

RESEARCH REPORT

Enucleation Refusal for Retinoblastoma: A Global Study

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ABSTRACT

Background: Enucleation (eye removal) is often the only curative treatment for the childhood eye cancer retinoblastoma, yet parental refusal of enucleation commonly contributes to treatment delay and poor survival globally.

Methods: Physicians who treat retinoblastoma were surveyed to glean underlying reasons for treatment refusal.

Results: Refusal rates were higher when less time was spent with parents explaining retinoblastoma/enucleation, and where fewer support services were available. Reasons for refusal included parental belief in alternative treatments, culture, and social stigma.

Conclusions: We suggest strategies to increase parental compliance with enucleation and save the lives of children with retinoblastoma.

Keywords: Enucleation refusal; global survival disparity; health inequalities; retinoblastoma; treatment compliance; treatment delay

INTRODUCTION

Retinoblastoma is the most common eye cancer in children, with a worldwide incidence of 1 in 15,000–20,000 live births.¹ The tumour is almost impossible to cure if it escapes the confines of the eye.² Enucleation, or surgical removal of the eye, is sometimes the only effective treatment to save the life of a child, particularly for International Intraocular Retinoblastoma Classification (IIRC) Group E eyes,³ where clinical features may suggest risk of extraocular spread.⁴ In low-resource countries, where most children with retinoblastoma live, enucleation is often the only available curative treatment, as chemotherapy and focal therapy (which can be used in combination to save eyes with good visual potential) are not always available.²

Parental refusal of enucleation is reportedly a major factor leading to delay in retinoblastoma treatment,⁵

particularly in low-and middle-income countries,^{6,7} and ultimately results in death that might otherwise be prevented.⁸ To our knowledge, the underlying reasons for parental refusal of enucleation have not previously been studied in great detail. By surveying a global pool of physicians who treat retinoblastoma, we attempted to identify factors contributing to parental refusal of enucleation, rationalizing that these answers might reveal strategies to increase compliance with treatment and therefore improve survival of children with retinoblastoma.

METHODS

Survey Population and Questionnaire

We identified 134 ophthalmologists and oncologists in 53 countries who treat retinoblastoma, through

Received 14 March 2014; revised 6 May 2014; accepted 15 June 2014; published online 14 July 2014

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published records available on the internet and/or those listed as authors of peer-reviewed publications and published abstracts about retinoblastoma.

Email correspondence with these physicians was initiated on December 16, 2011, in which we provided a web link to a survey (created on www.surveymonkey.com), explained the nature of the study, the approximate time it would take to complete (15 minutes) and offered a contact e-mail and phone number that allowed the respondents to seek further clarification if needed. Follow-up e-mails were sent on January 20, 2012 to those who had not yet responded. Completed responses were collected up until February 11, 2012.

Informed consent was explained, requested and acquired electronically via the first question in the survey (Supplementary Methods, Question 1). The questionnaire itself (Supplementary Methods – available online only) consisted of 14 questions (11 quantitative and 3 open-ended qualitative questions) and was designed based on a thorough review of the published retinoblastoma literature to identify gaps in knowledge in the area of enucleation refusal for retinoblastoma. Our questions aimed to elucidate the rate of enucleation refusal (defined as the proportion of cases where parents were initially opposed to enucleation even though the physician presented it as the primary option for treatment), as well as factors contributing to enucleation refusal, by asking physicians to comment on their experiences, their chosen communication methods with parents of retinoblastoma-affected children, and the general variety and availability of services for the visually impaired.

Data Analysis and Statistics

This study was approved by the University of Toronto Research Ethics Board and informed consent was obtained from each participant.

Data collected included respondent name, e-mail, hospital name, city, and country of each physician, along with their answers to the questionnaire. The economic status (high versus low- and middle-income) of each nation was classified according to the World Bank figures (<http://data.worldbank.org/country>). All statistical analyses were performed using StatPlus:mac software. Descriptive statistics included means, medians, standard errors and standard deviations. Student's *t*-test was used to test for significance for normally distributed, independent, and continuous variables. The Mann-Whitney test compared two independent, non-parametric sets of values derived from Likert scale questions (with possible responses on a scale of 1 to 5, 5 being "most common"), and Fisher's exact test was used to compare categorical variables. All *p* values were

two-tailed; *p* values of less than 0.05 were considered significant. The qualitative content (additional written comments of respondents) was analyzed inductively by open coding⁹ to derive prevalent themes.

