their parents completed the proxy questionnaire. Twelve of them had a unilateral and 3 a bilateral disease.

4.2 Health-Related Quality of life scores

The HRQoL total score and each dimension score of all participants are given in Table 3. All the scores are very high (1 being the worst and 5 the best by dimension, whereas the range for total score is between 10 and 50). The median of the total score is 43.1, and the medians scores by dimension vary from 4.17 to 4.67, none being lower than 4. Figure 3. illustrates the dimension scores by treatment group. Graphically Group 2, CT with focal treatment, did best in all dimensions, whereas treatment group 1, 3 and 4 showed more variation among the different dimensions.

Group 2 (primary CT group) was taken as a reference for statistical analysis and all comparisons. The choice was based on the fact that this group contained the biggest number of patients and because primary systematic chemotherapy combined with focal treatment was the standard treatment for a long period of time (over 15 years). The comparison between the four groups and the factors influencing the differences are summarized in Table 4. The scores are given as the mean difference from the reference score (β) and not as an absolute value.

With regard to the total quality of life score, participants who received primary systemic chemotherapy (group 2) scored significantly higher than the other groups. Their total score was 44.22 points (SD=0.61). Group 1 scored lower (β (p-value) = -2.21 (0.04), followed by group 4 (-2.61 (0.02)) and then group 3 (-2.96 (0.03).

Group 2 also scored significantly higher than all the other groups in the school environment dimension, with a score of 4.36 (SD=0.09) (β (p-value) = group 1(- 0.60 ($<10^{-4}$)), group 3 (- 0.73 ($<10^{-4}$)), group 4 (- 0.38 (0.03)).

Group 2 scored significantly higher than group 1 in the dimension of psychological well-being (β (p-value) = - 0.39 (0.02)) and financial resources (β (p-value) = - 0.4 (0.02)) and scored higher than group 3 in the dimension of self-perception (β (p-value = - 0.50 (0.05)) and autonomy (β (p-value) = -0.67 (0.01)). The score differences between the other groups weren't significant for these dimensions.

The groups did not differ in physical, moods and emotions, parent relations, social support and social acceptance domains.

Figure 4 represents the HRQoL scores according to demographic factors. The scores by domain did not vary significantly between patients with unilateral or bilateral disease, although the latter showed a trend for better results; they were similar in females and males, but better in proxy evaluation than patients' evaluation. As age at diagnosis and treatment varied among the treatment groups, the results were adjusted to age at study time and showed significantly the best total score for Group 2, that is CT with focal treatment (Figure 5).

Factors associated with a lower score were analysed by a robust linear regression model and showed to be:

- older age of the patient, at the study time, for total score and for physical well-being, moods and emotions, self-perception and school environment dimensions.
- older age at first examination at HOP and/or HJG for financial resources and school environment dimensions.
- self-reported questionnaire for physical well-being, moods and emotions and school environment dimensions.
- unilaterality for psychological well-being dimension.
- whereas gender had no significant influence on the scores.

5. Discussion

5.1 Interpretation of results

Our study assessed the HRQoL in a cohort of young retinoblastoma survivors, treated by four different treatment modalities during different time periods. For this evaluation the KIDSCREEN-52 questionnaire (child and adolescent self-report and parent proxy-report) was used with the aim to compare the total score and the scores of each dimension between these four different treatment types.

Our results showed that the perceived **global HRQoL** of children and adolescents cured of retinoblastoma was very satisfactory. The total score of each treatment group was over 40 (range 5 to 50) and all dimension scores were over 4 (range 1 to 5). Interestingly, our results showed that group 2 (systemic CT with focal treatment) scored significantly higher than the other groups in the **total HRQoL** and in the **school environment** dimension. Primary systematic chemotherapy combined with focal treatments was the standard treatment for a long period. New modalities of local chemotherapy such as intraarterial and intra-vitreous administration were developed in order to improve efficiency by higher concentration of chemotherapy close to the tumor, and to lessen general side effects such as alopecia, nausea/vomiting, myelosuppression with transfusion and febrile neutropenia. Our results didn't show as expected better HRQoL. However, we have to take some factors into account that may explain this result.

The age of the patients when they answered the questionnaire was a major factor that was associated to the scores. Patients who were older at the study time scored significantly lower in the total score and in four dimensions: physical well-being, moods and emotions, self-perception and school environment. In order to take into account the age effect, we performed an age-adjusted analysis for all scores. The HRQoL total score of group 4 remained significantly lower compared to group 2, which was not the case for the other groups (Figure 5). In other words, when adjusting to the age of the patient at study time, only the HRQoL total score of group 4 compared to group 2 remained significantly different. As the treatment modalities of group 4 were newer and the patients on average younger, the follow-up for this group was also much shorter with a mean of 5.2 years compared to group 2 that had a mean follow up of 9.3 years. Also did in group 2 mainly adolescents fill out the questionnaire while in the younger group 4 the parents were primarily in charge of filling out the questionnaire.

According to our statistical analysis, there was no significant difference in the total score on whether the child or the parent completed the report. However, it had an influence on the score of 3 dimensions: **physical well-being**, **moods and emotions** and **school environment**. Retinoblastoma survivors who answered the self-reported version scored lower. Their perception in these very subjective fields was worse than the parents'.

