Examinations under anaesthesia as a measure of disease burden in unilateral retinoblastoma: the London experience

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Synopsis

In this cohort of unilateral retinoblastoma patients, children that presented with International Intraocular Retinoblastoma Classification Group B or C underwent twice the number of examinations under anaesthesia as compared to group D or E cases.

ABSTRACT

Background

Early diagnosis strategies and advances in retinoblastoma (Rb) management have resulted in nearly 100% survival. More attention should, therefore, be given to quality of life considerations. We aimed to quantify the number of examinations under anaesthesia (EUAs) in a cohort of Rb patients, as a measure of disease burden.

Methods

A retrospective analysis of unilateral Rb patients that presented to the London Rb service from 2006-2013, were treated and had long-term follow-up. Correlations of clinical variables to number of EUAs were investigated.

Results

A total of 107 Rb patients were included that presented at a mean age of 26.51±22.68 months. The International Intraocular Retinoblastoma Classification (IIRC) was group B in 5 (5%), C in 13 (12%), D in 48 (45%) and E in 41 (38%) of the cases. Primary treatment was intravenous chemotherapy in 36 (34%) and enucleation in 71 (66%) of the cases. Mean number of EUAs was 20.67±6.62, 12.52±6.23 and 11.15±6.91 for combined groups B/C, group D and group E patients ($p<0.001$). On analysis, early age of presentation and conservative treatments were found to significantly correlate with increased number of EUAs ($p<0.001$). Mean follow-up time was 74.42±25.16 months and no metastasis or death were reported.

Conclusion

Families should be counselled regarding the number of EUAs associated with the patient's IIRC group, with B/C eyes undergoing twice the number as compared to D/E eyes. For group D cases, where both enucleation and conservative therapy are valid options, treatment choice has a significant impact on the number of EUAs.

INTRODUCTION

Retinoblastoma (Rb), the most common primary intraocular malignancy of childhood,[1] is potentially a deadly metastatic cancer. With recent advances, however, in Rb diagnosis and management,[2] survival rate in high-income countries is at present estimated to be nearly 100%.[3] Consequently, while saving life remains the main goal in Rb management, more attention is being given to quality of life considerations in these young patients.

Rb develops in the vast majority of cases before the age of 5 years. At presentation and throughout follow-up, especially in the early years, when the disease is active or can relapse, in order to perform a meticulous eye examination, patients are examined under anaesthesia (EUA). This allows for precise delivery of treatment without patient movement and for pain relief. It is common practice in Rb for children to undergo repeated EUAs, as needed, depending on various clinical factors and management decisions.[4] Patients' families, however, are increasingly questioning the need for additional EUAs and commonly ask about the potential risk associated with general anaesthesia in infancy. 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 psychological, socioeconomic, and possibly physical.[5–9]

In a previous study on International Intraocular Retinoblastoma Classification (IIRC)[10] group D cases, comparing patients that were treated conservatively to patients that underwent primary enucleation,[4] we found that the latter sub-cohort underwent on average 3-times less EUAs. To the best of our knowledge, there are no such other reports on any of the IIRC groups. Such information would be of added value when counselling patients and their families. The goal of the present study was to quantify the number of EUAs in a cohort of unilateral Rb cases from all IIRC groups, as well as to measure the total period of time (i.e. first to last) these patients had EUAs. In addition, we aimed to investigate possible associations to clinical variables and therapeutic interventions.

METHODS

This was a retrospective chart review of consecutive patients with unilateral Rb that presented to the London Retinoblastoma Service from 2006-2013, and were treated and monitored with long-term follow-up. Patients who presented with unilateral disease, but developed Rb in the fellow eye throughout follow-up were not included in this analysis. 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 patients' age at presentation, sex, laterality, presenting signs, clinical data at first examination, primary and additional treatments, genetic analysis results, data from operation notes, number and timing of EUAs, and follow-up clinical data until last examination.

