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Research Article

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A Model to Assess Time to Treatment in Children with Optic Pathway Gliomas

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Abstract

The objective of the present study is to identify factors that may be of prognostic value to predict the need for chemotherapy in paediatric patients with optic pathway gliomas (OPGs) and to propose a screening protocol where the hazard rate for the time from diagnosis to initiation of therapy can be estimated in each patient individually. A search in the national Low Grade Glioma (LGG) database was performed allowing identification of 93 children with OPGs from 21 participating centers in the UK. A variable selection procedure based on stepwise regression was applied to identify the significant risk factors that are of prognostic value to predict the need for treatment. A Receiver Operating Characteristic (ROC) curve was used to determine the optimal threshold for classifying the patients. The influence of the available risk factors on the time from diagnosis to initiation of therapy was assessed by a Cox proportional hazards model. Children without Neurofibromatosis type 1 (NF 1) were more likely to have tumour involvement of the most posterior visual pathway. Children with posterior tumour involvement and subjects with poor visual acuity (VA) and younger age at diagnosis were found to be the groups with the highest risk of receiving treatment. Three diagnostic groups (high, moderate, and low risk) were defined with respect to their estimated probability of receiving treatment. Individualized hazard function plots and point estimations for the probability of the need of treatment may modify the frequency and duration of follow-up evaluations in OPG patients.

Keywords: Chemotherapy, Neurofibromatosis, Optic glioma, Pediatric tumors

List of Abbreviations

OPG: Optic Pathway Glioma
NF 1: Neurofibromatosis type 1
VA: Visual Acuity
BCVA: Best Corrected Visual Acuity
LogMAR: Logarithm of the Minimum Angle of Resolution
MRI: Magnetic Resonance Imaging
ROC: Receiver Operating Characteristic
AUC: Area Under Receiver Operating Characteristic Curve

Introduction

Neuroimaging screening in Neurofibromatosis type 1 (NF 1) children at the time of diagnosis may reveal optic pathway gliomas (OPGs) in up to 15% of the cases [1]. Visual loss is the most concerning complication. Up to half of NF 1-associated OPG children become symptomatic whereas vision loss takes place in many, but not all, of those with sporadic tumours [2].

The natural history of OPGs is often unpredictable and therefore initial management involves close observation with serial neuro-ophthalmologic and magnetic resonance imaging (MRI) evaluations. A decline in visual acuity (VA) and radiographic tumour progression are the most common and accepted indications for treatment. Chemotherapy has become the favored initial treatment modality [3,4].

Given the unpredictable disease course and the variability in tumour progression patterns between studies, the frequency and duration of follow-up evaluations for NF 1-associated OPGs remains controversial. Many recommendations for follow-up evaluations exist [5,6].

The purpose of this study is to model the probability to offer treatment with regards to the available variables at the time of diagnosis and to predict the time to initiation of therapy in each patient.

An individualized follow-up protocol could be introduced that may help with regards to the management of OPG patients.

Methods

The study population consisted of a review of 93 paediatric patients younger than 16 years of age with a diagnosis of OPG. Neuro-ophthalmologic examination records were collected from 21 participating centers in the UK after a search in the national low grade glioma (LGG) database between January 2004 and December 2013. Children who had been treated previously with chemotherapy and radiotherapy were excluded.

Visual data at the time of diagnosis and MRI scans were reviewed. Additional data gathered included age, sex, NF 1 status and tumour location. Ophthalmic examination was performed by experienced neuro-ophthalmologists and senior orthoptists whereas brain MRI scans were reviewed by neuroradiologists at each site to determine tumour extent and location.

Best-corrected VA (BCVA) was assessed by Teller Acuity Cards, Snellen or Logarithm of the minimum angle of resolution (LogMAR) chart depending on patient`s age and cognitive ability. The LogMAR chart was used either in letter or LEA symbol format. VA data were corrected for age and converted to an 8-point scale (Table 1) as per previous study published by our team [7].

Table 1: Visual data were converted to an 8-point scale

	VA	
Grade	**Logmar**	**PL (cpd)**
8	0-0.2	>19.5
7	0.3-0.4	14.2-9.8
6	0.5-0.7	7.5-4.8
5	0.8-1.0	3.6-2.4
4	1.1-1.3	1.8-1.2
3	Hand/Toy Movement	
2	Perception of Light	
1	No Perception of Light	
PL, preferential looking; CPD, cycles per degree.		

