Primary Enucleation for Group D Retinoblastoma in the Era of Systemic and Targeted Chemotherapy: The Price of Retaining an Eye

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Synopsis

In this large cohort retrospective analysis of Group D retinoblastoma cases, conservative treatments initiated with intravenous chemotherapy resulted with up to 3 times more number of examinations under anaesthesia compared to primary enucleation.

ABSTRACT

Background

Chemotherapy is increasingly used as primary treatment for group D retinoblastoma, whereas primary enucleation is considered to have diminishing role. This study aimed to compare the management course, including number of examinations under anaesthesia (EUAs), of group D patients treated by enucleation versus chemotherapy.

Methods

A retrospective analysis of 92 group D patients, of which 40 (37 unilateral) underwent primary enucleation and 52 (17 unilateral) were treated with intravenous chemotherapy. Number of EUAs was compared between the treatment groups in respect to the whole cohort, using univariate and multivariate analysis, and to unilateral cases only.

Results

Patients were followed-up for a median of 61 months (mean: 66, range: 14-156), in which time primary enucleated patients had on average 7 EUAs and chemotherapy-treated patients 21 EUAs ($P<0.001$). Chemotherapy, young age, bilateral disease, multifocal tumours, familial and germline retinoblastoma were found on univariate analysis to correlate with increased number of EUAs ($P\leq0.019$). On multivariate analysis, however, only treatment type and presentation age were found significant ($P\leq0.001$). On subanalysis of the unilateral cases, patients undergoing primary enucleation had in average 7 EUAs, as compared to 16 in the chemotherapy group ($P<0.001$). Of the 55 unilateral-presenting patients, a new tumour developed in the fellow eye only in a single familial case.

Conclusion

Group D patients' families should be counselled regarding the significant difference in number of EUAs following primary enucleation versus chemotherapy when deciding on a treatment strategy. In this regard, primary enucleation would be most beneficial for older patients with unilateral disease.

INTRODUCTION

Retinoblastoma is potentially a deadly metastatic cancer. Early in the 20th century, when the only treatment was enucleation, survival rates were estimated at 50%. These rates have improved considerably since the middle of the last century as a result of better understanding of the disease, establishment of specialized centers and development of new management strategies. Currently, survival figures are estimated at 98% in developed countries.[1] Consequently, while saving life remains the primary treatment goal, the main challenge now in battling retinoblastoma is to maximise the quality of life for these patients.

Advanced disease causing irreversible ocular damage, i.e. International Classification of Retinoblastoma (ICRB)[2] group E eyes, are primarily enucleated. Many group D eyes have also been enucleated, but with the advent of conservative treatments, starting with plaque brachytherapy,[3] external beam radiotherapy (EBRT),[4] and chemotherapy,[5] treatment paradigms have shifted from eye removal to salvage. Currently a large armamentarium is available to battle group D retinoblastoma, including systemic and targeted chemotherapy,[6] together with additional local modalities. Primary enucleation on the other hand has a diminished role, and considered by many to be moving towards clinical obsolescence.

The question arises however, as to whether primary enucleation for D eyes has any advantages over eye-preserving techniques. One gain relates to its being the lowest-cost treatment strategy, compared to any other conservative treatment.[7] Another possible advantage would be that primary enucleation results in immediate and total cure in the vast majority of cases, whereas an eye-preserving approach usually involves numerous examinations under anaesthesia (EUAs), in which clinical evaluation and medical interventions are performed. In this sense, the number of EUAs may be regarded as a measure of disease burden, on patients, as well as on their families, and the burden comprised of socioeconomic,[7,8] mental[9] and possibly physical elements.[10] With respect to the latter, it was suggested that general anaesthesia early in life maybe associated with the development of neurobehavioral impairment.[10,11] Although this possible association was not unambiguously proven,[12] however patients' families are increasingly questioning the impact that this may have on the child with the choice of conservative treatment.