Other studies also compared child versus parents' perception and found different results. In India, Batra et al[9-10] evaluated quality of life using the PedsQL™ 4.0 generic score scale in 122 retinoblastoma survivors and compared the results to healthy siblings. They also compared the child versus parent's perspective of HRQoL. The parents reported worse results in **the emotional health** dimension, but other domains were similar to the patients' evaluation. Van Dijk[16] et al also reported on HRQoL results of retinoblastoma survivors, compared to the Dutch population, using the KIDSCREEN-52 self-report and proxy-report questionnaire and found a discordance between the evaluation done by 65 patients compared to their parents' perception. Parents judged the HRQoL of their child to be relatively poorer in all domains, especially in "moods and emotions" domain, which is again contradictory to our results. The mean age of the participants in their study was 12.7 years, very similar to the mean age of our participants (11.7 years). Most of the Van Dijk study's participants were treated by enucleation or radiotherapy whereas most of the participants of our study were treated by primary systemic CT. What is more relevant is that in our study, group 1 and 3 were fully composed of children

over 8 years old. They all answered by themselves, thus we collected only self-reported questionnaires for these two groups. In both previously mentioned studies, the questionnaire was given to both parents and patient of the same family and their responses were compared. We didn't make this comparison. We only looked at it as a potential influencing factor in the robust linear regression model.

The dimensions associated with a lower score in our study (physical well-being, moods and emotions and school environment) are very subjective and influenced by adolescence. As group 1 and 3 were composed by older children it can explain this result in our study.

Concerning the **school environment** dimension score, group 2 scored significantly higher than all the other groups with a score of 4.36 versus 3.98 for group 4, 3.76 for group 1 and 3.63 for group 3. These results remain significant when adjusted to the age of the patient at the study time and to the KIDSCREEN-52 version (self-reported or proxy). Generally, this score was still very high for the whole cohort (4.17) even when lower in some treatment groups. We compared these results with other studies, although it was not completely equivalent, as different assessment tools were used and comparisons between different groups done. The differences in scores for this dimension among Dutch pediatric patients with retinoblastoma compared to the norm population was not statistically significant[16]. Sheppard et al[13] used the PedsQL™ 4.0 and the Short-Form-36 in London to evaluate mothers' perception of HRQoL of retinoblastoma survivors compared to the normal population and concluded that there was excellent school attendance and school activities, whereas the global HRQoL score, and especially the physical and psychosocial functions, were lower. An Israeli[20] study reported that paediatric patients with retinoblastoma were affected by the disease and their daily activities were restricted, thus causing absences from schools and reductions in participation in all type of activities, which significantly affected the children's scores in the school dimension. In our study, retinoblastoma survivors from groups 1 (primary enucleation) and 3 (secondary enucleation and/or EBR) scored lower. They were more often aesthetically impacted and their time cure was longer, with more intensive treatments. This could have had consequences on their school life and psychosocial well-being and explain our results.

In the dimension of **psychological well-being,** group 1 scored significantly lower than group 2. Although all pediatric patients had an ocular prothesis implantation completed, an impact on self-perception could still be observed. There were also some personal letters sent to the study team reporting on the suffering after enucleation, especially during the period of adolescence, mainly for aesthetical reasons. An adolescent depicted in an impressive and moving way the loss of self-esteem related to the ocular prothesis and the difficulty in accepting this difference during adolescence. Two parents also reported on the bullying of their child at school for the same reason. This was in line with Zhan et al[11] who evaluated HRQoL using the the PedsQL™ 4.0–in 71 retinoblastoma survivors after enucleation in China. They compared this specific group with healthy children and found that social, school dimensions and total scores were significantly lower. These results were more relevant for children with bilateral eye disease, age at diagnosis ≥ 18 months and in those who considered ocular prosthesis unsatisfactory. After unilateral enucleation pediatric patients with retinoblastoma changed from binocular vision to monocular vision. It has been shown that patients with monocular vision experience many difficulties in daily activities and social role playing, which significantly affects their well-being[21].

Group 3 scored significantly lower than group 2 in the dimension of **self-perception and autonomy**. The self-perception dimension is significantly associated with an older age and this can explain our results, as group 3 was generally composed of older patients than group 2. When we adjusted this score to the patient's age at study time, the significance of the difference between these two groups in "self-perception" disappeared. However, this was not the case for the autonomy dimension, which was not associated with any socio-demographic

factor that we considered. These are mainly patients that have received either additional chemotherapy or EBR for relapsing or resistant disease. Thus, their time to cure was longer, with more intensive treatments, which can easily induce over-protectiveness of parents towards their children.