The decision to initiate treatment was based on clinical and radiographic progression of the tumour on MRI. A VA decrease of one line according to the 8-point scale or 2 LogMAR lines below the baseline VA was considered as progression sufficient to initiate treatment, while close observation was the preferred management in those cases not meeting the criteria to treat.

Patients were divided into 3 groups based on tumour extent and location by MRI at the time of initial diagnosis. The Dodge classification was applied to MRI scans. This system was based upon the localization of tumour in relation to the optic nerves (Dodge 1), optic chiasm with or without optic nerve involvement (Dodge 2) and hypothalamic or other adjacent structure (Dodge 3).

A logistic regression was carried out to model the probability of receiving treatment. The fitted full model includes all available variables at presentation including covariates with low predictive ability. Therefore, a variable selection procedure based on stepwise regression was also applied to include a smaller subset of covariates that are of prognostic value and to exclude those with no statistically significant effect on the need for treatment [8,9].

A Receiver Operating Characteristic (ROC) curve was used to determine the optimal threshold for classifying the patients enabling the identification of high-risk patients and potentially change their monitoring protocol [10].

The influence of the available variables on the time from diagnosis to initiation of therapy was assessed by a Cox proportional hazards model [11,12]. A stepwise procedure was carried out to identify the significant factors and estimate the "best" model. The relative risk for receiving treatment of any of the available variables is assumed to remain proportional over time. The proportional-hazards assumption was tested by both the overall test for proportionality using the Schoenfeld residuals and the corresponding variable-by-variable test and was analyzed graphically by plotting the log-log transformation of the survival function, namely -log(-log(S(t)), against log(t) [13].

The Pearson correlation coefficient and the Chi-Square test statistic for testing the independence of two categorical variables were also applied in the initial stages of the analysis to reveal any association between the variables in the study.

Results

Patient Characteristics

Our study cohort consisted of 48 (51.61%) female and 45 (48.39%) male patients. 46 (49.64%) patients had NF 1 and 47 (50.54%) did not. Ten (10.75%) patients had tumours involving the optic nerves alone (Dodge 1), 28 subjects (30.11%) were classified as Dodge 2 and the rest of the cohort (59.14%) was diagnosed with post-chiasmal tumours (Dodge 3) (Table 2).

Table 2: The Logistic regression (left panel) and Cox proportional hazard regression (right panel) models

Logistic regression model					Cox regression model			
Full model			**Selected model from the stepwise procedure**		**Full model**		**Selected model from the stepwise procedure**	
Variable	Odds Ratio	p-value	Odds Ratio	p-value	Hazard ratio	p-value	Hazard ratio	p-value
Sex	3.764	0.079	3.769	0.065	1.176	0.537		
NF 1status	0.301	0.150	0.313	0.145	0.598	0.537	0.603	0.074
Age	0.648	**0.005**	0.674	0.002	0.836	**0.001**	0.831	**0.001**
BCVA right eye	1.855	0.254			1.167	0.186	1.243	**0.022**
BCVA left eye	1.251	0.630			0.914	0.315		
Dodge status								
2	7.166	0.095	4.879	0.131	2.252	0.152	2.369	0.126
3	55.223	**0.005**	31.135	**0.005**	3.543	**0.022**	3.869	**0.013**
Min BCVA	0.374	0.125	0.683	**0.050**	0.877	0.304	0.792	**0.005**
Constant	3.485	0.654	27.171	0.024				
Reference groups: Male (Sex), Non NF 1(NF 1status), Dodge 1(Dodge status)								

Seventy out of 93 patients included in the study eventually received treatment. The mean time from diagnosis to initiation of therapy was 8.26 months (Table 2). The rest of the cohort was followed until the age of 16 years and was discharged thereafter.

The youngest patient at the time of diagnosis was 4 months old. Most patients were under ten years (89.25%). The mean age at diagnosis in our cohort was 4.4 years. In our study, no association was found between sex and NF 1 status ($P = .255$).

Dodge status seems to be independent of sex ($P = .793$). On the contrary, tumour extent and location as per Dodge classification was strongly correlated with the NF 1 status of the patient. Non-NF 1 children were more likely to have involvement of the most posterior visual pathway compared to the NF1 group ($P = .029$).