RESULTS

Study Population

Of the total of 134 physicians contacted by e-mail, 45 (34%) completed the online survey. Twenty-four of 45 respondents (53%) were doctors from high-income countries (HICs) and 21 (47%) were from low- and middle-income countries (LMICs) (Supplementary Table 1 – available online only). Forty-one (91%) were ophthalmologists, and 4 (9%) were oncologists (not shown).

Global Refusal of Enucleation: An Overview

The mean proportion of patients who required enucleation at time of diagnosis (upfront enucleation) as reported by respondents was 62%, and did not vary significantly between HICs and LMICs (Table 1). We asked doctors to comment on the frequency with which parents refused enucleation when it was first presented to them (initial refusal). More doctors in LMICs reported high initial refusal rates, never as low as 0, and often as high as 100% of cases, while in HICs, the initial refusal rate ranged only from 0–25% (Table 1). Our statistical analysis did not reveal if one parent was more commonly responsible for the treatment decision than the other, if it was more often a joint decision, or if parents bowed to community pressure. However we noticed a trend in more respondents pointing to fathers being most influential in this regard (Table 1). Additional responses from physicians suggested that grandparents may also influence refusal of enucleation in both HICs and LMICs (Table 1).

Doctor-Parent Communication

We asked doctors how much time on average they spend with parents to explain the concepts of retinoblastoma and enucleation after diagnosis; the question did not specify if this timing was all at once, or over multiple sessions (Supplementary Methods, Question 4). Doctors in HICs reported spending more time on average (54 minutes, SD 26, SE 5.3) than doctors in LMICs (37 minutes, SD 19, SE 4) (*p*=0.02) (Table 1). Most doctors (92% (22/24) in HIC; 86% (18/21) in LMIC) reported using visual tools to educate parents (Table 1). Doctors less commonly reported using community groups and the church, and some facilitated meetings between

TABLE 1. Global enucleation refusal: an overview.

	HIC		LMIC		<i>p</i>
	<i>n</i>	%	<i>n</i>	%	
Respondents ^a	24	53	21	47	–
Proportion of cases where enucleation is indicated at diagnosis					
Mean (%)		43		53	0.18 ^b
Proportion of cases where enucleation is initially refused?					
0%	5	21	0	0	0.035
1–25%	19	79	9	43	0.014
26–50%	0	0	8	38	0.00094
51–75%	0	0	3	14	0.094
76–100%	0	0	1	5	0.47
Parent(s) that most commonly refuses enucleation					
Father	3	13	6	29	0.17
Mother	1	4	2	10	0.36
Both	11	46	5	24	0.11
Neither (pressure from community)	2	8	5	24	0.15
Other	4	17	3	14	0.73
Time spent by physicians on parent education					
Mean time (minutes)	54	–	37	–	0.02
Methods used to educate parents about enucleation ^c					
Visual methods	22	92	18	86	0.42
Community groups	3	13	4	19	0.42
Church	1	4	0	0	0.53
Other	10	42	4	19	0.094
Methods used to follow-up with parents about additional concerns with enucleation ^c					
Follow-up appointment	18	76	16	76	0.67
Telephone	11	46	8	38	0.8
Leave it up to the parent	7	29	10	48	0.17
E-mail	4	17	3	14	0.73
Other	5	21	6	29	0.4
Physician's strategy after parents refuse enucleation					
Try to get parents to change their mind	15	63	20	95	0.0086
Provide option of other therapy	9	38	12	57	0.15
Nothing; parents get other opinion	2	8	1	5	0.76
Other ^d	11	46	4	19	0.055
Success at reversing refusal decision					
Respondents	16		21		
Doctors who had ever successfully reversed an enucleation refusal decision	14	88	21	100	0.18
Would additional supports for the blind increase acceptance of enucleation?					
Yes ^e	10	42	16	76	0.03
No	14	58	5	24	

^aSee Supplementary Table 1

^bStudent's *t*-test was used for this *p* value; Fisher's test was used in the other calculations.

^cMultiple responses allowed

^dSee Supplementary Table 2

^eSee Supplementary Table 3

Italics indicate significance, *p* < 0.05

affected families and counseling by a registered psychologist.