We have therefore attempted to quantify the burden of disease by the number of EUAs received by patients in our institution who had group D eyes, where comparison was made between those treated by primary enucleation and those undergoing attempts at globe salvage by chemotherapy. The risk to the fellow eye and the age of the child at presentation are also important considerations in the treatment choice of a group D eye. Such information would be of great value when counseling patients' families regarding possible treatment strategies, and especially when considering primary enucleation.

METHODS

This was a retrospective chart review of consecutive ICRB[2] group D eyes that presented, were treated by primary enucleation or systemic chemotherapy and monitored at the London Retinoblastoma Service from 2002-2014. The study was approved by the Barts Health NHS Trust institutional review board (number 6622) in accordance with the tenets of the Declaration of Helsinki.

Data retrieved from medical records included age of presentation, gender, family history of retinoblastoma, presenting signs, clinical data of first examination, initial and adjuvant treatments, genetic analysis, number of EUAs, dates of first and last EUA, and follow-up clinical data until last examination.

Recommendation of a primary treatment, i.e. enucleation or chemotherapy, was based on several factors, including disease laterality, patient's age at presentation, family history of retinoblastoma, clinical findings in first EUA, in both eyes, and additional considerations with a decision tree shown in **Figure 1**.

Patients treated by means of primary systemic chemotherapy were given 6 courses of vincristine, etoposide and carboplatin (VEC), via a central line, approximately once every 3 weeks. Adjuvant/salvage treatments used as per clinical scenario included transpupillary thermotherapy (TTT), cryotherapy, ruthenium plaque radiotherapy, intra-vitreous chemotherapy (IViC, from 2013)), intra-ophthalmic artery chemotherapy (IAC, from 2009) and EBRT.

In patients who underwent enucleation, after having their eye removed, a vicryl mesh-coated hydroxyapatite implant, to which the extraocular muscles were attached, was inserted, or an acrylic implant, in which case a myoconjunctival technique was used.[13] After eye removal, tissue was harvested for *RB1* mutation analysis and the eye sent for histopathologic evaluation.

EUAs were performed for tumour treatment or screening and were spaced, tailored per eye/s status, with additional considerations that included patient's age, family history of retinoblastoma, presence of *RB1* mutation, previous treatments and the responses to these treatments. Frequency of EUAs ranged from once a week, in case of active vitreous seeds that required repeated IViC, to once every 6 months in controlled cases. At the age of approximately 5 years, after at least one year with no treatments for active tumours, and depending also on a child's cooperation, an awake examination was attempted.

Statistical Analysis and Definitions

All calculations were performed using Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA) and SPSS software version 17.0 (SPSS, Inc., Chicago, IL). Patient characteristics and tumour features of both groups were compared using Chi-squared test. Number of EUAs consisted of all occasions in which a child was clinically evaluated or treated under general anaesthesia. Overall period of EUAs was defined as the time period in months from first (i.e. presentation) to last EUA, and frequency of EUAs was calculated as the number divided by the period in months of EUAs. The outcomes of the 2 treatment groups were compared using Fisher's Exact Test and T-Test, for categorical and

continuous variables, respectively. The data representing number of EUAs was analyzed as the square root of the number of EUAs in order to conform to the assumption of normally distributed data. Variables found significant ($P \leq 0.05$) on univariate analysis were further evaluated using multivariate analysis.

RESULTS

During the study period there were 92 group D retinoblastoma patients (104 eyes). Of these, 40 (43%) patients (40 (38%) eyes) underwent primary enucleation and 52 (57%) patients (64 (62%) eyes) were treated by means of systemic chemotherapy followed by adjuvant/salvage therapies. **Figure 2** shows the distribution of type of primary treatment per year. Overall, most group D patients until 2009 were treated by means of primary enucleation, whereas from 2009 and on, most were treated with primary systemic chemotherapy, with only a single (4%) primary enucleation performed in the last 3 study years.