The scores of our four groups didn't differ in the **physical well-being** dimension, not even for those who had undergone an enucleation. Ruegg et al[12] reported on 1,593 survivors of childhood cancer compared to 695 healthy siblings using a Short Form-36 (SF-36) questionnaire in Switzerland. All survivors scored significantly lower than siblings, and retinoblastoma patients did particularly worse in the physical component summary. Similar results were found by Alessi et al[14] who performed a population-based study of childhood cancer survivors in Northern Italy. Both studies explained that impairment was due to the poor vision of the retinoblastoma survivors. One possible explanation for the different results in our study could lie in better preserved vision due to the newer treatment techniques which would allow the cured patients to participate in more daily activities and sports resulting thus in better perception of their physical well-being. It is, however, more likely to hypothesize that our very intensive daily patching treatment as prevention to amblyopia, starting from the very beginning, regardless of the child's age, allows a functional preservation of remaining retina even after various and burdensome treatment modalities. This needs to be analysed in future.

The present study assessed the HRQoL of a population of retinoblastoma survivors using the KIDSCREEN-52 questionnaire, as did others[15]. Van Dijk et al also used the self-report and the parent proxy-report questionnaire, however they compared patients to normal populations. We compared HRQoL not to healthy children or siblings, but between 4 groups of treatment modalities, which has not been done until now. Other studies used different questionnaires such as either the PedsQL 4.0 generic scale questionnaire or the Short-Form-36 disease specific questionnaire or just a specific local questionnaire. The PedsQL 4.0 generic scale has only 5 health domains (physical, social, emotional, school and psychosocial) and is less precise than KIDSCREEN-52. The Short-Form-36 questionnaire is divided into 4 physical, and 4 mental, components. All these questionnaires are general HRQoL instruments and measure only broad areas of HRQoL. They may not identify issues specifically associated with retinoblastoma, such as changes in facial appearance due to treatment, as the Van Dijk study also underlined. Thus, the difference between the studied and compared populations and between the assessment tools used may contribute to contradictory results and make precise comparison with other studies rather difficult.

5.2 Strengths and limitations

The small sample size of this study limits its statistical power. Although the questionnaire had been sent out to an important number of eligible cured patients, the response rate was only 49 %. Most of the other studies who evaluated HRQoL of retinoblastoma survivors had a response rate that was around 60%. An explanation for the lower response rate of this study may be the fact that almost 50% of the patients came from abroad and received the cover letter mainly in English. This might have discouraged them from responding, in spite of the fact that the questionnaires were all in the patients' language. It is also possible that some letters did not reach their destination.

The heterogeneity of the origins of the survivors and their sociodemographic factors, as the participants lived in many different European and non-European countries, gave us certainly a more global aspect, but may also directly have affected the HRQoL of the participants, which can partially be related to cultural specificities. We didn't collect data on sociodemographic factors such as parents' education, migration background and country of residence which certainly could affect the quality of life.

Another limitation that we shared with other childhood cancer survivor studies was the use of self-reported health problems, as well as the bias of parents-proxy report versus child self-report questionnaire. We used the KIDSCREEN-52 self-report version for retinoblastoma survivors over 8 years old and the KIDSCREEN-52 proxy version for retinoblastoma survivors under 8 years old. All families answered to only one version. In other studies, families responded to both versions and the perceptions of the parents could be compared with the one of the children. It would be interesting to have both opinions for all families and to compare the results.

Another aspect are the adolescents who tend to be more critical about their conditions, without giving the possibility to know for sure whether the explanation is related to the age period or to received treatments. However, the robust linear regression model tells us that an older age at study time has a significant influence on a lower score given to physical, moods and emotion, self-perception and school environment dimensions.

We decided to compare the HRQoL between 4 treatment groups within the same disease, which is independent of population-related norms or comparison with siblings. To our knowledge, this is the first time that quality of life in patients cured of retinoblastoma has been evaluated in relation to the specific treatments.

6. Conclusions and future perspectives

Our results show that the perceived HRQoL by retinoblastoma survivors is globally good and that the HRQoL differes according to the treatment received. Patients treated with EBR have, as expected, the worst HRQoL. The aesthetically sequalae's caused by enucleation had a big impact on the HRQoL, especially during the adolescent period. To our surprise, systemic chemotherapy, although related to more general side effects, scored best in almost all domains, even when compared to the newer local chemotherapies (IAC/IVC).

This research gave us relevant results, that we didn't expect, and allowed us to consider the HRQoL comparison between these four different treatment modalities as something important to understand the effect of the treatments on retinoblastoma survivors' lives. It consolidates the efforts that have been made to develop new conservative treatment techniques with the aim of avoiding EBR and enucleation and encourages the use of local treatments that permit maintenance of good vision and with no aesthetical sequalae's.

We would like to expand our study by increasing participation in order to strengthen the obtained data. For this we plan to contact again the non-responders by sending the cover letter and the Informed Consent Form, in addition to the questionnaire, in the mother language of every patient in order to obtain a higher response rate. It would be also interesting to add more sociodemographic factors such as parents' education, migration background and country of residence that certainly affect the quality of life. We used the KIDSCREEN-52 self-report version for retinoblastoma survivors over 8 years old and the KIDSCREEN-52 proxy version for retinoblastoma survivors under 8 years old. It would be interesting to send both versions to all families in order to compare the parent's vision versus the retinoblastoma survivors' vision.