In this cohort, primary treatments included intravenous chemotherapy (IVC) or enucleation. Patients treated by means of IVC 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 radiotherapy and intra-ophthalmic artery chemotherapy (IAC). Primary or secondary enucleation was performed as previously described.[4] Patients in which high-risk histopathology features were detected after enucleation were also treated with IVC to reduce the risk of systemic spread.[11]

Examinations, all focal treatments and central line insertion and removal for VEC administration were performed under general anaesthesia. For general anaesthesia, the majority of patients had a gas induction with sevoflurane (up to 8%) in oxygen and nitrous oxide. Older children or children with indwelling lines were induced intravenously with propofol (titrated up to 4mg/kg). Unless there was a contraindication, the airways of children over 5 months of age were managed with a laryngeal mask. The trachea of younger children was intubated. Anaesthesia was maintained with sevoflurane (0.5 – 4% titrated according to response) in oxygen and nitrous oxide.

In patients with active disease, tumour response to treatment and need for further intervention dictated the timing of the next EUA. In treated patients with tumour/s under control, the frequency of screening EUAs was dictated by the patient's age and genetic status (i.e. germline vs non-germline). Patients with known family history of Rb and/or patients with multifocal disease were considered to be germline cases, hence were examined more often than patients with no family history or patients with unifocal disease. All study patients were referred for *RB1* genetic testing. Peripheral blood samples were collected from all new patients and fresh tumour samples from all enucleated eyes. Genetic testing employed a variety of

methods to cover all types of *RB1* mutations.[12,13] According to the *RB1* mutation analysis results, the treating clinician titrated the frequency of EUAs. 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.

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). Number of EUAs consisted of all occasions in which a child was clinically evaluated or treated under general anaesthesia. For analysis, IIRC groups B and C were combined as both represented a small proportion of the entire cohort, which comprised mainly of patients with group D and E Rb. Correlations to number of EUAs and to the time interval from presentation to last EUA was 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).

RESULTS

The study cohort comprised of 107 patients (107 eyes). Of these, 59 (55%) were males and in 58 (54%), the right eye was involved. The IIRC was group B in 5 (5%) cases, C in 13 (12%), D in 48 (45%) and E in 41 (38%) of the cases, and AJCC[14] primary tumour site was cT1b in 5 (5%) cases, cT2a in 16 (15%), cT2b in 47 (44%), cT3b in 13 (12%), cT3c in 18 (17%) and cT3d in 8 (7%) of the cases. There were no cases of IIRC group A in this cohort. Of the study cohort, 22 (21%) patients had germline disease, 2 (2%) of which had positive family history of Rb. The mean (±SD) age of presentation was 26.51±22.68 months and mean interval from presentation to genetic analysis results was 3.97±2.53 months.

Primary treatment was IVC in 36 (34%) and enucleation in 71 (66%) of the cases. Of the children with Group D and E Rb, 31 (65%) and 40 (98%), respectively, underwent primary enucleation, whereas all group B and C, 17 (35%) of the group D cases and 1 (2%) group E case were treated initially by means of IVC. In the primary IVC group, secondary IAC was performed in 8 (22%, 1-6 procedures) patients, TTT in 16 (44%, 1-19 treatment sessions), cryotherapy in 18 (50%, 1-14 treatment sessions) and secondary enucleation in 11 (31%). Of all enucleated patients (i.e. primary and secondary procedures; n=82), in 20 (24%), high-risk histopathology features were found on histopathology assessment, necessitating adjuvant IVC, and 3 (2%) underwent an implant repair procedure due to implant exposure. Mean follow-up time was 74.42±25.16 months and mean age at last visit was 100.93±33.29 months. All patients remained with unilateral disease throughout follow-up, none was diagnosed with metastatic disease and all were alive at final visit.