Regarding VA, the value of their Pearson correlation coefficient ($r = 0.303$) showed a weak linear correlation between both eyes which was statistically significant ($P = .0032$). Therefore, in children with OPGs, VA of one eye was not found to have considerable weight in anticipating VA of the fellow eye.

Influence of Available Variables on Time from Diagnosis to Treatment

Younger age at tumour diagnosis was found to be a strong predictor of the probability to administer chemotherapy ($P = .005$). We demonstrated that the likelihood of receiving treatment decreases by a factor of 0.831or by 17% with every year increase in age at the time of diagnosis ($P = .001$).

The probability to offer treatment was strongly related to the worse VA. The likelihood of initiating treatment was found to decline by a factor of 0.792 with every line increase in the minimum VA on the 8-point-scale ($P = .005$).

Dodge status is a strong predictor of the probability to treat. Subjects with posterior visual pathway tumour involvement (Dodge 3) were shown to be the group with the highest risk for receiving treatment ($P = .005$). These patients had a 3.869 times higher risk of receiving treatment compared to those with anterior gliomas ($P = .013$). The hazard rate of receiving treatment in patients classified as Dodge 2 was 2.369 times larger compared to those classified as Dodge 1. However, this was not found to be statistically significant ($P = .126$).

Female patients were 3.769 times more likely to need treatment compared to male ($P = .079$). In contrast, NF 1 subjects were less likely to receive treatment by a factor of 0.603 compared with the non-NF 1 group ($P = .074$). The relative risk of receiving treatment in these patients decreased by 40%.

The effect of the available variables on the time from diagnosis to initiation of treatment was assessed by the Cox proportional hazards model as shown in Table 3. The proportional hazards assumption test showed that the relative risk for any of these variables included in our study remained proportional over time. This was reflected in Figure 2 presenting the *-log(-log(S(t)) vs log(t)* plots with regards to Dodge and NF 1 status.

Table 3: Clinical Characteristics

Patient clinical characteristics (total 93 patients)	
Sex (female)	48 (51.61%)
Age at diagnosis in years (mean, SD)	4.4, ±
NF 1 positive	46 (49.64%)
Dodge tumour classification	Dodge 1: 10 (10.75%)
	Dodge 2: 28 (30.11%)
	Dodge 3: 55 (59.14%)
Received treatment	70 (75.3%)
Time in months from diagnosis to treatment (median, IQR)	8.26,
IQR: interquartile range; NF: Neurofibromatosis; SD: standard deviation	

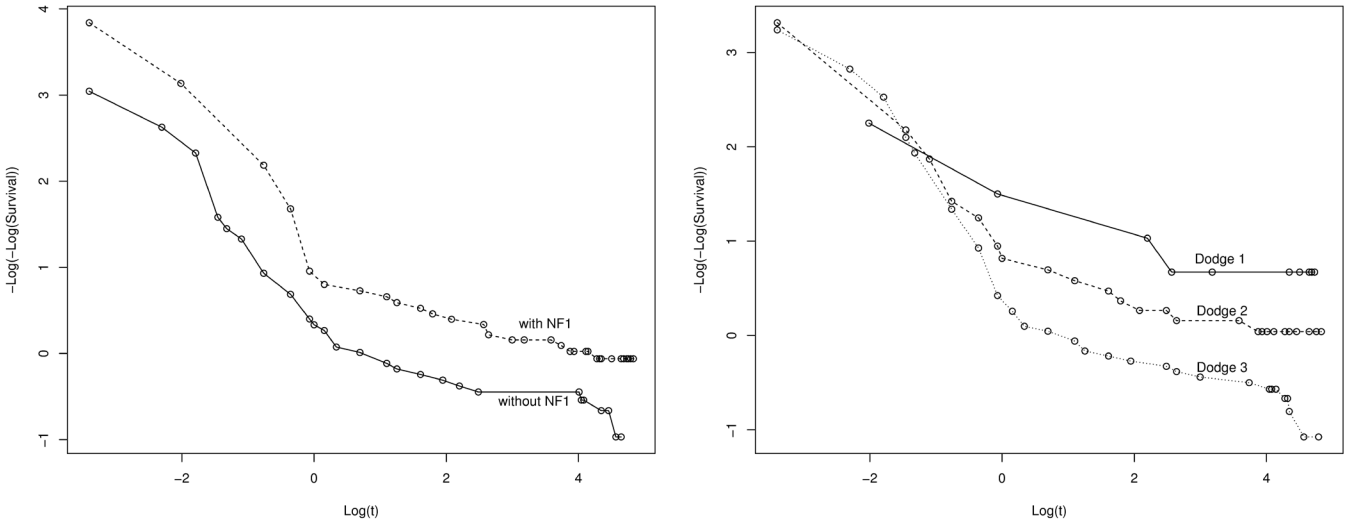

Figure 2: The -log(-log(S(t)) vs log(t) with regards to NF 1 status (left plot) and tumour extent and location as per Dodge classification (right plot)