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8. References

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9. Appendices

Appendix 1: Classification for Intraocular retinoblastoma

Table 1. Reese–Ellsworth Classification for Conservative Treatment of Retinoblastoma

Group	Likelihood of Globe Salvage*	Features
I	Very favorable	a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator b) Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator
II	Favorable	a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator b) Multiple tumors, 4 to 10 disc diameters in size, behind the equator
III	Doubtful	a) Any lesion anterior to the equator b) Solitary tumors larger than 10 disc diameters behind the equator
IV	Unfavorable	a) Multiple tumors, some larger than 10 disc diameters b) Any lesion extending anteriorly to the ora serrata
V	Very unfavorable	a) Massive tumors involving over half the retina b) Vitreous seeding

*Refers to chances of salvaging the affected eye and not systemic prognosis.

Table 2 International Classification System (IIRC)

Group A	Small tumors (≤3mm) confined to the retina (no seeding), at least 3mm from the fovea and 1.5mm from optic nerve.
Group B	Tumors (>3mm) confined to the retina in any location, with clear subretinal fluid ≤ 5mm from the tumor margin
Group C	Localized vitreous and/or subretinal seeding (<5mm in total from tumor margin). If there is more than 1 site of subretinal/vitreous seeding, then the total of these sites must be <6mm. Up to 1 quadrant subretinal seeding may be present.
Group D	Diffuse vitreous and/or subretinal seeding (≥5mm in total from tumor margin). Seeding more extensive than Group C. Retinal detachment >1 quadrant
Group E	Massive retinoblastoma with anatomic or functional destruction of the eye with one or more of the following - Neovascular glaucoma - Massive intravitreal hemorrhage - Aseptic orbital cellulitis - Tumor anterior to anterior vitreous face - Tumor touching the lens - Diffuse infiltrating tumor - Phthisis or pre-phthisis

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Figure 1: Participants and response rate of retinoblastoma survivors