Primary enucleation versus primary systemic chemotherapy for group D eyes: characteristics of patients and Eyes

The comparison between the two primary treatment groups in terms of demographics, variables at presentation and genetic analysis is shown in **Table 1**. Overall, in both treatment cohorts patients presented across a relatively wide age range, with no significant difference between groups (P=0.286). There were no cases of known family history of retinoblastoma in the enucleation group, compared with 8 (15%) in the chemotherapy group (P=0.009), and positive *RB1* blood mutation, available approximately 3 months after presentation, was found significantly more frequently in the chemotherapy group (73 % vs 20%, P<0.001).

Table 1. Demographic, presentation variables and genetic analysis of group D retinoblastoma patients: primary systemic chemotherapy versus primary enucleation.

Parameter	Primary chemotherapy N=52 (%)	Primary enucleation N=40 (%)	Significance
Gender			P=1.000
Male	28 (54)	22 (55)	
Female	24 (46)	18 (45)	
Uni/bilateral retinoblastoma			P<0.001
Unilateral at presentation	18 (35)	37 (93)	
Bilateral at presentation	34 (65)	3 (7)	
Fellow eye ICRB Group			
A	5 (15)	0	
B	6 (17)	2 (67)	
C	5 (15)	0	
D	12 (35)	0	
E	6 (18)	1 (33)	
Age of diagnosis (months)			P=0.286
Median (mean, range)	11.0 (18.6, 0.6-144.0)	24.0 (23.7, 1.0-60.0)	
Presenting signs			P=0.040
Leucocoria	29 (56)	32 (80)	
Strabismus	13 (25)	7 (17.5)	
Leucocoria and strabismus	4 (8)	1 (2.5)	
Other[a]	6 (12)	0	
Family history of retinoblastoma			P=0.009

Negative (sporadic) Positive (familial)	44 (85) 8 (15)	40 (100) 0	
RB1 Blood mutation Negative Positive	 14 (27) 38 (73)	 32 (80) 8 (20)	P<0.001
[a] Other presenting signs included periorbital swelling in one patient, floaters and flashing lights in 3 children >8-year old and nystagmus in 2 patients. ICRB – International Classification of Retinoblastoma.			

The comparison of clinical characteristics at presentation between the primary treatment groups is shown in **Table 2**. In the primarily enucleated group, significantly more eyes (P≤0.008) presented with unifocal tumours (97.5% and 64% for the primary enucleation and systemic chemotherapy groups respectively) and with tumours obscuring the optic disc (95% and 73% for the primary enucleation and systemic chemotherapy groups respectively). With respect to the decision tree shown in **Figure 1**, during the 13-year study period, 97% of patients observed the criteria shown for initial treatment.

Table 2. First clinical examination results of group D retinoblastoma eyes: primary systemic chemotherapy versus primary enucleation.

Parameter	**Primary chemotherapy N=64 (%)**	**Primary enucleation N=40 (%)**	**Significance**
Tumour focality Unifocal Multifocal	 41 (64) 23 (36)	 39 (97.5) 1 (2.5)	P<0.001
Tumour dimensions (mm) Median (mean, range) Height Base	 9.7 (10.1, 4.4-19.2) 13.0 (12.6, 7.8-19.0)	 10.4 (10.4, 6.9-13.7) 14.2 (14.1, 9.2-17.5)	P=1.000
Quadrants of retinal detachment No detachment Local 1 2 3 4	 6 (9) 12 (19) 3 (5) 7 (11) 7 (11) 29 (45)	 2 (5) 6 (15) 3 (7.5) 3 (7.5) 8 (20) 18 (45)	P=0.708
Optic disc obscured Not obscured Obscured	 17 (27) 47 (73)	 2 (5) 38 (95)	P=0.008
Fovea involvement Not involved Sub-foveal fluid Foveal tumour	 11 (17) 11 (17) 42 (66)	 2 (5) 6 (15) 32 (80)	P=0.156
Retinoblastoma seeds No seeds Sub-retinal	 9 (14) 41 (64)	 0 25 (62.5)	P=1.000