We asked respondents to comment on their approach to handling additional concerns parents may have about enucleation. They included scheduling another appointment, discussing concerns by telephone or email, or leaving it to the discretion of the parent to contact the doctor (Table 1). Additional approaches included contacting the family doctor of the child, speaking about additional concerns prior to surgery, enlisting the support of nurses involved in the patient's care, and using outreach services (Supplementary Table 2 – available online only). We found no significant differences in range or type of

tools (mainly visual images) or approaches reportedly used by doctors in HICs and LMICs (Supplementary Table 2).

Actions of Doctors after Parental Refusal of Enucleation

Doctors in LMICs (20/21, 95%) more commonly made an attempt to change the parent's mind compared to those in HICs (15/24, 63%) (*p* = 0.0086) (Table 1). Doctors in both HICs and LMICs reported that they had sometimes offered a different therapy, such as a cycle of chemotherapy, or referred the patients to other centers to receive second opinions (Table 1, Supplementary Table 2).

Underlying Factors Contributing to Enucleation Refusal

We asked respondents to comment on their perception of why parents refuse enucleation. Physicians from LMICs more commonly cited lack of support programs for the visually impaired ($p=0.00008$), a prevailing societal belief in alternative treatments ($p=0.0009$), fear of social stigma ($p=0.00085$), and cultural reasons ($p=0.0095$) as contributors to parental enucleation refusal than did physicians in HICs (Table 2). Physicians from both HICs and LMICs cited fear of children not adjusting ($p=0.08$) and religious beliefs ($p=0.61$) as contributing factors (Table 2). Additional reasons provided by HIC respondents included “irrational fear” and the belief that “future scientific advances will allow a blind eye to see,” while respondents from some LMICs referenced parental beliefs that “the spreading cancer does not pose a true danger” and that “monks can cure any disease.”

Availability and Variety of Post-enucleation Support

Access to post-enucleation support for patients and their families, such as websites ($p=0.00025$), organizations ($p=0.0029$), and educational materials ($p=0.032$) were more commonly reported as available in HICs than LMICs. We found no difference in the availability of prosthetic eyes ($p=0.19$), financial support services ($p=0.57$), and culturally sensitive counseling ($p=0.71$) between HICs and LMICs (Table 3).

Factors that Contribute to Reversal of Enucleation Refusal Decision

After initial parental refusal of treatment, all LMIC doctors (21/21, 100%) indicated that they had at some point experienced success in eventually obtaining enucleation acceptance, as did the majority of doctors in HICs who had ever experienced an enucleation refusal in the first place (14/16, 88%) ($p=0.18$). Respondents elaborated on the methods they used to reverse the initial decision of parents to refuse enucleation. Three common themes emerged: (1) education of parents, (2) cross-consultation, and (3) family support (Supplementary Table 2).

Recommended Strategies to Increase Compliance with Enucleation

Significantly more doctors in LMICs (16/21, 76%) than HICs (10/24, 42%) responded that they believed

TABLE 2. Reasons for enucleation refusal. Respondents rated each of the stated reasons as 1 = least common, 5 = most common.

	Mean	Median	SD	p^a
Lack of support programs				
HIC	1.29	1	0.55	<i>0.00008</i>
LMIC	2.71	3	1.2	
Belief in alternative treatments				
HIC	2.83	2.5	1.31	<i>0.00009</i>
LMIC	4.48	5	0.81	
Social stigma				
HIC	2.58	3	1.2	<i>0.00085</i>
LMIC	4.05	5	1.1	
Cultural				
HIC	2.54	2.5	1.41	<i>0.0095</i>
LMIC	3.86	5	1.42	
Lack of education				
HIC	2	2	1.25	<i>0.012</i>
LMIC	3.14	3	1.35	
Fear of adverse effects				
HIC	1.79	1	1.2	<i>0.014</i>
LMIC	2.62	2	1.32	
Financial				
HIC	1.04	1	0.2	<i>0.04</i>
LMIC	1.81	1	1.21	
Fear of child not adjusting				
HIC	2.46	2	1.44	0.08
LMIC	3	3	1.1	
Religious				
HIC	2.17	2	1.27	0.61
LMIC	2.38	2	1.4	

^aMann-Whitney test

Italics indicate significance, $p < 0.05$

implementation of additional supports could help parents accept enucleation ($p=0.03$). Doctors in HICs more commonly responded that continuing to promote the use of supports that are already available, such as counseling, would help increase treatment compliance. Four major themes emerged from responses of doctors in LMICs on how to increase parental acceptance of enucleation: (1) A team approach to care, (2) increased time with parents, (3) a focus on transition planning, and (4) improved supports for the visually impaired (Supplementary Table 3 – available online only).

