Number, Frequency and Time Interval of Examinations Under Anesthesia in Bilateral Retinoblastoma

[1,2,3]Ido Didi Fabian, [2]Vishal Shah, [3]Noa Kapelushnik, [1]Zishan Naeem, [1]Zerrin Onadim, [1]Elizabeth A Price, [1,4]Catriona Duncan, [5]David Stansfield, [1,2,6]Mandeep S Sagoo, [1,2]M. Ashwin Reddy

[1]Retinoblastoma Service, Royal London Hospital, [2]Moorfields Eye Hospital, London, UK; [3]Ocular Oncology Service, Goldschleger Eye Institute, Sheba Medical Center, Tel-Aviv University, Tel Aviv, Israel; [4]Paediatric Oncology Department, Great Ormond Street Hospital, [5]Anaesthetic Department, Royal London Hospital, [6]University College London, Institute of Ophthalmology, London, UK

Corresponding author: Ido Didi Fabian, Ocular Oncology Service, Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, 52621, Israel

E-mail address: didi@didifabian.com

Tel.: +972 3 5302874

Fax: +972 3 5302822

ABSTRACT

Purpose

Current practice in retinoblastoma (Rb) has transformed this malignancy into a curable disease. More attention should therefore be given to quality of life considerations, including measures related to examinations under anesthesia (EUAs). We aimed to investigate EUA measures in bilateral Rb patients, and compare the findings to EUAs in unilateral Rb.

Methods

A retrospective analysis of bilateral Rb patients that presented to the London Rb service from 2006-2013, were treated and had long-term follow-up.

Results

A total of 62 Rb patients, 15 (24.2%) of which had International Intraocular Retinoblastoma Classification (IIRC) group A/B/no Rb at presentation, 26 (41.9%) C/D, and 21 (33.9%) were E in at least one eye. The mean number of EUAs was 35.8±21.5, mean time from first to last EUA was 50.6±19.9 months and mean EUA frequency was 0.715±0.293 EUAs/month. IIRC group was found not to correlate with any of the EUA measures. Age at presentation inversely correlated with time interval from first to last EUA and to EUA frequency ($p \leq 0.029$). Rb Family history correlated with the latter measure ($p=0.005$) and intra-ophthalmic artery chemotherapy and brachytherapy correlated with all EUA measures ($p \leq 0.029$). Mean follow-up time was 80.1±24.3 months. When compared to a previously reported cohort of unilateral Rb, the present group underwent 3x more EUAs ($p<0.001$) over nearly double the time ($p<0.001$).

Conclusions

Families should be counselled on anticipated EUA burden associated with bilateral Rb. In this respect age at presentation and family history were found to have a predictive role, whereas IIRC group did not.

Keywords: retinoblastoma, examination under anesthesia, chemotherapy, enucleation

INTRODUCTION

Retinoblastoma (Rb) is the commonest primary intraocular malignancy of childhood,[1] and is a potentially life-threatening metastatic condition. Advances in Rb management have transformed the disease into a curable one, with survival rates in high-income countries that are estimated at nearly 100%.[2] This necessitates the need to consider quality of life implications associated with the various management options.

Examinations under anesthesia (EUAs) are necessary in Rb at presentation and during follow-up because the majority of cases develop before 5 years of age, treatments require precision and can be painful. It is therefore common for these children to undergo repeated EUAs over the course of their treatment, the frequency of which is governed by a variety of clinical factors. Rb patients' parents and guardians, however, are increasingly questioning the need for additional EUAs and ask about the potential associated risk. The number of EUAs, in this sense, may be regarded as a measure of disease burden, on patients and their families, and the burden comprises many elements, including mental, socioeconomic, and possibly physical.[3–7]

Previous studies have shown that treatment choice has a significant impact on the number of EUAs, with unilateral cases treated by means of primary intravenous chemotherapy (IVC) found to undergo three times as many EUAs as those treated with primary enucleation.[8, 9] On review of unilateral Rb cases that presented to the London Rb Service from 2006-2013, the International Intraocular Retinoblastoma Classification (IIRC)[10] was found also to play a role, with B/C eyes undergoing twice the number of EUAs as D/E eyes.[8] The aims of this study were: (1) to quantify EUA burden in a cohort of bilateral Rb cases from all IIRC groups; (2) to investigate possible associations between the number, period of time and frequency of EUAs and clinical and therapeutic factors; and (3) to compare the number of EUAs in the present cohort of bilateral Rb to the number reported previously on unilateral Rb.[8]

METHODS

This was a retrospective analysis of consecutive patients with bilateral Rb whom presented to the London Retinoblastoma Service from January 2006 – December 2013, were treated and monitored with long-term follow-up (until June 2018). Patients who presented with unilateral, but developed bilateral disease during follow-up were also included, and so were patients with family history of Rb who were initially screened with normal findings, but eventually developed bilateral disease. 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 at first EUA, sex, laterality at presentation and during follow-up in case of patients with no Rb or unilateral disease at presentation, IIRC group,[10] primary and additional treatments, data from operation notes, number and timing of EUAs, and follow-up clinical data until last examination.

Patients treated by means of IVC, the main modality used in our centre for bilateral Rb, were given 6 courses of vincristine, etoposide and carboplatin (VEC), via a central line, approximately once every 3 weeks. Adjuvant and/or salvage treatments used as per clinical scenario included transpupillary thermotherapy (TTT), cryotherapy, ruthenium plaque brachytherapy, intra-ophthalmic artery chemotherapy (IAC) from 2009 using melphalan, topotecan and/or carboplatin, intravitreal chemotherapy (IViC) from 2013 using melphalan and/or topotecan, and external beam radiotherapy (EBRT) used only in the early study years before the introduction of IAC in our centre.