Vitreous	28 (44)	26 (65)	

Of the primary chemotherapy group, 61 (95%) eyes received additional treatments. Of these, 50 (78%) had additional TTT and/or cryotherapy, 12 (19%) underwent plaque radiotherapy, and 5 (8%) were treated with EBRT. Of the latter 5 patients, all were eventually enucleated. Twenty patients (31%) underwent IAC and 4 (6%) IViC. Twenty four (46%) patients (24 (37.5%) eyes) underwent secondary enucleation. Treatments to the fellow eye in the bilateral cases included TTT and/or cryotherapy in 33 (87%) eyes, plaque radiotherapy in 5 (13%), EBRT in 6 (16%), IAC in 10 (26%), IViC in 1 (3%) and enucleation (primary or secondary) in 17 (45%) eyes.

Primary enucleation versus primary systemic chemotherapy for group D eyes: examinations under anaesthesia

The median number of EUAs for the whole cohort was 14 (mean: 16; range: 2-63). The median number of EUAS for the primary chemotherapy group was 18 (mean: 21; range: 4-63) and for the primary enucleation group, 7 (mean: 7; range: 2-14; P<0.001; **Figure 3**).

On univariate analysis (**Table 3**), in addition to the primary treatment type, the following variables were found to associate with increased number of EUAs: young age of presentation, bilateral disease, eyes harboring multifocal tumors, family history of retinoblastoma and positive *RB*1 mutation (P≤0.019). On multivariate analysis, however, only age of presentation (P<0.001) and treatment type (P=0.001) were found to significantly correlate with number of EUAs (**Figure 4** and **Table 4**). The median overall period of EUAs for the whole cohort was 33 months (mean: 35; range: 2-106) and for the chemotherapy and enucleation groups, 40 and 27 months (mean: 40 and 27; range: 4-106 and 2-66) , respectively (P=0.001). The median frequency of EUAs for the whole cohort was 0.48 EUAs/month (mean: 0.52; range: 0.13-1.43) and for the chemotherapy and enucleation groups, 0.51 and 0.31 EUAs/month (mean: 0.58 and 0.43; range: 0.31-1.37 and 0.13-1.43), respectively (P=0.022).

Table 3. Clinical and treatment parameter correlations with number of examinations under anaesthesia: univariate analysis.

Parameter	**Number of EUAs*** Median (mean, range)	**Significance**
Primary treatment type		P<0.001
Enucleation	7 (7, 2-14)	
Systemic chemotherapy	18 (21, 4-63)	
Age of presentation	NA**	P=0.001
Disease laterality		P<0.001
Unilateral	9 (10, 3-27)	
Bilateral	19 (22, 2-63)	
Tumour focality		P=0.019
Unifocal	11 (14, 3-57)	
Multifocal	18 (21, 2-63)	

Germline disease Yes No	 18 (19, 2-57) 9 (10, 3-27)	P<0.001
Family history of retinoblastoma Yes No	 20 (26, 17-57) 12 (14, 2-63)	P=0.004
* EUAs – examinations under anaesthesia. ** Non-applicable (continuous variable; **Figure 4**).		

Table 4. Clinical and treatment parameter correlations with number of examinations under anaesthesia: multivariate analysis (Stepwise Linear Regression).

Parameter	Unstandardized Coefficients (β)	95% Confidence Interval for β	Significance
Primary treatment type – systemic chemotherapy	0.98	0.41-1.55	P=0.001
Age of presentation*	-0.42	(-0.06)-(-0.02)	P<0.001
* Continuous variable.			