For the whole cohort, mean number of EUAs was 13.36±7.32 and mean time from presentation to last EUA was 31.27±14.75 months (**Figures 1 and 2**). All patients at last visit were examined awake or referred for an awake examination. Investigating the different IIRC groups, mean number of EUAs was 20.67±6.62 for combined groups B+C, 12.52±6.23 for group D and 11.15±6.91 for group E patients ($p<0.001$). For the interval from presentation to last EUA, the mean time was 40.55±8.03 months for combined groups B+C, 30.60±14.45 months for group D and 27.98±14.75 months for group E ($p=0.009$). Age of presentation of combined groups B+C patients was 14.78±13.62 months whereas that of groups D and E patients was 29.24±25.87 and 28.46±20.58 months, respectively. The difference showed a trend that was non-significant ($p=0.053$).

Evaluating clinical correlations with number of EUAs (**Table 1**), parameters that were found to reach statistical significance were age of presentation (inversely) and type of initial treatment (IVC associated with more EUAs; $p<0.001$ for both). Parameters that were found to significantly correlate to the time interval from presentation to last EUA (**Table 1**) were the time interval from presentation to genetic analysis results (direct correlation; $p=0.013$), age at presentation and initial treatment ($p<0.001$). On multivariate analysis (stepwise linear regression, ($R^2=0.561$)), initial treatment with IVC (B=10.181, 95% confidence interval (CI) for B: 8.173 - 12.188) and age of presentation (B=-0.087, 95% CI for B: (-0.129) – (-0.045)) were

found to be significant factors (p<0.001) predicting the number of EUAs. For the time interval from presentation to last EUA, the following parameters were found on multivariate analysis (stepwise linear regression, (R^2=0.486)) to be significant predicting factors: primary treatment with IVC (B=8.419, 95% CI for B: 3.844-12.994, p<0.001), age of presentation (B=-0.36, 95% CI for B: (-0.455) – (-0.264), p<0.001) and time interval to genetic tests results (B=1.444, 95% CI for B: 0.593-2.294, p=0.001).

Table 1. number of examinations under anesthesia and time interval from presentation to last examinations under anesthesia in 107 unilateral retinoblastoma patients: univariate analysis.

		Number of EUAs		Presentation-last EUA (months)	
		Mean (St. Dev)	P-value	Mean ± St. Dev	P-value
Age of presentation*		26.51 (22.68)	<0.001	26.51 (22.68)	<0.001
Sex	Male	13.42 (7.56)	0.926	30.07 (15.82)	0.351
	Female	13.29 (7.10)		32.75 (13.33)	
Laterality	Right	12.12 (5.69)	0.055	29.51 (13.62)	0.179
	Left	14.84 (8.71)		33.36 (15.87)	
IIRC**	A	NA	<0.001	NA	0.009
	B+C	20.67 (6.62)		40.55 (8.03)	
	D	12.52 (6.23)		30.60 (14.45)	
	E	11.15 (6.91)		27.98 (15.92)	
Germline	Yes	14.91 (6.93)	0.269	35.53 (15.36)	0.129
	No	12.96 (7.40)		30.17 (14.48)	
Time to genetic results*		3.97 (2.53)	0.328	3.97 (2.53)	0.013
Initial treatment	IVC	20.53 (7.52)	<0.001	38.21 (12.88)	<0.001
	Enucleation	9.73 (3.62)		27.76 (14.46)	

* continuous variables (Fisher exact test).

** Analysis of variance (between groups).

EUA - examinations under anesthesia, IIRC – International Intraocular Retinoblastoma Classification, NA – non-applicable, IVC – intravenous chemotherapy

Sub-analysis of the primary IVC-treated patients (n=36, **Table 2**), on multivariate analysis (stepwise linear regression, R^2=0.648), the following parameters were found to be significant predictors of number of EUAs: cryotherapy (B=4.394, 95% CI for B: 0.753-8.035, p=0.02), TTT (B=6.308, 95% CI for B: 2.806-9.811, p=0.001), IAC (B=9.23, 95% CI for B: 4.645-13.814, p<0.001) and age of presentation (B=-0.086, 95% CI for B: (-0.149) - (0.023), p=0.009). On multivariate analysis (stepwise linear regression, R^2=0.190) of parameters that correlate with

the time interval from presentation to last EUA, only age of presentation was found to be a significant factor (B=-0.193, 95% CI for B: (-0.333) - (0.054), p=0.008).