All focal treatments (i.e. plaque brachytherapy, TTT and cryotherapy), IAC, IViC, enucleation, each fractionated EBRT session (1/day, 5 days a week for 4 weeks), central line insertion and removal for VEC administration, and implant exposure repair were performed under general anesthesia. General anesthesia was performed as described previously.[8]

Frequency of EUAs in cases of active disease was dictated by tumor response and need for further treatment. Screening examinations to detect tumor relapse or new tumors were also performed under general anesthesia. Screening protocol for patients with germline disease (all patients in the present study) included an EUA once every 4-6 weeks until the age of 12 months, once every 2-3 months from 12-24 months, once every 4 months from 24-36 months and every 6 months thereafter, until seen awake. These time intervals were shortened in case of tumor relapse or development of a new tumor (i.e., active disease). At around the age of 5 years, depending on the patient's cooperation and after at least one year of no active disease, an awake examination was attempted.

Definitions and Statistical Analysis

All calculations were performed using Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA) and SPSS software version 17.0 (SPSS, Inc., Chicago, IL). Number of EUAs consisted of all occasions in which a child was clinically evaluated or treated (focal and non-focal treatments) under general anesthesia. The EUA time interval was the time from first to last EUA (in months) and the frequency of EUAs was the number of EUAs/month. For analysis, the cohort was divided into 3 sub-groups: (1) presentation with group A, B (i.e. tumors confined to the retina) or normal fundi in both eyes (0/0, 0/A, 0/B, A/B, B/B), (2) presentation with group C or D (Rb seeds and/or retinal detachment) in one or both eyes, but not group E (0/C, 0/D, A/C, A/D, B/C, B/D, C/C, C/D, D/D) and (3) group E in at least one eye (0/E, A/E, B/E, C/E, D/E, E/E). Correlations to number of EUAs, time interval from first to last EUA and to frequency of EUAs were performed via univariate analysis using Fisher's Exact Test and T-Test, for categorical and continuous variables, respectively. Variables found significant ($P \leq 0.05$) on univariate analysis were further evaluated using multivariate analysis (Stepwise Linear Regression). A comparison to EUAs (number, time interval and frequency) in a cohort of 107 unilateral Rb[8] was also performed.

RESULTS

The study cohort comprised of 62 patients (124 eyes), 35 (56.5%) of which were males. Of these, 15 (24.2%) were classified as sub-group 1, 26 (41.9%) as 2, and 21 (33.9%) as sub-group 3. The detailed IIRC groups are shown in Table 1 and Figure 1. The mean age at first EUA was 11.8 (±20.5) months, 19 (30.6%) of the patients had positive family history of Rb and underwent screening, and the remaining had sporadic Rb. Of the 62 patients, 51 (82.3%) were diagnosed with bilateral Rb at first EUA. The remaining patients had no Rb at presentation (n=3, all had family history of Rb and underwent screening) or unilateral Rb at presentation (n=5 with family history of Rb and n=3 with sporadic Rb). In this sub-cohort, the mean time interval from first EUA to development of bilateral Rb was 4.8 (±2.0) months.

Initial management included IVC with or without focal therapy in 40 (64.5%) patients, enucleation and IVC in 12 (19.4%) patients, enucleation of one eye and observation (in case of no Rb) or focal therapy in the fellow eye in 5 (8.1%) patients, focal therapy only in 2 (3.2%) patients and observation only in 3 patients (no Rb at first screening EUA). Further management included IVC in 4 (6.5%) patients (two had no Rb at first EUA and two had IIRC group A/B at presentation and were initially treated by means of focal therapy), salvage IAC in 30 (48.4%) patients, IViC in 4 (6.5%) patients, laser TTT in 36 (58.1%) patients, cryotherapy in 49 (79.0%) patients, ruthenium plaque brachytherapy in 15 (24.2%) patients, secondary enucleation (post previous IVC) in 23 (37.1%) patients, salvage EBRT in 10 (16.1%) patients, and repair of exposed implant in 3 (4.8%) patients.

Mean follow-up time was 80.1±24.3 months and mean age at last visit was 91.8±27.8 months. None of the patients developed metastatic spread and all were alive at last visit.

Overall, the mean number of EUAs was 35.8±21.5, mean time from first to last EUA was 50.6±19.9 months (Figure 1) and mean EUA frequency was 0.715±0.293 EUAs/month. Excluding the 10 patients who underwent salvage EBRT, the mean number of EUAs was 30.6±16.9, mean time from first to last EUA was 48.9±19.2 months and mean EUA frequency was 0.636±0.2083 EUAs/month. All patients at last visit were examined awake.

Table 2 shows the univariate analysis results for number of EUAs, interval from first to last EUA and for EUA frequency. Various interventions were found to significantly correlate with more EUAs, including IAC, IViC, plaque brachytherapy, EBRT and implant repair ($p \leq 0.039$). Of the variables known at time of presentation, there was a trend towards young age at presentation though statistical significance was not reached ($p=0.053$). The remaining variables were found not to play a role ($p \geq 0.403$). For the time interval from first to last EUA, younger age at presentation correlated with a longer time interval ($p<0.001$). Further variables that reached statistical

significance were enucleation surgery, IAC, plaque brachytherapy and implant repair ($p \leq 0.016$). Lastly, younger patients and independently patients with positive family history of Rb were found to undergo EUAs significantly more frequently ($p \leq 0.029$), and so did patients that were treated by means of secondary IAC, IViC, plaque brachytherapy and/or EBRT ($p \leq 0.029$).

On multivariate analysis, various interventions were found to have a significant role (Table 3). In terms of variables at presentation, age at presentation was found to significantly correlate with the time interval from first to last EUA as well as to EUA frequency. For the latter variable, familial Rb was also found to be a significant factor.