Of the bilateral cases, the fellow eye was still active while the D eye was already controlled or removed in only 7% of eyes. After excluding these cases from analysis, in order to obtain an evaluation of EUAs attributed mainly to D eye, differences between the 2 groups for the number of EUAs remained unchanged (mean of 21 versus 7 EUAs for the chemotherapy and enucleation groups, respectively; P<0.001). On subanalysis, comparing only the unilateral cases that underwent primary enucleation (n=37) to those unilateral cases treated with primary systemic chemotherapy (n=17), again the latter group underwent significantly more EUAs (average of 7 and 16 EUAs for the enucleation and chemotherapy groups, respectively; P<0.001; **Figure 5**). Further subanalysis on unilateral cases presenting with unifocal tumours, no family history of retinoblastoma and no germline disease, treated by means of primary enucleation (n=32) versus primary intravenous chemotherapy (n=14), showed that the latter group underwent significantly more EUAs (average of 8 and 15 EUAs for the enucleation and chemotherapy groups, respectively; P<0.001). Investigating the treatment course of both eyes in the bilateral cases (excluding D/D cases), in 19/23 (83%) of those treated with systemic chemotherapy, the limiting factor in terms of number of EUAs was the D eye, rather than the fellow eye which showed tumour control earlier in the course of disease. This analysis included also all cases in which a D eye underwent secondary enucleation; in these cases the fellow eye was found stable before the D eye was secondarily enucleated. Analyzing the bilateral cases in which the D eye was primarily enucleated, obviously, in the two B/D patients, the non-D eye was the limiting factor.

<u>Development of new tumours in the fellow eye in patients presenting as unilateral group D</u>
The median age of presentation of the unilateral-presenting D patients (n=55) was 24 months (mean: 26, range: 0.6-144) and they were followed-up for a median time of 60 months (mean: 61, range: 15-125). All these patients, but one, remained with unilateral disease throughout follow-up. This single patient had a positive family history of retinoblastoma and was found positive for *RB*1 gene on cord blood examination. He was

diagnosed with unilateral group D retinoblastoma at the age of 2 weeks and involvement of the second eye at the age of 8 months, 4.5 months after completion of 6 VEC cycles. Of note, of the unilateral cases, in 9 (16%), a blood *RB*1 mutation was detected.

Follow-up, metastatic spread and survival

Study patients were followed-up for a median time of 61, 54 and 73 months (mean: 66, 64 and 69; range: 14-156, 14-156 and 19-125) for the whole cohort, systemic chemotherapy and enucleation groups, respectively (P=0.466). In this time period, no cases of systemic metastatic spread and no cases of death were recorded.

DISCUSSION

The treatment of retinoblastoma is complex, and many considerations need to be taken into account when deciding on a management strategy. A particularly important time point is at the first examination when essential factors are used to inform a risk/benefit assessment, and an optimal treatment plan formulated, where the alternatives are eye removal or preservation. In the last 50 years conservative treatment modalities have evolved significantly to become the mainstay practice for group D eyes, whereas primary enucleation nowadays is considered by many to be declining.[6] This trend is reflected in our study with a watershed time point in our department in 2009, when the rate of group D primary enucleations reduced from 60% to 19%. This coincided with the introduction of IAC and later IViC as salvage treatments over EBRT.[14] The improved success of these modalities over EBRT prompted the attempt at salvage of more eyes than before.

The disadvantages of primary enucleation are obvious and include total loss of vision and relative disfigurement on the affected side. The main advantage however over eye retention is that it provides immediate cure in the vast majority of cases, hence patients are exposed to less medical interventions and less EUAs. With regard to the latter, another advantage of primary enucleation is that is facilitates detection of tumour *RB1* mutation, or its ruling out, hence enabling the planning of fellow eye screening with EUAs earlier in the course of disease. In the present study, primary enucleation for group D retinoblastoma was found to result in significantly less consecutive EUAs as compared to primary chemotherapy followed by adjuvant/salvage treatments. This was true for the whole cohort, showing a threefold difference between treatment groups, as well as for the unilateral cases alone, showing an over two-fold difference between treatment groups. It was also the case when patients with unilateral, unifocal, negative family history of retinoblastoma and non-germline disease were compared, showing a nearly two-fold difference between treatment groups. Overall period of EUAs also differed significantly, with some chemotherapy-treated patients continuing assessments for up to 10 years. Interestingly, the primary chemotherapy group patients also underwent EUAs more frequently, as well as for longer, further emphasizing the highly significant differences in number of EUAs between the groups.