Patients` Classification with Regards to the Risk of Treatment

A ROC curve was created to identify, at the time of diagnosis, a high-risk patient. The area under the ROC curve (AUC) evaluates the ability of the proposed model to distinguish between those who will receive treatment and those who will not.

In our study, the AUC equals 0.9168, indicating an excellent performance of the procedure (Figure 1, left plot). This observation suggests that a randomly selected patient who eventually receives treatment is rated higher at presentation than a patient who does not.

The optimal cut-off probability of receiving treatment was determined at 0.808, based on several criteria including point on curve closest to the (0, 1) and Youden index, representing the highest percentage (84.95%) of correctly classified individuals in our sample (Figure 1, right plot) [14-16]. The minimum cut-off probability was equal to 0.629. Therefore, the following three diagnostic groups were defined with respect to their estimated probability $\hat{p}$ of receiving a treatment:

- High risk: $\hat{p} > 0.808$
- Moderate risk: $0.629 < \hat{p} < 0.808$
- Low risk: $\hat{p} < 0.629$

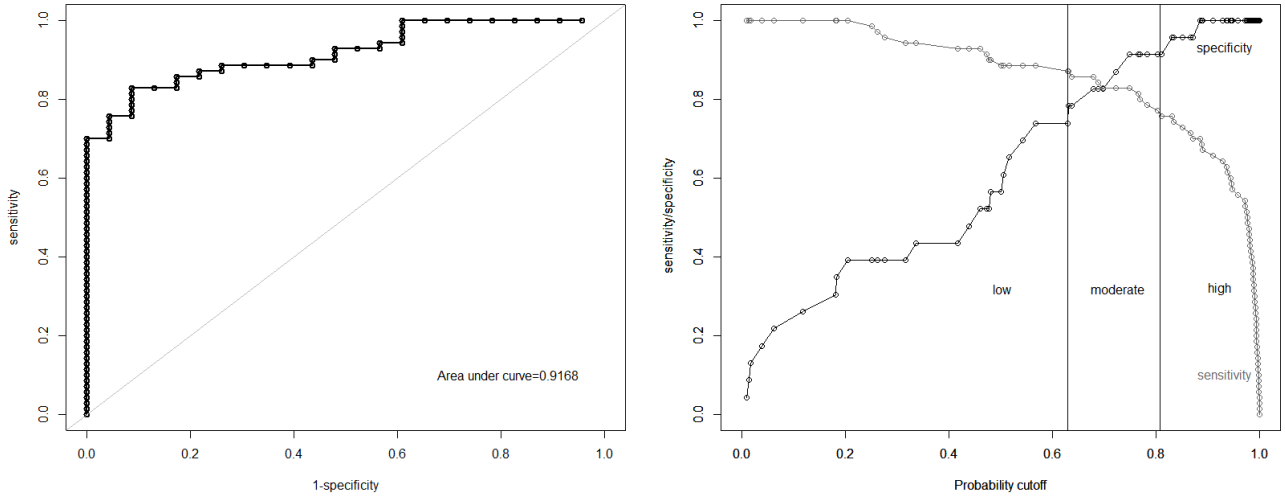

Figure 1: The ROC curve (left plot) and the plot of sensitivity (true positive rate) and specificity (true negative rate) versus all possible cut-off classification probability values (right plot). The two verticals lines on the right plot define the three diagnostic groups

Screening of OPGs Patients

The hazard rate over time of an individual to receive treatment can be assessed by the Cox proportional hazards model. A baseline survival and hazard function was calculated based on the Breslow estimator of the cumulative baseline hazard [17]. In our study, the baseline was defined as the case where the available variables at presentation take the following values: Sex = (Male), NF 1 status = (with), Age = , BCVA right eye = , BCVA left eye = , Dodge status = .