Comparing bilateral Rb cases (present cohort) to a cohort of 107 unilateral Rb patients[8] (Figure 2), patients from the latter cohort underwent in average nearly 3 times less EUAs ($p<0.001$) and for a significantly shorter time interval (nearly half the time, $p<0.001$). Differences in EUA frequency between cohorts were found to be non-significant ($p=0.127$).

DISCUSSION

Patients with bilateral Rb in the present study underwent on average 35.8 ± 21.5 EUAs over an average period of 50.6 ± 19.9 months, at an average frequency of 0.715 ± 0.293 EUAs/month until they were deemed suitable for examination while awake.

Interestingly, these results did not differ significantly depending on the disease stage at presentation, when comparing pooled subgroups based on IIRC classification (no Rb/A/B vs C/D vs E group). This is in contrast to our previous report of unilateral cases,[8] which found B/C groups to undergo twice the number of EUAs as D/E, highlighting a key difference between unilateral and bilateral Rb. A possible explanation to these differences between the unilateral and bilateral cohorts is that many of the advanced unilateral patients underwent primary enucleation, after which EUA frequency was significantly reduced. Most patients in the bilateral cohort, even if underwent enucleation of one eye, the fellow eye was conservatively treated and monitored, necessitating additional frequent EUAs. Further differences between the two cohorts were noted related to the number of EUAs; patients in the present cohort underwent nearly 3-times more EUAs compared to those with unilateral disease and for nearly double the time (from first to last EUA), and differences were found to be highly significant. Patients with bilateral Rb also underwent EUAs more frequently (x1.3); differences however in this respect were non-significant. It should be pointed out that patients with unilateral-presenting Rb can develop bilateral disease during the course of their disease, as occurred in eight (12.9%) patients in the present cohort. Therefore we recommend in this scenario, in those cases that present relatively young, without a family history of Rb (n=3 in the present cohort), to perform frequent EUAs (as indicated in the Methods section), until the genetic status is clarified.

Number of EUAs, time interval from first to last EUA and EUA frequency are different variables that can be used to illustrate the overall EUA burden when counselling parents/guardians. Findings of the present study revealed that several clinical factors significantly correlated with the various EUA variables. A useful way to subgroup these factors is as follows: (1) factors known at time of diagnosis, such as age and bilaterality at presentation and family history of Rb, (2) factors that evolve early after diagnosis, such as the primary treatment type, and (3) those that evolve later during the course of disease, such as salvage treatments. While the first two subgroups are of potential predictive value, the latter reflect disease activity and is thus of little to no predictive value.

Of the factors known at presentation, age at presentation was found to play a significant role in respect to both EUA interval and frequency, and showed a trend towards more EUAs ($p=0.053$). These findings are in agreement with previous findings of a large group D Rb cohort, which comprised also of unilateral cases,[9] and are likely a result of the screening protocol used in our service.

All patients in the present study, by definition, had germline disease and of them, 30.6% had a positive family history of Rb. This was found to significantly correlate with length of duration in months from first to last EUA, likely related to the implicit need for screening in these patients.

Primary enucleation was found to significantly correlate with EUA time interval only on univariate analysis. Of note, in some clinical scenarios both enucleation and conservative therapy are valid options that need to be offered and discussed. In the present study, on multivariate analysis these did not differ in respect to the EUA burden, in contrast to the known impact, in this context, of primary treatment in cases of unilateral Rb.[8]

Various salvage therapies were also found to significantly correlate with EUA burden, including IAC, IViC, plaque brachytherapy, EBRT and implant repair, reflecting active disease or implant exposure in case of the latter intervention. While IAC and IViC are gaining popularity as efficient modalities for certain clinical scenarios, EBRT is now largely obsolete because of the associated increased risk of developing secondary tumors in germline cases.[11] This is a reflection of the historical cohort that comprises this study. In this context, repeated EUAs, once a day for four weeks in cases of EBRT, significantly increased EUA burden.

While the focus of the present study was on EUAs as a measure of disease burden, saving life remains the main goal in Rb management. Furthermore, the quality of life of patients diagnosed with Rb depend on multiple factors, including treatment choice and response to treatment, need for uni/bilateral enucleation, treatment-related adverse effects and complications, and impact on vision and visual functions. The need for repeated EUAs and its potential adverse impact is merely one factor among others that need to be taken into account when deciding on the appropriate treatment strategy for a specific patient.

The quality of life of Rb survivors was evaluated in several studies, some of which showed comparable results to healthy controls,[12, 13] others less favorable results.[14, 15] EUAs were not investigated in any of these studies, nor discussed. The present study adds to the body of knowledge that focuses on quality of life measures associated with Rb.

This study has several limitations. It was a retrospective analysis of case notes; as such we were unable to account for internal bias relating to data collection. Nevertheless, we were able to obtain rich data on 62 patients (124 eyes), encompassing all EUAs and treatments received; as shown in Table 2. IIRC group did not correlate to any of the EUA measures; a possible explanation could be the simplified division into 3 subgroups. It could also be a result of low statistical power. The study captured cases managed by the London Rb service over the stated interval period, reflecting centre-specific management algorithms; limiting the external validity of our results. The study however, together with previous reports from our

centre on EUA burden in Rb,[8, 9] may be used as a benchmark for further such investigations by other centres.

In summary, patients with bilateral Rb in the present study underwent on average 36 EUAs for a period of over 50 months until examined awake, significantly more compared to a cohort of unilateral cases that were previously reported by our centre. Age at presentation and positive family history were found to significantly correlate with parameters of EUA burden in the bilateral cohort; however, IIRC group did not, in contrast to the unilateral cohort. The information provided by this work is essential for families in order for them to understand the nature of the patient journey their child will undertake. Similar work would be useful in other subspecialties heavily reliant on EUAs such as congenital glaucoma.

COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest Ido Didi Fabian declares that he has no conflict of interest, Vishal Shah declares that he has no conflict of interest, Noa Kapelushnik declares that she has no conflict of interest, Zishan Naeem declares that he has no conflict of interest, Zerrin Onadim declares that she has no conflict of interest, Elizabeth A Price declares that she has no conflict of interest, Catriona Duncan declares that she has no conflict of interest, David Stansfield declares that he has no conflict of interest, Mandeep S Sagoo declares that he has no conflict of interest, and M. Ashwin Reddy declares that he has no conflict of interest.

Research involving human participants and/or animals
Non-applicable.

Informed consent
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 who granted a waiver of informed consent.

Funding

No funding was received for this research

Acknowledgment

The authors gratefully acknowledge the contribution of Dr Tanzina Chowdhury to the work presented herein.

REFERENCES

1. Kivelä T (2009) The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol 93:1129–1131.

2. Fabian ID, Onadim Z, Karaa E, et al (2018) The management of retinoblastoma. Oncogene 37:1551–1560.

3. Stargatt R, Davidson AJ, Huang GH, et al (2006) A cohort study of the incidence and risk factors for negative behavior changes in children after general anesthesia. Paediatr Anaesth 16:846–859.

4. Aziz HA, LaSenna CE, Vigoda M, et al (2012) Retinoblastoma treatment burden and economic cost: Impact of age at diagnosis and selection of primary therapy. Clin. Ophthalmol. 6:1601–1606.

5. Stratmann G, Lee J, Sall JW, et al (2014) Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. Neuropsychopharmacology 39:2275–2287.

6. Loepke AW, Soriano SG (2008) An Assessment of the Effects of General Anesthetics on Developing Brain Structure and Neurocognitive Function. Anesth Analg 106:1681–1707.

7. Wilson MW, Haik BG, Rodriguez-Galindo C (2006) Socioeconomic impact of modern multidisciplinary management of retinoblastoma. Pediatrics 118:e331–e336.

8. Fabian ID, Shah V, Kapelushnik N, et al (2019) Examinations under anaesthesia as a measure of disease burden in unilateral retinoblastoma: The London experience. Br J Ophthalmol bjophthalmol-2018-313556.

9. Fabian ID, Stacey AW, Johnson KC, et al (2018) Primary enucleation for group D retinoblastoma in the era of systemic and targeted chemotherapy: The price of retaining an eye. Br J Ophthalmol 102:265–271.

10. Linn Murphree A (2005) Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am 18:41–53, viii.

11. Draper GJ, Sanders BM, Kingston JE (1986) Second primary neoplasms in patients with retinoblastoma. Br J Cancer 53:661–71.

12. van Dijk J, Huisman J, Moll AC, et al (2007) Health-related quality of life of child and adolescent retinoblastoma survivors in the Netherlands. Health Qual Life Outcomes 5:65.

13. Weintraub N, Rot I, Shoshani N, et al (2011) Participation in daily activities and quality of life in survivors of retinoblastoma. Pediatr Blood Cancer 56:590–4.

14. van Dijk J, Imhof SM, Moll AC, et al (2007) Quality of life of adult retinoblastoma survivors in the Netherlands. Health Qual Life Outcomes 5:30.

15. van Dijk J, Oostrom KJ, Huisman J, et al (2010) Restrictions in daily life after

retinoblastoma from the perspective of the survivors. Pediatr Blood Cancer 54:110–5.

TABLES

Table 1. Bilateral retinoblastoma (Rb) in 62 patients: International Intraocular Retinoblastoma Classification (IIRC) at presentation and division into three sub-groups.			
Sub-group	**IIRC eye**	**IIRC fellow eye**	**Number of cases**
No Rb, IIRC group A or B (sub-group 1)	No Rb	No Rb	3
	A	No Rb	1
	A	A	1
	B	No Rb	2
	B	A	3
	B	B	5
			Total: 15
IIRC group C or D in one or two eyes, excluding group E in the fellow eye (sub-group 2)	C	No Rb	1
	C	A	1
	D	No Rb	2
	D	A	3
	C	B	2
	D	B	5
	C	C	0
	D	C	5
	D	D	7
			Total: 26
IIRC group E in one or two eyes (sub-group 3)	E	No Rb	2
	E	A	3
	E	B	5
	E	C	5
	E	D	5
	E	E	1
			Total: 21

Table 2: Number of EUAs, time interval from first to last EUA and EUA frequency in 62 patients with bilateral Rb: univariate analysis.