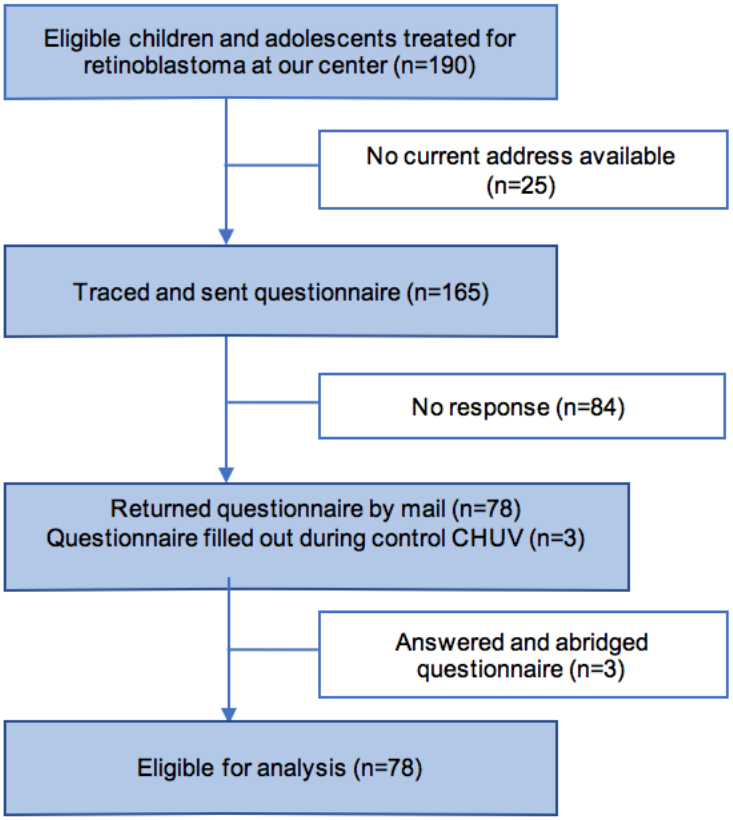


Figure 2: Distribution of patient's age

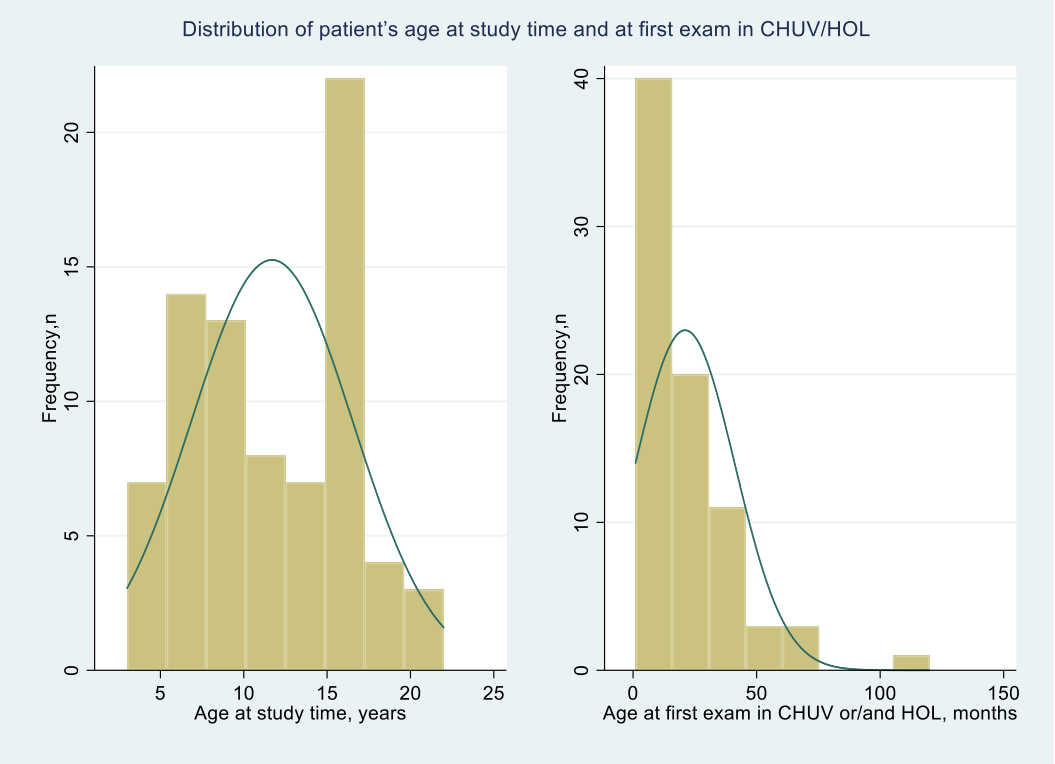


Figure 3: HRQoL scores of all dimensions by treatment group