The baseline and the estimated survival and hazard function of a randomly selected patient are shown in Figure 3. The risk of receiving treatment for this patient is larger by a factor of 3.98 compared to the baseline (left plot). As a result, the corresponding survival function decreases faster than the baseline`s (right plot).

The relative risk for receiving treatment for each OPG patient and the corresponding hazard function plot can be calculated individually using an online tool considering all variables at the time of diagnosis. Patients can be classified as low, moderate and high risk subjects to need treatment with regards to the available variables. The frequency of follow-up examinations can be determined by the hazard function coefficient estimated at any time on corresponding hazard function plots.

According to the hazard function plot, the risk of receiving treatment appears to be higher considerably during two periods• the first 2 years after diagnosis and thereafterin year 6 (Figure 3, left plot).

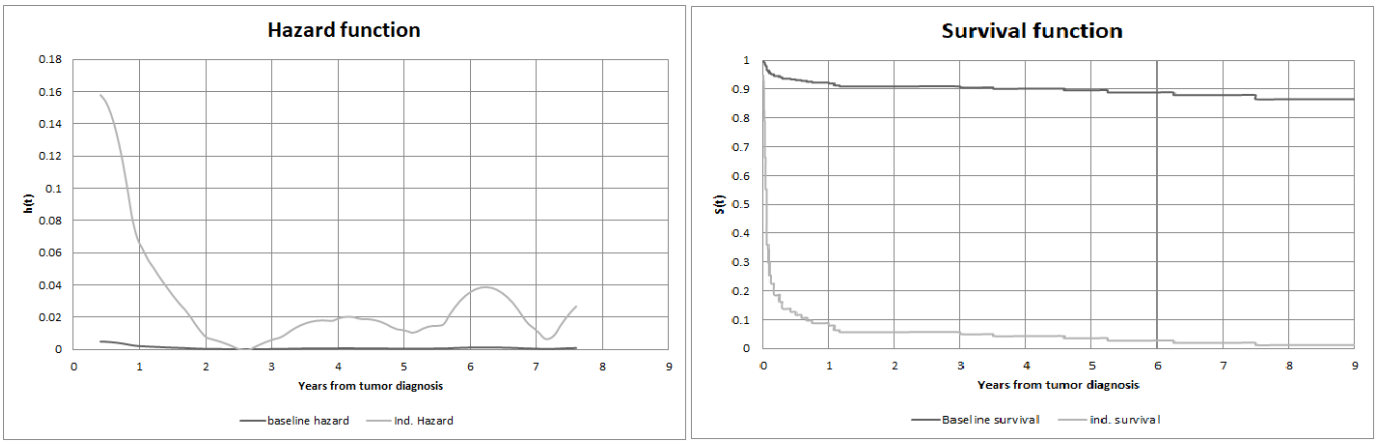

Figure 3: The baseline (black line) and the estimated survival and hazard function (grey line) of a two-year old, non NF 1 male patient with post-chiasmal tumour involvement and VAs equal to 3

Discussion

OPGs show a highly variable growth pattern ranging from indolent to rapidly progressive. Several case series have demonstrated a variable clinical course showing stabilization, progression and even spontaneous regression [5,18].

The majority of these tumours present by age 6 years although the potential for late-stage tumour progression has been reported [19]. Chemotherapy has taken on a prominent role in the management of paediatric low grade gliomas showing efficacy in addressing newly diagnosed, progressive and recurrent disease. Despite lack of agreement on indications for treatment, most clinicians advocate treatment once new or progressive VA loss has been detected [20].

Because of their unpredictable behavior, OPGs are among the most complex and challenging of brain tumours in children. The unpredictability is reflected in the literature with varied recommendations for OPG patients [21].

Previous studies showed that visual loss related to these tumours is most likely to occur during the early childhood years and progression is expected within the first two years after tumour diagnosis [22,23]. However, there appeared to be no absolute age during childhood beyond which the likelihood of vision loss becomes insignificant and therefore vigilant observation with close neuro-ophthalmologic and radiologic follow-up of patients was recommended through adolescence.

The importance of close monitoring in early childhood was confirmed in our study since the risk of receiving treatment was higher during the first two years following tumour diagnosis and was significantly reduced beyond this period.

Similar to previous publications, the need for treatment was apparent early. In the study conducted by Fisher et al, the median time from diagnosis to initiation of treatment was 41/2 months [23]. A slightly larger value was demonstrated in our study since the corresponding median time was 8.26 months.