			Number of EUAs		First to last EUA (months)		EUA frequency (EUAs/month)	
		Number (%)	Mean (Std)	P value		P value		P value
Age at presentation*				0.053		<0.001		0.029
Sex	Male	35 (56.5)	34.3 (20.2)	0.551	48.9 (19.6)	0.440	0.710 (0.300)	0.874
	Female	27 (43.5)	37.7 (23.4)		52.8 (20.3)		0.722 (0.288)	
Sub-group**	1	15 (24.2)	32.6 (9.2)	0.492	56.1 (15.0)	0.259	0.582 (0.086)	0.107
	2	26 (41.9)	39.7 (29.0)		51.7 (22.1)		0.733 (0.302)	
	3	21 (33.9)	33.3 (16.4)		45.3 (19.5)		0.787 (0.351)	
Bilaterality at presentation	Yes	49 (79.0)	37.0 (23.7)	0.403	50.6 (20.2)	0.976	0.726 (0.305)	0.578
	Unilateral or no Rb	13 (21.0)	31.3 (9.2)		50.7 (19.4)		0.674 (0.249)	
Familial Rb	Yes	19 (30.6)	35.0 (18.4)	0.850	57.5 (15.5)	0.069	0.591 (0.155)	0.005
	Sporadic	43 (69.4)	36.1 (23.0)		47.6 (20.9)		0.770 (0.323)	
Primary enucleation	Yes	17 (27.4)	28.4 (14.2)	0.098	40.8 (19.5)	0.016	0.763 (0.378)	0.429
	No	45 (72.6)	38.6 (23.3)		54.3 (18.9)		0.697 (0.256)	
Primary IVC	Yes	52 (83.9)	36.9 (22.6)	0.366	52.5 (19.5)	0.084	0.699 (0.275)	0.348
	No	10 (16.1)	30.1 (14.5)		40.7 (19.9)		0.795 (0.377)	
Adjuvant / salvage TTT	Yes	36 (58.1)	38.7 (22.0)	0.219	53.2 (21.5)	0.232	0.742 (0.297)	0.397
	No	26 (41.9)	31.8 (20.6)		47.0 (17.1)		0.677 (0.288)	
Adjuvant / salvage cryotherapy	Yes	49 (79.0)	37.8 (22.6)	0.156	53.1 (19.7)	0.051	0.712 (0.288)	0.866
	No	13 (21.0)	28.2 (15.6)		41.1 (18.1)		0.727 (0.320)	
Salvage IAC	Yes	30 (48.4)	47.3 (24.2)	<0.001	57.9 (21.4)	0.004	0.845 (0.336)	<0.001
	No	32 (51.6)	25.0 (10.9)		43.7 (15.8)		0.593 (0.175)	
Adjuvant / salvage IViC	Yes	4 (6.5)	57.3 (33.5)	0.038	52.6 (43.0)	0.834	1.289 (0.390)	<0.001
	No	58 (93.5)	34.3 (20.1)		50.5 (18.0)		0.675 (0.243)	
Salvage plaque	Yes	15 (24.2)	59.7 (28.1)	<0.001	68.7 (21.0)	<0.001	0.858 (0.291)	0.029
	No	47 (75.8)	28.1 (11.3)		44.8 (15.7)		0.669 (0.281)	
Salvage EBRT	Yes	10 (16.1)	62.8 (23.8)	<0.001	59.3 (22.0)	0.132	1.124 (0.338)	<0.001
	No	52 (83.9)	30.6 (16.9)		48.9 (19.2)		0.636 (0.208)	
Implant repair	Yes	3 (4.8)	60.7 (31.0)	0.039	84.2 (20.6)	0.002	0.693 (0.187)	0.897
	No	59 (95.2)	34.5 (20.5)		48.9 (18.4)		0.716 (0.298)	

* Continuous variable

** Sub-group 1: no Rb – group B, sub-group 2: group C or D but not E, sub-group 3: group E

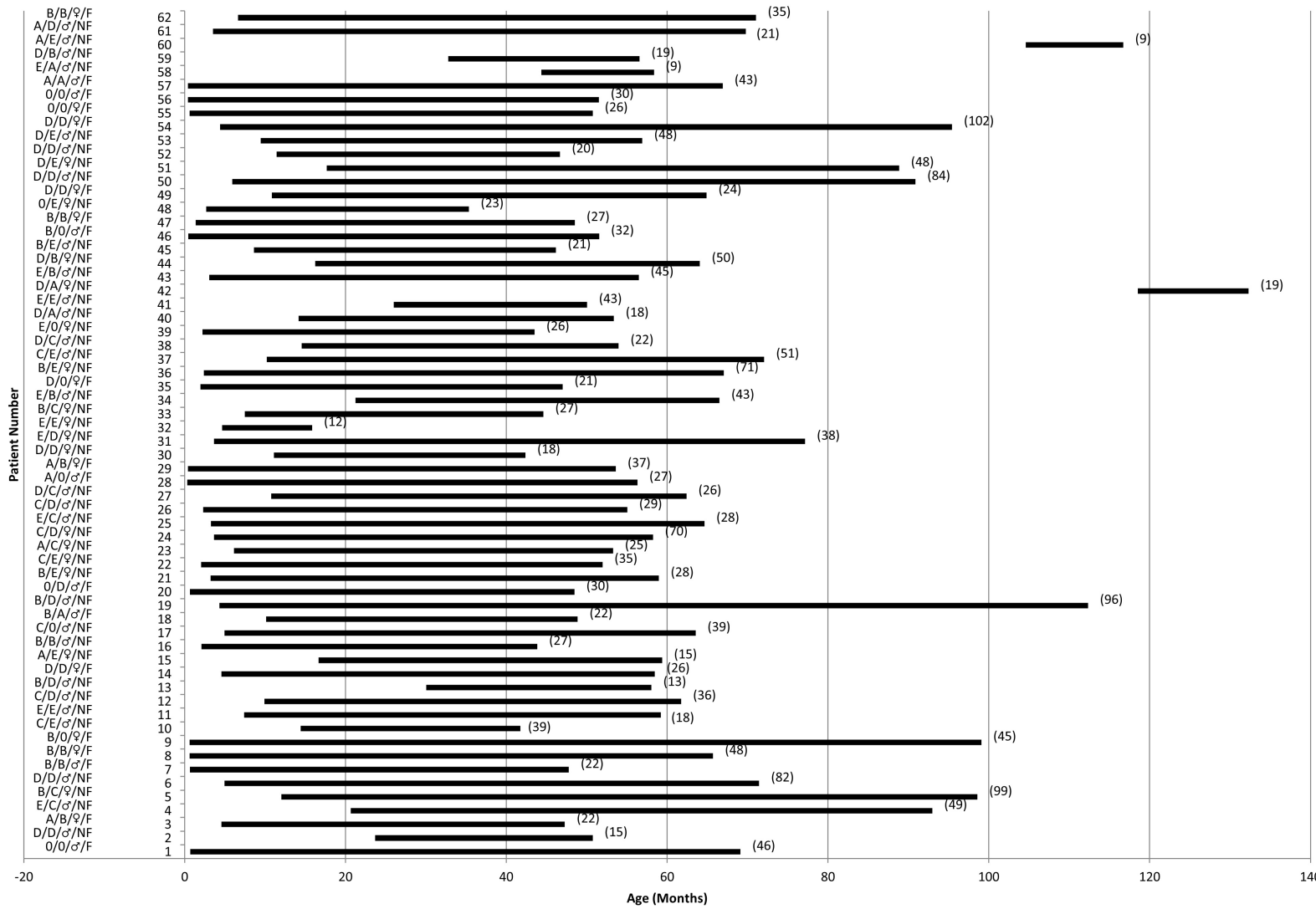
EUAs – examinations under anaesthesia, Rb – retinoblastoma, IVC – intravenous chemotherapy, TTT – transpupillary thermos therapy, IAC – intra-ophthalmic artery chemotherapy, EBRT – external beam radiotherapy