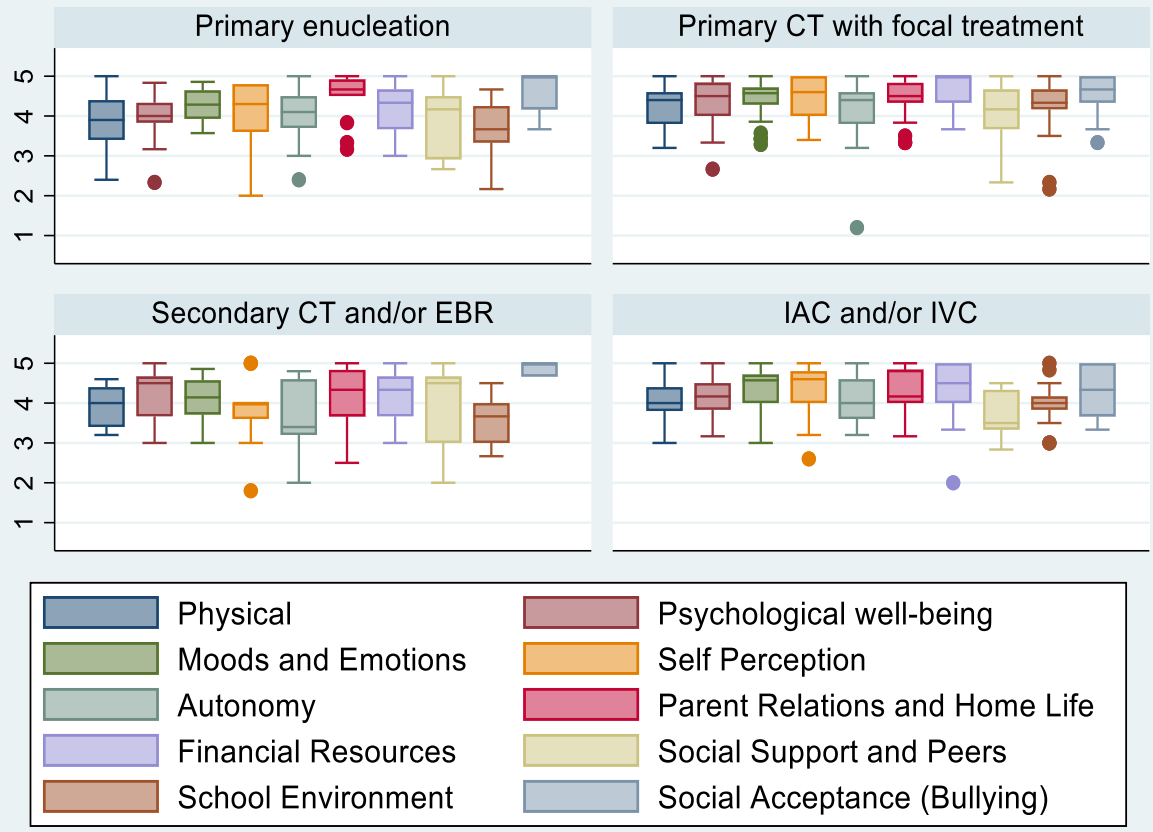
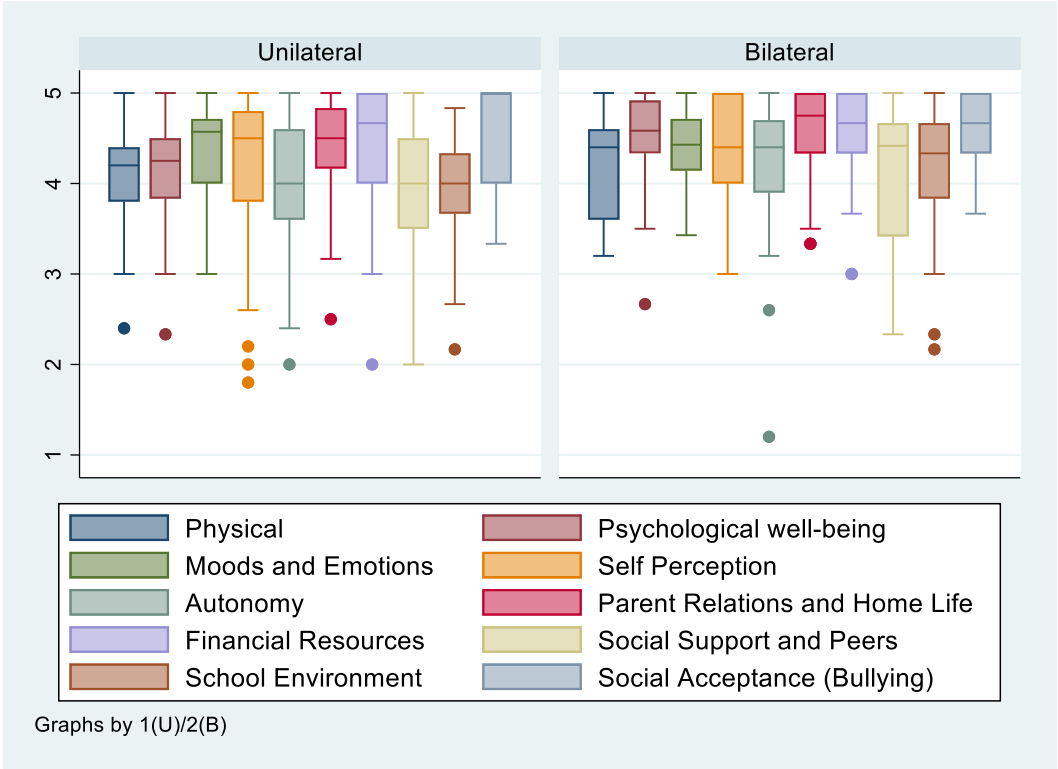
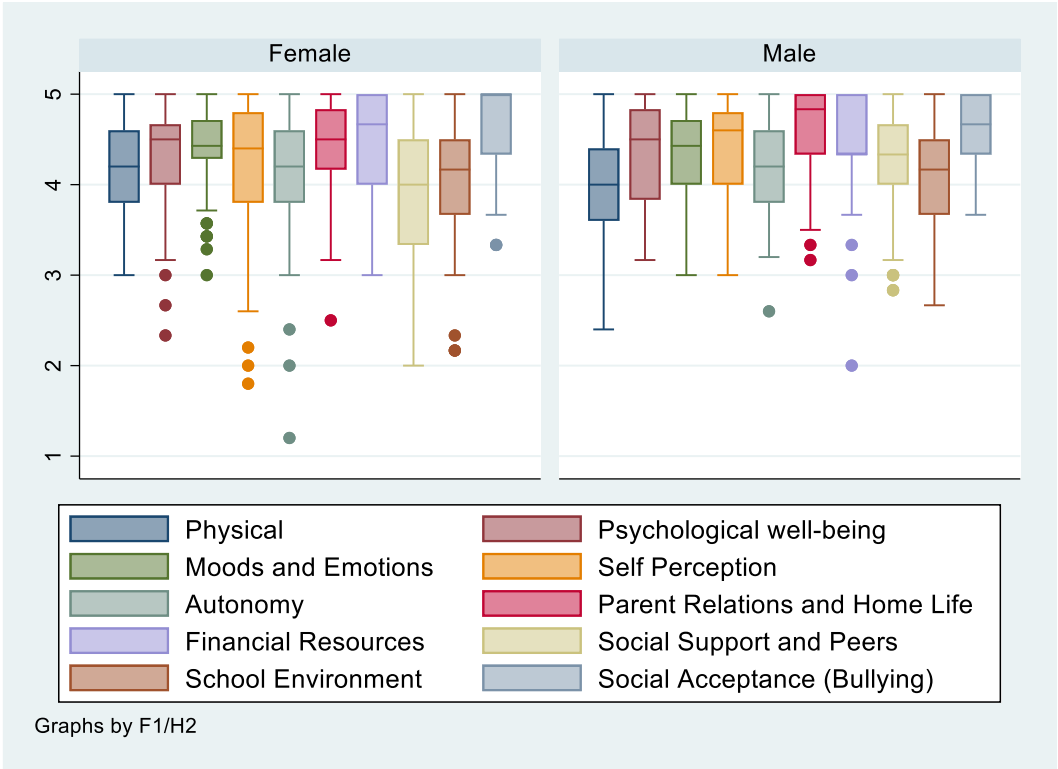
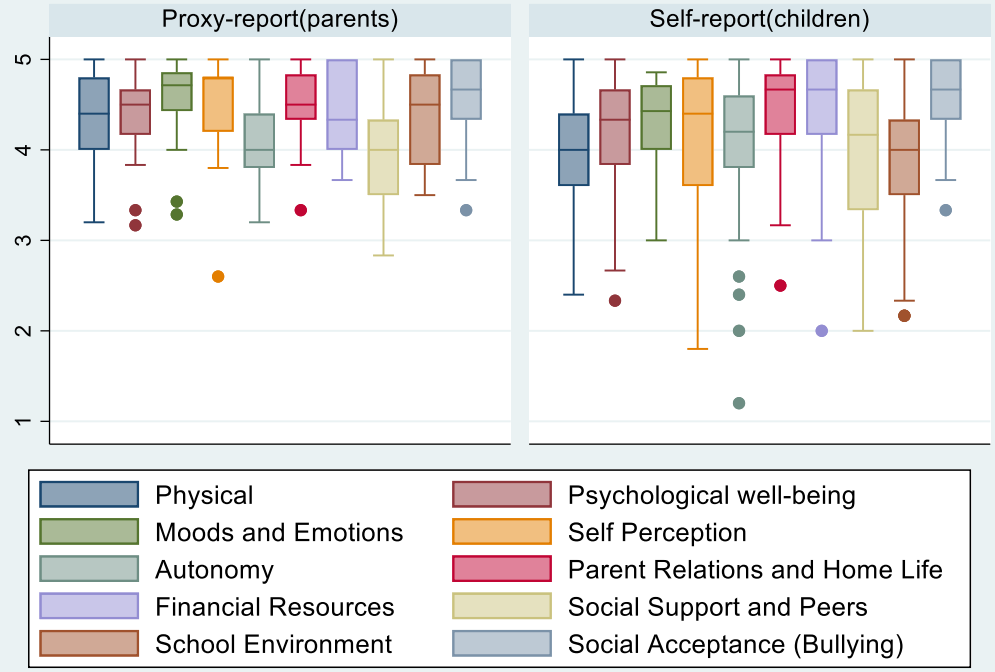