DISCUSSION

The ideal outcome of retinoblastoma treatment is preservation of both life and vision.² The physician's decision to enucleate an eye is affected by various factors, including the stage of disease and risk to patient's life, visual potential of the affected eye, the tumor and/or vision status of the other eye, and the array of other treatment options available to them. In the presence of various socioeconomic factors contributing to delay in diagnosis, inhibited access to specialist medical care, and the lack of availability of vision-saving therapies in many LMICs (where most

TABLE 3. Post-enucleation support services available for families. Respondents rated availability in their countries as 1 = least common, 5 = most common.

	Mean	Median	SD	<i>p</i> ^a
Websites				
HIC	3.58	4	1.25	<i>0.00025</i>
LMIC	2.1	2	1.18	
Organizations				
HIC	3.71	4	1.27	<i>0.0029</i>
LMIC	2.48	2	1.36	
Educational material				
HIC	3.5	4	1.5	<i>0.032</i>
LMIC	2.57	2	1.36	
General counseling				
HIC	4.33	5	1.2	0.054
LMIC	3.81	4	1.08	
Networking				
HIC	3.54	3.5	1.14	0.095
LMIC	2.95	2	1.63	
Prosthetic Eyes				
HIC	4.83	5	0.82	0.19
LMIC	4.33	5	1.35	
Financial help				
HIC	3.17	3	1.34	0.57
LMIC	2.95	3	1.53	
Culturally sensitive counseling				
HIC	2.92	3	1.38	0.71
LMIC	2.76	3	1.27	

^aMann-Whitney test

Italics indicate significance, p < 0.05

retinoblastoma patients live), enucleation is often the only choice to save the life of a patient.^{8,10,11} Even for resource-rich countries, the only evidence-based curative therapy for IIRC Group E eyes³ is enucleation, followed by histological analysis to determine if adjuvant chemotherapy is needed.¹²

Unfortunately, globally many parents refuse enucleation,¹³ even when it is the only choice for cure. Indeed, our study showed that while the number of indicated upfront enucleations did not differ between HICs and LMICs, the proportion of enucleation refusals did (Table 1), consistent with previous anecdotal reports that identify parental refusal of enucleation as a critical issue in LMICs.^{5,8}

Enucleation refusal, even when other courses of therapy subsequently follow, can have devastating consequences for the life of a patient,⁴ but often physicians appear to be opposed by parents, who ultimately decide how treatment will proceed (or if at all). Even in our study population, doctors indicated that sometimes the only way they could obtain parental acceptance of enucleation was after attempting another therapy that eventually failed (Supplementary Table 2), which for advanced intraocular cases, essentially puts the child's life at risk.⁴ Previously, survival of children whose parents refuse enucleation temporarily was found to be only 20%, while the survival rate for children whose parents did not refuse the treatment was 70%.⁴ It is expected

that for children whose parents refused treatment indefinitely, none would have survived.⁴

The root of conflict between patients/families and their healthcare providers on treatment decisions is presumed to be a clash of values.⁴ Families tend to be guided by hope and focus on the positive possible outcomes, even when the prognosis is poor, while the health care professionals weigh the potential benefits and harms before deciding on an intervention. Refusal of enucleation has previously been attributed to social, cultural, religious and other parental beliefs.^{6,14} Consistent with this, our results showed that beliefs in alternative treatments, fear of social stigma, and additional cultural factors appear to influence parental decision making; we found these more commonly cited by doctors in LMICs, where enucleation refusal was highest. While at face value these appear to be insurmountable obstacles that go beyond the reach of medical practice, our survey shows that thorough attention by physicians to the education of parents can reverse an initial decision to refuse enucleation, even in societies where these sociocultural factors exist (Supplementary Table 2).