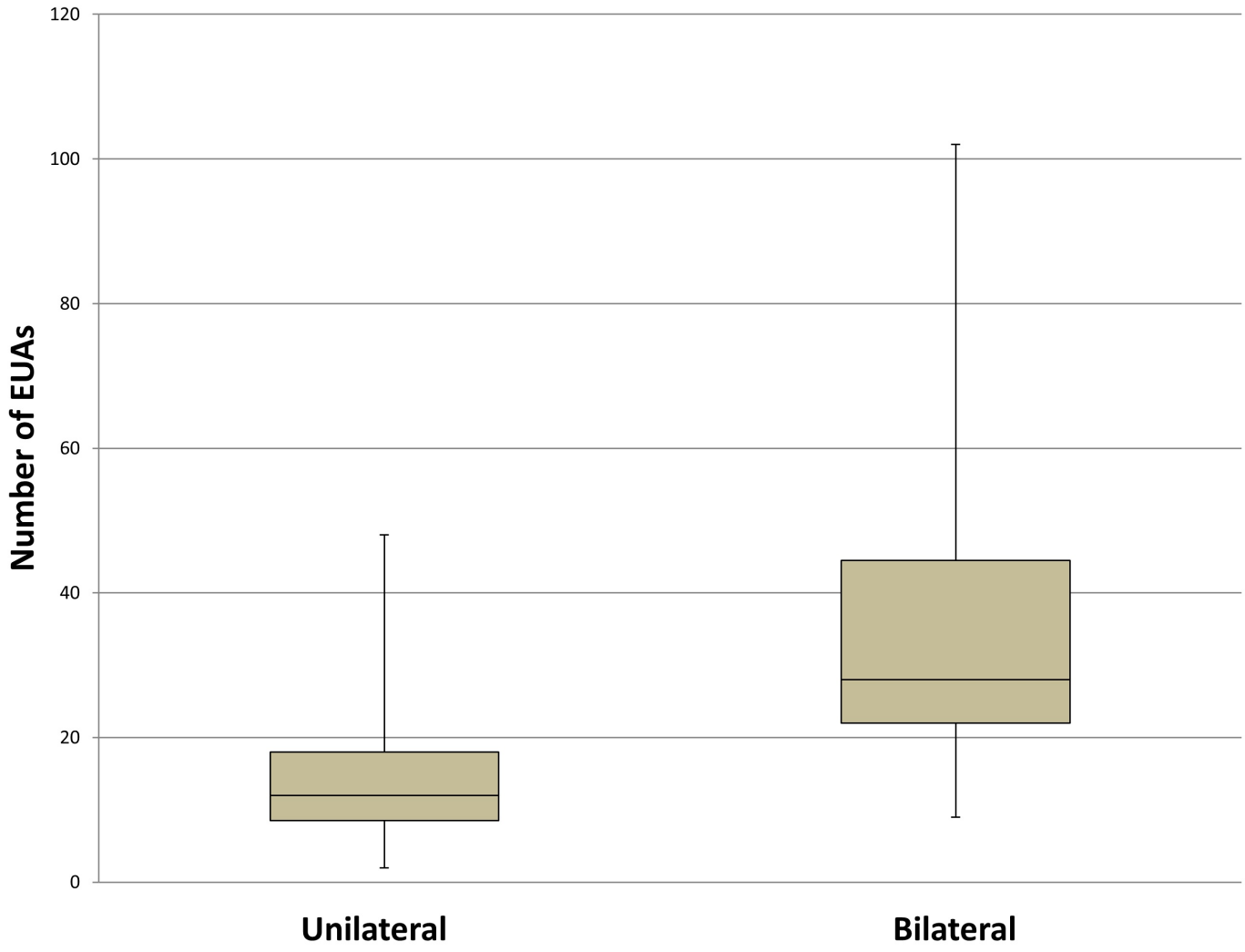
Table 3. Number of EUAs, time interval from first to last EUA and EUA frequency in 62 patients with bilateral Rb: multivariate analysis.					
	Unstandardized Coefficients			95.0% CI for B	
	B	Std. Error	P value	Lower bound	Upper bound
Number of EUAs					
Plaque	20.381	3.252	<0.001	13.871	26.892
EBRT	19.275	3.782	<0.001	11.704	26.845
IAC	9.597	2.863	0.001	3.867	15.328
Interval from First to last EUA (months)					
Plaque	17.581	4.156	<0.001	9.261	25.901
Age at presentation	-0.402	0.086	<0.001	-0.573	-0.231
Implant repair	24.924	8.217	0.004	8.475	41.373
EUA frequency (EUAs/month)					
EBRT	1.003	0.139	<0.001	0.726	1.281
IViC	0.941	0.224	<0.001	0.493	1.389
Familial Rb	-0.244	0.112	0.033	-0.468	-0.020
IAC	0.267	0.107	0.016	0.052	0.482
Age at presentation	0.005	0.003	0.049	0.000	0.011
EUAs – examinations under anaesthesia, Rb – retinoblastoma, CI – confidence interval, EBRT – external beam radiotherapy, IAC – intra-ophthalmic artery chemotherapy, IViC – intra-vitreous chemotherapy					