Table 2. number of examinations under anesthesia and time interval from presentation to last examinations under anesthesia in 36 unilateral retinoblastoma patients treated by intravenous chemotherapy: univariate analysis.

		Number of EUAs		Presentation-last EUA (months)	
		Mean (St. Dev)	P-value	Mean ± St. Dev	P-value
Age of presentation*		25.24 (23.69)	0.435	25.24 (23.69)	0.008
Sex	Male	21.63 (6.94)	0.359	36.82 (14.65)	0.503
	Female	19.29 (8.15)		39.76 (10.81)	
Laterality	Right	18.40 (6.38)	0.154	32.57 (12.40)	0.024
	Left	22.05 (8.03)		42.24 (11.92)	
IIRC**	A	NA	<0.001	NA	0.057
	B+C	20.67 (6.62)		40.55 (8.03)	
	D	18.82 (5.48)		34.33 (15.39)	
	E	47.00		62.07	
Germline	Yes	20.40 (5.17)	0.951	41.65 (9.64)	0.129
	No	20.58 (8.33)		36.89 (13.87)	
Time to genetic results*		4.31 (2.74)	0.355	4.31 (2.74)	0.071
IAC	Yes	26.38 (10.30)	0.01	35.18 (14.19)	0.459
	No	18.86 (5.72)		39.08 (12.63)	
Plaque brachytherapy	Yes	24.75 (5.6)	0.071	36.74 (7.99)	0.719
	No	19.32 (7.64)		38.63 (14.06)	
TTT	Yes	24.69 (8.30)	0.002	39.21 (10.30)	0.684
	No	17.20 (4.84)		37.41 (14.85)	
Cryotherapy	Yes	24.83 (7.81)	<0.001	38.46 (10.26)	0.911
	No	16.22 (4.01)		38.00 (15.37)	

* continuous variables (Fisher exact test).

** Analysis of variance (between groups).

EUA - examinations under anesthesia, IIRC – International Intraocular Retinoblastoma Classification, NA – non-applicable, IAC – intra-arterial chemotherapy, TTT – transpupillary thermotherapy

DISCUSSION

Patients with unilateral Rb in the present cohort underwent on average 13 EUAs and for an average period of less than 3 years until they were examined and started to be monitored awake. These results, however, differed, depending on the disease group at presentation. Patients diagnosed at an early stage, i.e. IIRC groups B and C, underwent significantly more EUAs (x1.8) and for a longer period of time (x1.4), compared to advanced intraocular Rb (IIRC groups D and E). Comparing IIRC groups B and C to group E, the 2 main differences were the early age of presentation of the prior sub-cohort and the primary treatment used, and indeed, these 2 variables were found to be the only predicting factors on multivariate analysis of number of EUAs. While unilateral IIRC groups B and C are commonly preserved, with high success rate,[15] and group E eyes undergo primary enucleation in most practices, there is no consensus regarding the preferred management of unilateral group D cases. In the present study, 65% of patients with group D eyes underwent primary enucleation and in 35% conservative treatment was first attempted. There are many factors to be considered when deciding on a treatment strategy for Rb. Patients' families need also to be aware of the difference in number of EUAs in case conservative treatment is chosen over primary enucleation (x2.1 in case of IVC, for all IIRC groups), and this consideration is relevant especially in case of IIRC group D, as we showed in the present study and in a previous one.[4]

Evaluating the total period of time patients in this cohort had EUAs, the time lag from presentation to the point at which genetic results were available for the treating clinicians was found to significantly correlate (in addition to age of presentation and primary treatment type). It is estimated that up to 18% of unilateral Rb cases are germline (i.e. carry one *RB1* mutation in their constitutional cells).[16] Precise analysis and identification of the *RB1* mutation is crucial, especially in unilateral-presenting cases, and was shown to enhance the quality of management of affected patient, as well as of their relatives.[17,18] Results of the present study show that having the analysis results available in a timely manner is also important to shorten the total period of time patients undergo EUAs.