Apart from primary treatment type, young age of presentation was found to independently correlate with increased number of EUAs. Repeated EUAs after primary enucleation of a unilateral D eye, especially at young age, are mainly for screening purposes, to closely monitor the fellow eye in case new tumours develop, where genetic testing has not been able to rule out a germline mutation. In cases of unilateral group D eyes treated by primary systemic chemotherapy, screening of the fellow eye is only a small part of the EUA burden, as retaining a D eye is a difficult process, requiring repeated interventions and examinations performed under anaesthesia. Further variables found to correlate with number of EUAs were presence of multifocal tumours and positive *RB*1 gene, variables known to be linked.[15] These patients are at increased risk of developing new tumours and therefore regularly undergo more EUAs. Retinoblastoma patients with positive family history are at even greater risk to developing new tumours, and are managed in a similar manner. Interestingly, these variables were non-significant on multivariable analysis, further emphasizing the impact of age of presentation, a given parameter, and more so, of primary treatment type, a selected one.

Our overall findings regarding differences in EUAs between the treatment groups and associated predisposing risk factors may intuitively be predicted. The main added value however of this report is that we have approached disease burden not in terms of clinical parameters such as number of tumours or genetic information alone, but by the number of EUAs. The approach was first a conceptual one - the focus on EUAs as a measure of disease burden and secondly to quantify the number, overall period and frequency of EUAs. Amongst the many clinical parameters that must be weighed up by treating specialists, including the aim of retaining the eye and some vision, this new information is helpful for families to decide which path they may wish to follow. The latter may vary by geographical location and available resources to the healthcare system and the individual families.

The potential consequences of general anaesthesia in infancy also need to be borne in mind. Recent paediatric and anaesthetic literature finds this to be safe in the short term.[16] However, some studies, mainly in animal models but also in humans, have pointed toward the possibility of long-term neurological impairment after anaesthesia early in life.[10,17] Most of these were after a single event of general anaesthesia, but the question arises as to whether multiple EUAs may lead to future neurologic or cognitive impairment. In a disease like retinoblastoma the effect of anaesthesia on these would be difficult to tease out, as there may be other important factors such as visual loss, disfigurement from surgery as well as effects of chemotherapy or radiotherapy. There may be therefore instances where enucleation is desired for a reduction in the number of anaesthetics. It is not known, however, whether a two or three-fold reduction is of clinical significance.

In this study we also determined the chances of a unilateral-presenting group D patient to develop new tumours in the fellow eye, and found it to be less than 2%, in a single patient less than 6 month of age and with positive family history of retinoblastoma. Our findings are in keeping with those reported by Abramson et al[18] and Wilson et al,[19] who found family history and young age of presentation to be associated with increased risk of developing new tumours. Interestingly, 8 (15%) of the unilateral patients in the present study (not including the abovementioned one) were found to be genetic cases, however these too remained unilateral throughout follow-up. Based on the present findings, the genetic status in sporadic cases, which is usually not known at presentation, does not play a large role in treatment-decision making at the first EUA, with age and tumour multifocality being more immediate pointers to a strategy. Primary enucleation is clearly not recommended in cases of bilateral disease and these findings are reassuring in that it could be offered to children presenting with unilateral group D disease with no family history. Being on the safe side and taken together with the abovementioned findings regarding EUAs, the best candidates for primary enucleation would be older group D patients with unilateral disease.