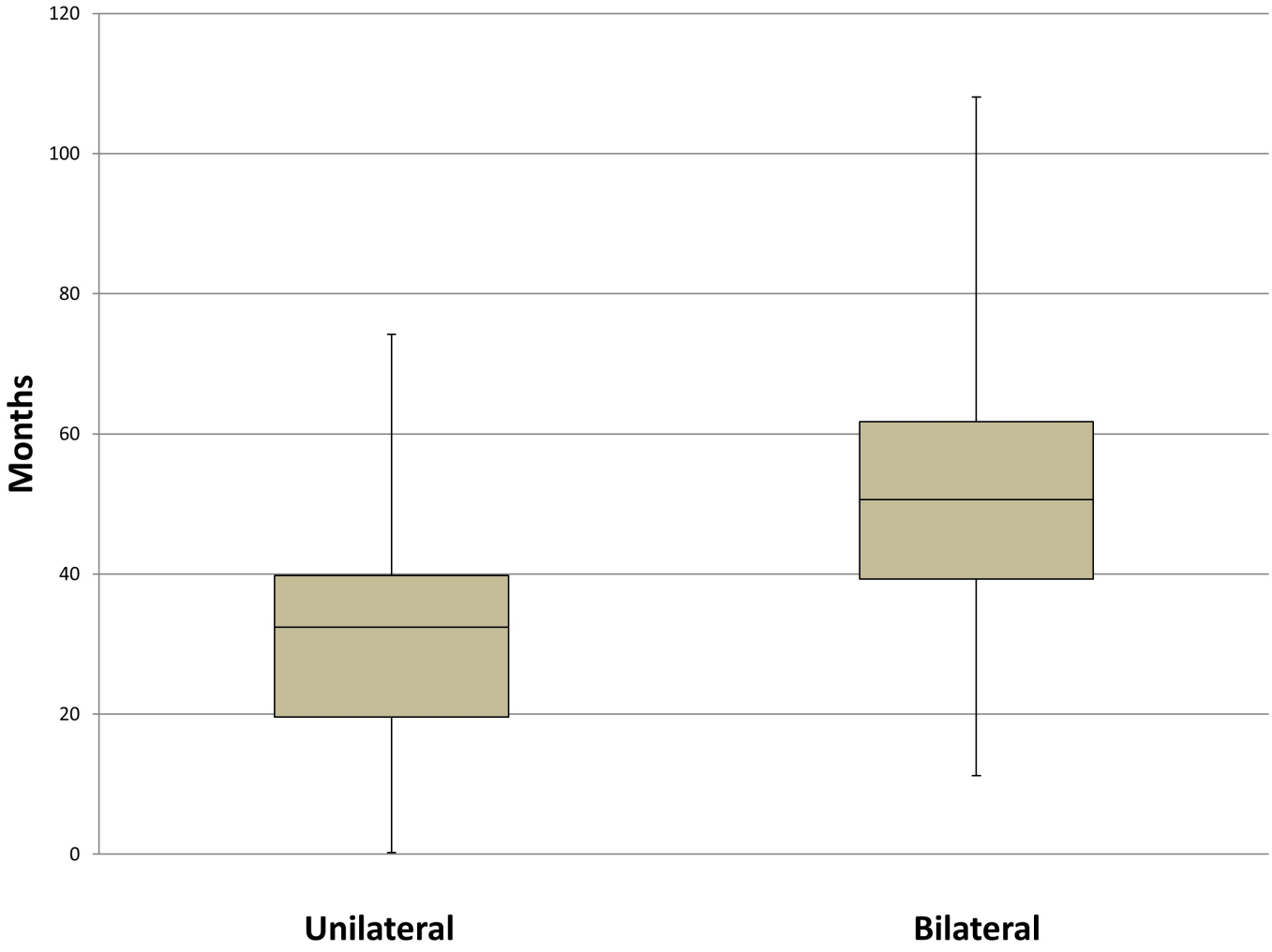
FIGURE LEGEND

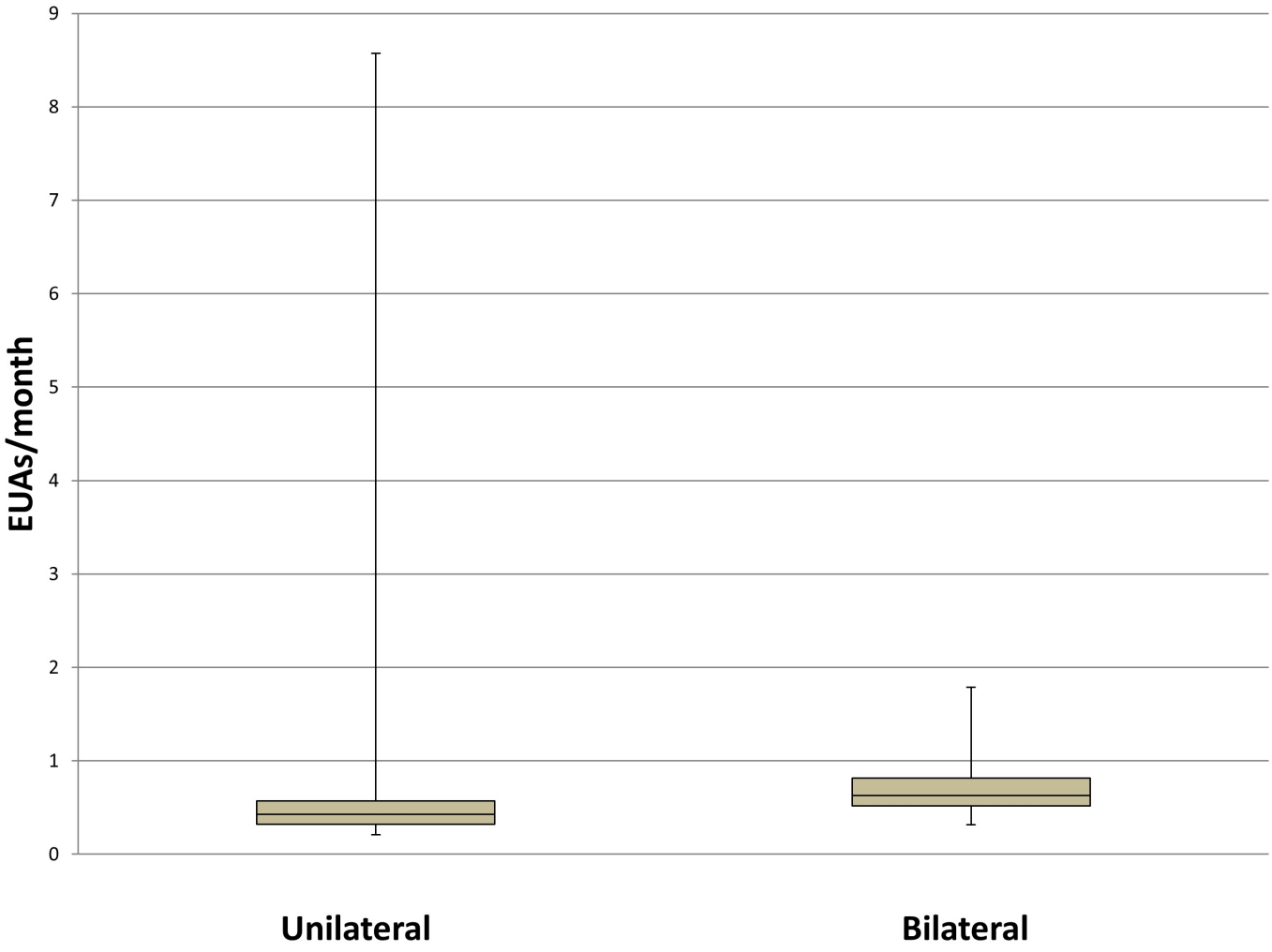
Figure 1 – examinations under anesthesia (EUA) in 62 patients with bilateral retinoblastoma (Rb). The horizontal bars represent the time interval from first to last EUA (X axis in months). The number of EUA per patient are shown in brackets. For each patient (Y axis), the IIRC for both eyes are the first two letters, followed by the patients' sex and whether the patient had positive family istory of Rb (F) or not (NF).

Figure 2 – (a) number of examinations under anesthesia (EUAs) in the present cohort (bilateral cases; n=62 patients) and previous report [8] on unilateral cases (n=107). Differences were found to be statistically significant ($p<0.001$). (b) time interval from first to last EUA in both cohorts ($p<0.001$), and (c) EUA frequency in bth ($p=0.127$).


Patient Number
B/B/♀/F
A/D/♂/NF
A/E/♂/NF
D/B/♂/NF
E/A/♂/NF
A/A/♂/F
0/0/♂/F
0/0/♀/F
D/D/♀/F
D/E/♂/NF
D/D/♂/NF
D/E/♀/NF
D/D/♂/NF
D/D/♀/F
0/E/♀/NF
B/B/♀/F
B/0/♂/F