On sub-analysis of the primary IVC group, that is all group B and C, some of the group D cases and a single group E case, number of EUAs and the total time patients had EUAs, again, correlated with age of presentation, the prior also with secondary treatments, including cryotherapy, TTT and IAC. Age is a given parameter, known at presentation, hence can be used in this context as a predicting factor associated with EUAs (number and length). Secondary treatments, however, in case of conservatively treated patients, reflect active disease (in contrast to screening EUAs). In addition, the need for secondary treatments is obviously not known at presentation, hence is less useful to serving as a predicting factor in this context.

This was a retrospective study; hence its inherent limitations relate to data collection and randomization. Nevertheless, we were able to collect detailed data from medical charts on all 107 patients and eyes, including all EUAs and treatments performed, as shown in **figures 1 and 2**. Most unilateral Rb cases (>80%) presented with group D or E, and in this sense the cohort presented herein is considerably large. There were no unilateral group A cases in this cohort, however, and only a few group B and C cases, necessitating us to combine the two latter sub-cohorts for analysis. Larger-cohort studies are required to better characterize, in terms of number and length of EUAs, cases that are diagnosed with early phase disease. The time under anaesthesia was difficult to quantify in this retrospective study as in many charts, especially in the early study years, these data were missing, but it would be an important factor in future prospective studies. In this respect, number of EUAs is a much clearer parameter to relate to, as compared to the time under anaesthesia. Last but not least, the results reported in the present study reflect the management algorithm used in the London Rb service at that particular time period. They should be carefully interpreted as treatment algorithms are rapidly changing with the use of first line IAC and secondary intravitreal chemotherapy to salvage eyes that would have previously been enucleated. Nevertheless, given that there are no studies on this subject, this and the previous report focusing on IIRC group D cases, can serve as a benchmark for future work in this area. In this sense, it would be interesting to investigate and compare the required number of EUAs following primary IAC.[19]

In summary, in this cohort, patients that presented with unilateral IIRC group B or C underwent on average 21 EUAs until transferred to awake examinations. In contrast, patients with advanced unilateral disease, presenting with IIRC group D or E, underwent in average only 12 EUAs until seen awake. Early age of presentation and conservative primary treatment were found to be risk factors for more EUAs and for a longer period of time. The latter variable was also dependent on the time lag from presentation to genetic analysis being available. These data are valuable additions when consulting patients' families.

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Contributorship Statement:

IDF and MAD had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. Study concept and design: IDF and MAD. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: IDF and MAD. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical or material support: all authors. Study supervision: IDF and MAD.

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LEGEND

Figure 1 – detailed map of examinations under anesthesia and treatments in 36 patients with unilateral retinoblastoma treated initially with intravenous chemotherapy. EUA - examination under anesthesia; IVC – intravenous chemotherapy; TTT – transpupillary thermotherapy; IAC – intra-arterial chemotherapy. On Y axis: G – germline, NG – non-germline, F – familial retinoblastoma, NF – non-familial retinoblastoma, B-E – International Intraocular Retinoblastoma Classification.

Figure 2 – detailed map of examinations under anesthesia and treatments in 71 patients with unilateral retinoblastoma treated initially by enucleation. EUA - examination under anesthesia; IVC – intravenous chemotherapy. On Y axis: G – germline, NG – non-germline, F – familial retinoblastoma, NF – non-familial retinoblastoma, D-E – International Intraocular Retinoblastoma Classification.