Previous data supported the use of systemic chemotherapy to slow down or suppress tumour growth [24]. However, previous authors showed that up to 60% of children demonstrated tumour progression after 5 years [5,25]. In our study, we found that the risk of receiving treatment in OPGS children reemerged six years after initial tumour diagnosis.

Clinical features, such as presence of NF 1, anterior tumour location and older age at diagnosis have been shown to have a more favorable outcome [26]. We modeled the probability of receiving treatment with respect to the available variables at the time of diagnosis. Children with posterior tumour involvement of the optic tracts and radiations and subjects with poor VA and younger age at diagnosis were found to be the groups with the highest risk for receiving treatment. In contrast, male and NF 1 patients were less likely to need therapeutic intervention.

In our study, we managed to model the probability of receiving chemotherapy proportionally with respect to changes, among others, in VA and age. More specifically, three diagnostic groups (high, moderate, and low risk) were defined with respect to their estimated probability $\hat{p}$ of receiving treatment.

Given the tumour's varied and unpredictable growth pattern, many recommendations for follow-up exist [21]. A standard international monitoring protocol is not available. In Leeds, the current practice for the follow-up of children with identified OPG include neuro-ophthalmologic examinations at 3-month intervals during the first 12 months following tumour diagnosis. Thereafter, neuro-ophthalmic assessment is performed at 6-month intervals for 2 years, then annually through adolescence [27].

Our study suggests that all children with OPGs should be closely monitored, considerably during two periods• the first 2 years after diagnosis and thereafterin year 6. Specifically, the risk of tumour deterioration appears to be extremely high within the first 24 months following diagnosis, during which paediatric patients with OPGs appear to be susceptible to need chemotherapy at any stage. The hazard rate shows a tendency to decline towards the end of this period.

Estimated hazard function plots show this period to be the most critical for tumour growth and subsequent need for treatment and therefore intensive follow-up is recommended. The interval between visits and the frequency of follow-up examinations is determined by the hazard function coefficient applied at any time as defined by corresponding hazard function plots.

The risk of receiving treatment is substantially diminished after the age of 2 and remains extremely low until the end of year 5. Therefore, this period may be considered as a low risk period and the frequency of follow-up evaluations could be reduced. We therefore recommend that, during this period, neuro-ophthalmologic examinations should be performed at 6-month intervals.

Interestingly, our study showed chemotherapy risk recurrence in year 6 after initial presentation with a tendency to decline over the following 12 months. Subsequently, children should be followed more closely during this period with ophthalmic examinations at 3-month intervals. Beyond this age, ophthalmic assessment should be performed annually until the age of 16.

Limitations of our study include the relatively small number of recruited patients and the extreme young age in some cases that precluded reliable vision examination, as very young subjects are often difficult to examine. Additional limitation may be considered the observation that the proposed protocol applies more thoroughly in the case of OPG children classified as high risk patients.

Screening can be loosened up in case of low and moderate risk subjects but further study is required to determine by what factor.

In summary, our study shows that the hazard rate for the time from diagnosis to initiation of therapy can be estimated for each patient individually, thus recommending a new practice for follow-up in paediatric subjects with OPG with or without NF 1. Individualized hazard function plots and point estimations for the probability of the need of treatment can modify the frequency and duration of follow-up evaluations in OPG patients. Individuals with high probability of receiving treatment should be monitored more frequently especially over periods with large values of their estimated hazard function.

The corresponding hazard function plot for each patient and point estimation of the need of treatment may be obtained by an online tool at the authors` webpage. Larger prospective multicenter studies are required to draw safe conclusions regarding the efficacy of the proposed screening protocol. In any case, a critical approach and great diligence is required by all clinicians involved in the management of OPG during adoption and implementation of the suggested protocol.

Availability of Data and Materials: The data and materials are available by the corresponding author upon requesting

Authors' Contributions

Dr Evangelos Drimtzias: Study Design, Data Collection and Drafting
Mr Polychronis Economou: Statistical Analysis
Dr Kevin Falzon: Study Design and Revising the Manuscript
Dr Susan Picton: Study Design
Dr Ian Simmons: Study Design and Revising the Manuscript

Ethics approval and consent to participate

Patient consent for publication

Competing interests: Non-declared

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