B/E/♂/NF
D/B/♀/NF
E/B/♂/NF
D/A/♀/NF
E/E/♂/NF
D/A/♂/NF
E/0/♀/NF
D/C/♂/NF
C/E/♂/NF
B/E/♀/NF
D/0/♀/F
E/B/♂/NF
B/C/♀/NF
E/E/♀/NF
E/D/♀/NF
D/D/♀/NF
A/B/♀/F
A/0/♂/F
D/C/♂/NF
C/D/♂/NF
E/C/♂/NF
C/D/♀/NF
A/C/♀/NF
C/E/♀/NF
B/E/♀/NF
0/D/♂/F
B/D/♂/NF
B/A/♂/F
C/0/♂/NF
B/B/♂/NF
A/E/♀/NF
D/D/♀/F
B/D/♂/NF
C/D/♂/NF
E/E/♂/NF
C/E/♂/NF
B/0/♀/F
B/B/♀/F
B/B/♂/F
D/D/♂/NF
B/C/♀/NF
E/C/♂/NF
A/B/♀/F
D/D/♂/NF
0/0/♂/F
62 61 60 59 58 57 56 55 54 53 52 51 50 49 48 47 46 45 44 43 42 41 40 39 38 37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
(35) (21) (9) (19) (9) (43) (30) (26) (102) (48) (20) (48) (84) (24) (23) (27) (32) (21) (50) (45) (19) (43) (18) (26) (22) (51) (71) (21) (43) (27) (12) (38) (18) (37) (27) (26) (29) (28) (70) (25) (35) (28) (30) (96) (22) (39) (27) (15) (26) (13) (36) (18) (39) (45) (48) (22) (82) (99) (49) (22) (15) (46)
-20 0 20 40 60 80 100 120 140
Age (Months)


120
100
80
60
40
20
0
Number of EUAs
Unilateral
Bilateral


120
100
80
60
40
20
0
Months
Unilateral
Bilateral


9
8
7
6
5
4
3
2
1
0
EUAs/month
Unilateral
Bilateral