Cancer survival depends not only on the current limits of scientific and medical knowledge, but also on a therapeutic alliance between physician and patient¹⁵ and the ability of the healthcare provider to communicate effectively with patients. Studies have suggested that abandonment rates for childhood cancer treatment are influenced by the quality and quantity of communication by the health care provider.¹⁶ Positive therapeutic alliances can increase compliance with cancer treatment.¹⁷ Time spent by doctors with parents contributes to a positive therapeutic alliance, and indeed we noticed that even though there was no difference in the methods doctors used to communicate with parents, more time was spent by doctors with parents in regions where higher treatment compliance was also reported. Spending more time with parents was also suggested by the LMIC respondents as a method to increase treatment compliance (Supplementary Table 3). It is possible that the extra time spent by doctors correlates with how well the parents' psychosocial needs are met, contributing to their ability to understand and cope with the diagnosis. However, health care systems are often strained in LMICs, and doctors face numerous pressures that limit their time with individual patients and families, such as low resources and higher patient numbers.⁸ Sharing the role of educating parents within a multidisciplinary healthcare team, including counselors, nurses or social workers where available, may be an effective approach to increase time spent on parental education in these settings (Supplementary Tables 2 & 3).

Our qualitative data show that an interdisciplinary approach is vital for children's survival. A coordinated multidisciplinary team approach may assist in

improving follow up and compliance with therapy. A number of joint programs have been established in Central America and have demonstrated a significant decrease in extraocular disease (from 73% to 35%) after implementation of early diagnosis programs.¹⁴

Our study also points to the general lack of post-enucleation support resources and services available in LMICs compared to HICs (Table 3). Parents may perceive their cancer-afflicted children to have a lower quality of life.¹⁸ For retinoblastoma patients facing enucleation, this may be amplified when support services, such as schools for the visually impaired, are rare or not available. Improved access and availability of such supportive services, and education of parents so that they are knowledgeable about them, may increase compliance with enucleation. Indeed, the majority of respondents from LMICs indicated that additional support services are needed (Table 1), and that strategies such as encouraging linkages between affected families or involving more family members in treatment education and decision making, may contribute positively to treatment compliance (Supplementary Tables 2 & 3).

Our survey did not verify the factors leading to the physician's recommendation for upfront enucleation, such as stage at diagnosis or local availability of eye-salvage treatments. It is possible that enucleation refusal may have been influenced by information accessed by the parents, which pointed to eye-salvage treatments available at other centers. However, the seeking of second opinions emerged as a strategy to increase treatment compliance (Supplementary Table 2), suggesting the initial recommendation for upfront enucleation was appropriate. While the authors concur that support for enucleation by multiple practitioners can encourage parents to comply, we wish to stress that the act of seeking a second or even third opinion may cause significant delay in treatment, or cause further confusion and stress. Anecdotal evidence indicates that when patients seek a second opinion, particularly families from LMICs seeking opinions and care in HICs, this can have negative consequences on the financial and emotional stability of the family, and rarely results in saving the eye.¹⁹

Our study is not without its limitations. First, our findings are based on the individual experiences and perceptions of physicians rather than the parents themselves. Additional analysis of the physician's working environment (e.g. working within a multi-disciplinary retinoblastoma team) would add further insight into this study. However, we believe for this initial study, surveying physicians allowed us to get a general view of a larger patient pool, allowing respondents to draw from their years of experience with retinoblastoma. Also, we were unable to study low and middle income countries in two distinct groups, as very few doctors from low-income

countries responded to our survey ($n=3$; Supplementary Table 1). We suspect that the rate of enucleation refusal and available support in low-income countries is likely different than that reflected in our study of LMICs. Finally, we acknowledge that due to the low survey response rate, study results have low overall power.

In conclusion, we have identified significant factors that may contribute to parental refusal of enucleation for retinoblastoma. Approaches to be studied to increase compliance include increasing time spent with parents to thoroughly educate about retinoblastoma and enucleation, as well as improving post-enucleation support services. This will require more collaboration with medical care teams, families and the community at large.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of the physicians who participated in the survey, and Dr Timothy W. Corson who provided some assistance in the editing of this manuscript.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary Material Available Online

Supplementary Survey Questionnaire

Supplementary Tables 1, 2 and 3

Supplementary material for <Olteanu C, Dimaras, H>, <Enucleation Refusal for Retinoblastoma: A Global Study>, <Ophthalmic Genetics>, <2014>