Figure 1

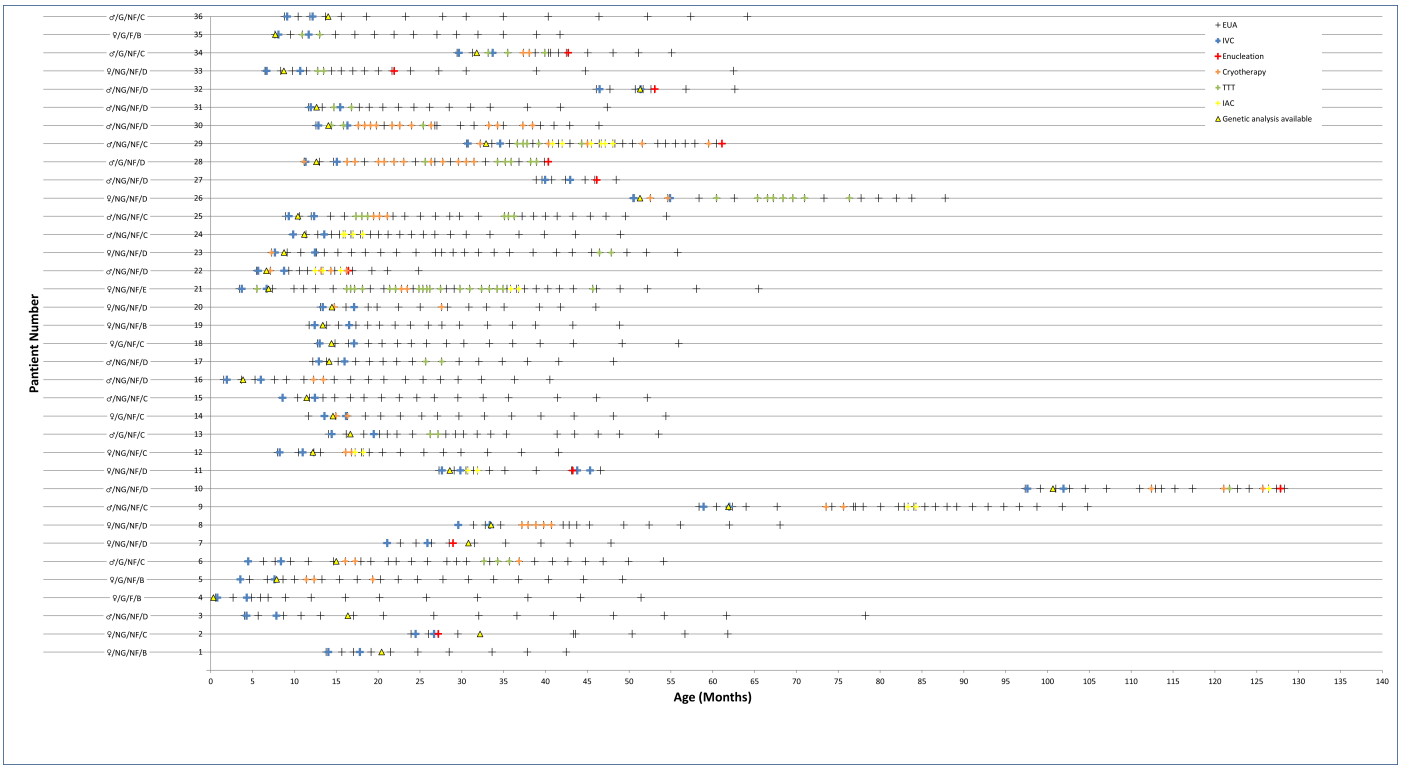
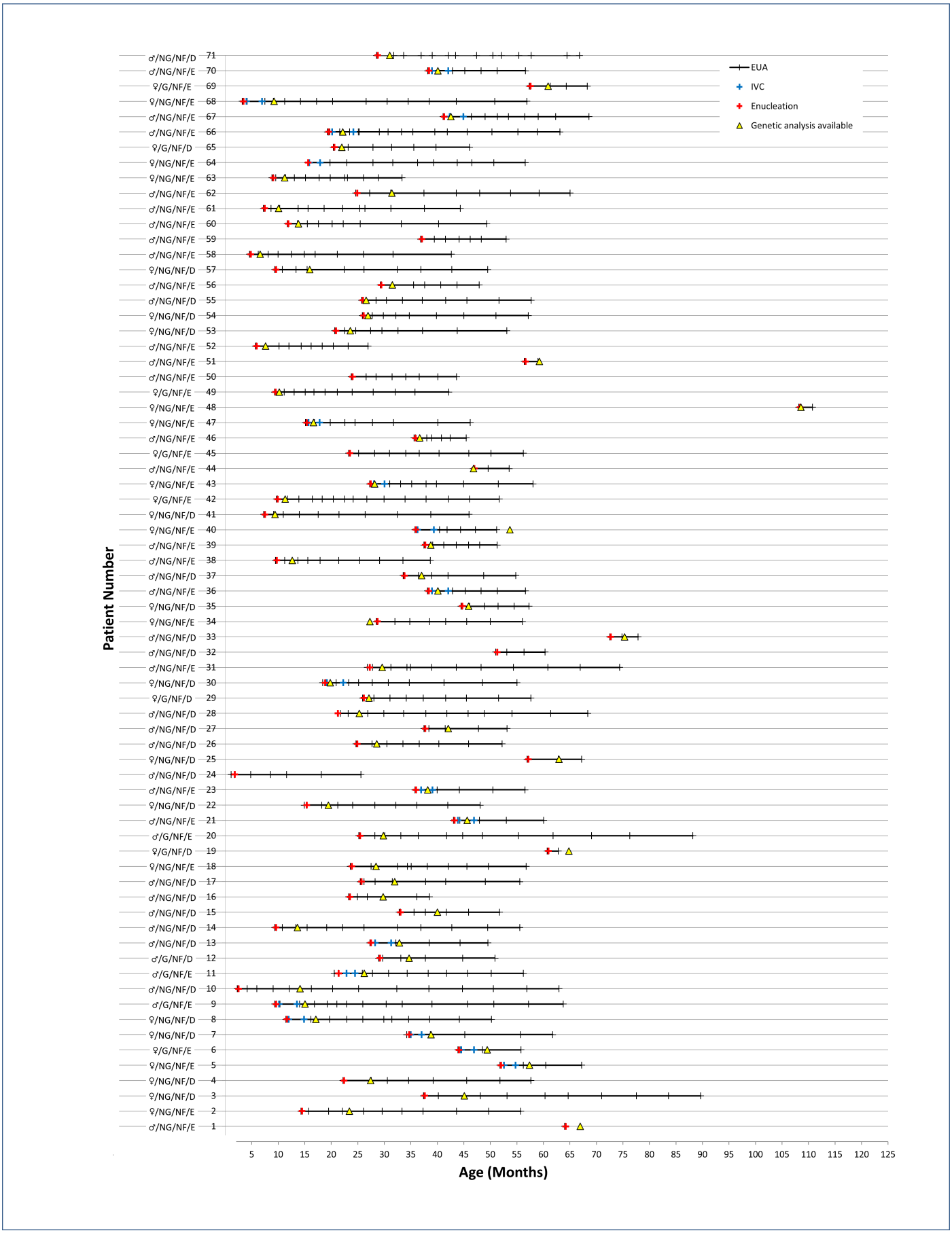

Pantient Number
Age (Months)
EUA
IVC
Enucleation
Cryotherapy
TTT
IAC
Genetic analysis available

Figure 2


♂/NG/NF/D 71
♂/NG/NF/E 70
♀/G/NF/E 69
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Patient Number
EUA
IVC
Enucleation
Genetic analysis available
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125
Age (Months)