Figure 4: HRQoL scores according to demographic factors







Graphs by Parent (1)/Enfants(2)

Figure 5: HRQoL total score adjusted to patient's age at study time

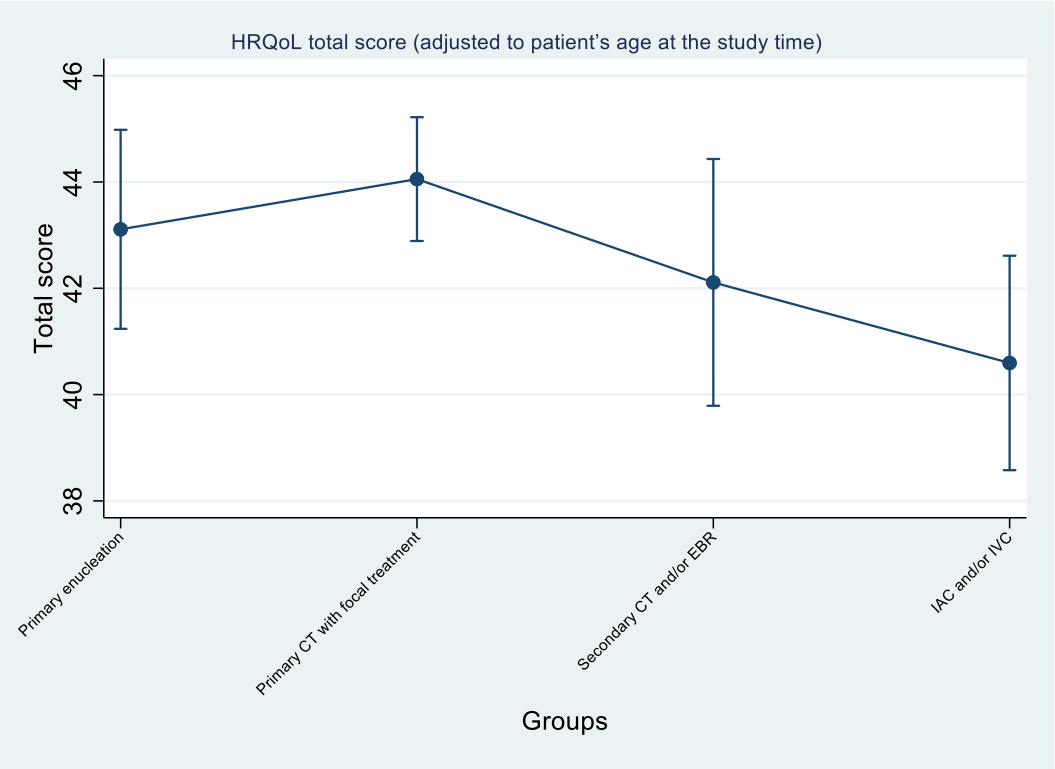


Table 1: Baseline characteristics of the cohort

	Participants (n=78)
Age (years), median (iqr)	12.00 (9.00)
Age at first exam (months), median (iqr)	15.00 (22.00)
Gender, n(%)	
male	37 (47.5%)
female	41 (52.5%)
Laterality, n(%)	
unilateral	50 (64%)
bilateral	28 (36%)
KIDSCREEN-52 version, n(%)	
self-report	57 (73%)
proxy	21 (27%)
Treatment received, n(%)	
Primary enucleation	16 (20.5%)
Primary systemic chemotherapy	38 (48.7%)
Secondary chemotherapy and/or EBR	9 (11.5%)
Intraarterial and/or intravitreous chemotherapy	15 (19.3%)