While disease laterality, age of presentation, tumour focality and fellow eye ICRB Group are crucial factors in treatment strategy planning, additional factors may also play a role. Unilateral cases in which the optic disc was obscured were significantly more often treated by enucleation because of potential optic nerve involvement and hence metastasis. However, optic disc obscuration is a common finding in Group D retinoblastoma that was found in 82% of eyes in the present study; hence it was not used as a major factor in the decision tree. Presence of *RB1* mutation is another important consideration, as the fellow eye is at risk of tumour formation. However, this information is often not available at first EUA in a sporadic case, when treatment planning is done. In a simple treatment planning

decision tree there will be some features that cannot be integrated and indeed new treatments will emerge which may change such an algorithm. In many centres IAC is commonly used as first line treatment for Group D retinoblastoma, but high risk histopathology features can occur, in our series in 13%.[20] As these features carry a risk of metastatic spread, centres such as ours used systemic chemotherapy as the main conservative treatment modality for Group D eyes with IAC for salvage. For the purposes of the present report, this enabled comparison of outcomes after primary enucleation versus systemic chemotherapy in a large, long follow-up, Group D retinoblastoma cohort. As more safety data for IAC emerge, our decision algorithm will also evolve, but this large cohort of systemic chemotherapy eyes will serve as a benchmark for number of EUAs, enucleation rate, systemic outcomes, high risk histopathology features and visual acuity in salvaged eyes.[14,20,21]

This was a retrospective study, hence its inherent limitations relate to data collection and randomization. Primary chemotherapy was found to be the main treatment modality since 2009. The later study subjects that presented in those years have been followed-up for a shorter time, likely resulting in underestimation in the increased EUAs seen in patients treated with primary chemotherapy. Analysing the primary enucleation group, two bilateral cases resulted in an increased number of EUAs, because the fellow non-D eye was still being treated and monitored. Altogether, there were factors contributing to potential bias in calculation of number of EUAs in both treatment groups. In addition, there are no strict guidelines as to how often EUAs should be performed or when to convert to awake examinations. Despite these reservations, we believe that our findings regarding differences in EUAs between the treatment groups represent the overall perspective of one of the largest group D cohorts reported to date in the literature.

In summary, in this cohort, primary enucleation for group D retinoblastoma resulted with 3 times less EUAs, as compared to eye-preserving chemotherapy followed by additional treatments. Number of EUAs was found to dependent on treatment type and age of presentation, with younger patients treated with systemic chemotherapy being prone to undergo more examinations. In addition, late involvement of the fellow non-D eye in unilateral-presenting group D patients was found in this study to be a rare occurrence, noticed only in a single 6 months-old patient with family history of retinoblastoma. These results are useful additions for counselling families regarding treatment alternatives. Taken together, the most appropriate candidates to benefit from the advantages related to primary enucleation are older patients with unilateral disease and no family history of retinoblastoma.

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FIGURE LEGEND

Figure 1 –Decision tree used for primary treatment planning and recommendation to patients' parents. Additional factors may play a role. RB – retinoblastoma, IVC – intravenous chemotherapy.

Figure 2 – Number of group D eyes per year of presentation and primary treatment modality.

Figure 3 – Differences in number of examinations under anaesthesia (EUAs) between the treatment groups. Analysis of the whole cohort (N=104). Primary enucleation resulted with x3 less EUAs in average as compared to primary systemic chemotherapy (P<0.001).

Figure 4 – Relations between primary treatment type, age of diagnosis and number of examinations under anaesthesia (EUAs). Young presentation age and primary chemotherapy (in contrast to primary enucleation) were found on multivariate analysis to be significant factors associated with increased number of EUAs (P≤0.001).

Figure 5 - Differences in number of examinations under anaesthesia (EUAs) between the treatment groups. Analysis of unilateral cases only (N=54). Primary enucleation resulted with x2.3 less EUAs in average as compared to primary systemic chemotherapy (P<0.001).