Table 2: Baseline characteristics of each group

	Primary enucleation (n=16)	**Primary systemic chemotherapy (n=38)**	**Secondary chemotherapy and/or EBR (n=9)**	**Intraarterial and/or intravitreous chemotherapy (n=15)**
Age at evaluation (years), mean (SD)	16 (3.6)	10.76 (4.6)	15 (2.4)	7.5 (2.4)
Age at diagnosis (months), mean (SD)	30.6 (19)	14.05 (13.3)	27.4 (36.9)	24.7 (17.57)
Gender, n				
male	7	19	5	6
female	9	19	4	9
Laterality, n				
unilateral	15	20	3	12
bilateral	1	18	6	3
KIDSCREEN, n				
self-report	16	24	9	8
proxy	0	14	0	7

Table 3: Total score and score per dimension of all participants

	Scores Median (iqr)
Physical	4.20 (1.00)
Psychological well-being	4.50 (0.83)
Moods and Emotions	4.43 (0.71)
Self-Perception	4.40 (0.80)
Autonomy	4.20 (0.80)
Parent Relations and Home Life	4.50 (0.67)
Financial Resources	4.67 (1.00)
Social Support and Peers	4.17 (1.00)
School Environment	4.17 (0.83)
Social Acceptance (Bullying)	4.67 (0.67)
Total Score	43.10 (6.03)

Table 4: Comparison between the four treatment groups and factors influencing the results

Coloured in red: significant results of the comparison between the four treatment groups
Coloured in blue: significant factors influencing the results

Variables / β(p-value)	**Physical**	**Psychological well-being**	**Moods and Emotions**	**Self-Perception**	**Autonomy**	**Parent Relations and Home Life**	**Financial Resources**	**Social Support and Peers**	**School Environment**	**Social Acceptance (Bullying)**	**Total**
Age	- 0.04 (0.01)	- 0.02 (0.12)	- 0.03 (0.00)	- 0.04 (0.00)	- 0.02 (0.23)	+0.02 (0.16)	0.00 (0.75)	+0.01 (0.66)	- 0.04 (0.01)	+0.01 (0.45)	- 0.20 (0.04)
Age (1st examination)	- 0.01 (0.18)	- 0.01 (0.06)	0.00 (0.72)	0.00 (0.85)	0.00 (0.47)	0.00 (0.58)	- 0.01 (0.02)	+0.01 (0.08)	- 0.01 (0.02)	0.00 (0.96)	- 0.01 (0.60)
Sex (Male)	- 0.09 (0.55)	- 0.02 (0.85)	- 0.06 (0.57)	+0.10 (0.52)	0.00 (0.98)	+0.20(0.09)	- 0.03 (0.82)	+0.27 (0.14)	- 0.01 (0.96)	-0.07 (0.54)	+ 0.37 (0.68)
Group											
CT primary (ref)	4.28	4.49	4.47	4.44	4.31	4.57	4.67	4.19	4.36	4.61	44.22
Enucleation	- 0.34 (0.08)	- 0.39 (0.02)	- 0.19 (0.19)	- 0.25 (0.22)	- 0.26 (0.18)	+0.06 (0.69)	- 0.40 (0.03)	- 0.22 (0.34)	- 0.60 (0.00)	+0.07 (0.64)	- 2.21 (0.04)
CT second / EBR	- 0.32 (0.20)	- 0.18 (0.38)	- 0.29 (0.12)	- 0.50 (0.05)	- 0.67 (0.01)	- 0.27 (0.16)	- 0.33 (0.15)	- 0.05 (0.86)	- 0.73 (0.00)	+0.28 (0.14)	- 2.96 (0.03)
IAC/IVC	- 0.22 (0.26)	- 0.25 (0.14)	- 0.01 (0.93)	- 0.06 (0.78)	- 0.26 (0.19)	- 0.17 (0.27)	- 0.23 (0.24)	- 0.46 (0.06)	- 0.38 (0.03)	-0.26 (0.09)	- 2.61 (0.02)
Laterality (Bilateral)	- 0.07 (0.63)	+ 0.32 (0.01)	- 0.01 (0.94)	- 0.04 (0.78)	+0.26 (0.09)	+0.12 (0.32)	+ 0.11 (0.45)	+0.18 (0.33)	+0.27 (0.07)	- 0.01 (0.96)	+ 1.08 (0.25)
KIDSCREEN-52 version (self report)	- 0.32 (0.05)	- 0.11 (0.42)	- 0.29 (0.02)	- 0.28 (0.09)	+0.13 (0.43)	+0.03 (0.79)	+ 0.12 (0.43)	+0.12 (0.57)	- 0.43 (0.01)	- 0.01 (0.95)	- 1.79 (0.09)