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RESEARCH ARTICLE

Establishment of a formal program for retinoblastoma: Feasibility of clinical coordination across borders and impact on outcome

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Abstract

Retinoblastoma is an ocular tumor that occurs in young children, in either heritable or sporadic manner. The relative rarity of retinoblastoma, and the need for expensive equipment, anesthesia, and pediatric ophthalmologic expertise, are barriers for effective treatment in developing countries. Also, with an average age-adjusted incidence of two to five cases per million children, patient number limits development of local expertise in countries with small populations. Lebanon is a small country with a population of approximately 4.5 million. In 2012, a comprehensive retinoblastoma program was formalized at the Children's Cancer Institute (CCI) at the American University of Beirut Medical Center, and resources were allocated for efficient interdisciplinary coordination to attract patients from neighboring countries such as Syria and Iraq, where such specialized therapy is also lacking. Through this program, care was coordinated across hospitals and borders such that patients would receive scheduled chemotherapy at their institution, and monthly retinal examinations and focal laser therapy at the CCI in Lebanon. Our results show the feasibility of successful collaboration across borders, with excellent patient and physician adherence to treatment plans. This was accompanied by an increase in patient referrals, which enables continued expertise development. However, the majority of patients presented with advanced intraocular

Abbreviations: CCI, Children's Cancer Institute; EBRT, external-beam radiation therapy; EUA, examination under anesthesia; PFV, persistent fetal vasculature.

disease, necessitating enucleation in 90% of eyes in unilateral cases, and more than 50% of eyes in bilateral cases. Future efforts need to focus on expanding the program that reaches to additional hospitals in both countries, and promoting early diagnosis, for further improvement of globe salvage rates.

KEYWORDS
pediatric hematology/oncology, pediatric oncology, retinoblastoma

1 | INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy of childhood. When diagnosed in early stage, overall survival (OS) is close to 100%, with successful eye and vision salvage in the majority of cases.[1] Advanced intraocular disease requires more specialized treatment approaches, and in many cases necessitates enucleation of the affected eye, while extension beyond the globe results in significantly lower disease control and cure rates.[2–4] Treatment of children with retinoblastoma is focused on not only child survival, but also retained vision—which can be affected by disease extent at diagnosis, need for enucleation, and side effects of treatment modalities such as laser and radiation therapy. Globe salvage is also an important outcome measure, since enucleation can have psychological and psychosocial effects beyond simple cosmesis.[5]

In developing countries, the diagnosis of retinoblastoma is frequently made at later stages of the disease when extraocular dissemination has already occurred; therefore, ocular and patient survival rates are lower due to delayed presentation, cost barriers, and lack of specialized personnel and equipment.[6] Recently, the first multidisciplinary retinoblastoma program in Beirut, Lebanon, at the Children's Cancer Institute (CCI) at the American University of Beirut, addressed the goal of responding to the needs of children with retinoblastoma in Lebanon and surrounding countries. We hereby report the establishment of this program and its impact on patient treatment, and we compare patient numbers, characteristics, and outcome for those treated within the program (2012-2017) to those treated at the same institution before the program establishment (2002-2012).

2 | METHODS AND PROGRAM DETAILS

2.1 | Establishment of the retinoblastoma program

The CCI was established in 2002, as a multidisciplinary cancer center at the American University of Beirut Medical Center. Patients with retinoblastoma were accepted for treatment similar to other oncology patients. Pediatric oncology, pediatric ophthalmology, radiation oncology, radiology, and anatomic and molecular pathology expertise were all available, and were involved in patient care and discussion as deemed needed by the treating oncologist. The Children's Cancer Center of Lebanon Foundation provided financial coverage for treatment to all patients, such that no patient had to pay out-of-pocket expenses for therapy.

In June 2012, the Retinoblastoma Program was established through a program development initiative by St Jude Children's Research Hospital in Memphis, TN, USA. A pediatric ophthalmologist and a pediatric oncologist were assigned the central role of coordination for all children with retinoblastoma. The RetCam shuttle (Clarity, Massie Industries, Dublin, CA) was purchased to facilitate objective documentation of intraocular disease extent and allow formal response evaluation and review. A clinical nurse coordinator was assigned to ensure appropriate communication among physicians and departments, coordination of patient visits, treatment plans, and timing of evaluations/interventions, and other logistics. Monthly retinoblastoma team meetings were held, where the team reviewed all active cases in a multidisciplinary setting. Funds were allocated to allow acceptance of patients referred from other hospitals, such that diagnosis, treatment planning, and focal therapy would be administered at the CCI, but the patient could receive chemotherapy at their referring hospital. The retinoblastoma program nurse coordinator was responsible for coordinating treatment scheduling and follow-up details between the referring oncologist and the CCI. All centralized procedures (pathology review, staging, and local control procedures including focal laser therapy, enucleation, or radiation therapy) were performed at the CCI. Due to budget constraints, gene testing was financially covered only for patients with bilateral tumors, and those with unilateral tumor diagnosed at an age younger than 2 years, or patients with positive family history. Remaining patients were counseled on the benefits of gene testing.

2.2 | Patient treatment details

Patients with intraocular disease that has not been previously treated were eligible for acceptance. Upon diagnosis, patients were evaluated by both ophthalmology and pediatric oncology teams, and underwent examination under anesthesia (EUA), during which retinal images were captured by RetCam. Magnetic resonance imaging of the brain and orbits was performed at diagnosis. Disease extent was based on the International Intraocular Retinoblastoma Classification.[7] When indicated, chemotherapy was administered at the treating institution, consisting of six cycles of combination chemotherapy with vincristine, carboplatin, and etoposide, as per standard practice.[8]

Eye EUA was performed monthly, with focal therapy (thermotherapy and/or cryotherapy) done when indicated within 24 h of chemotherapy. Transpupillary thermotherapy was performed during EUA and delivered via an indirect ophthalmoscope-equipped infrared

TABLE 1 Patient characteristics

Patient characteristics number (%)		January 2002-June 2012 (*N* = 20)	July 2012-June 2017 (*N* = 40)
Mean number per year [range]		2 [0-3]	8 [6-12]
Nationality	Lebanese	13 (65%)	14 (35%)
	Syrian	5 (25%)	23 (58%)
	Iraqi	0	2 (5%)
	Other	2 (10%)	1 (2%)
Primary oncologist/chemotherapy site	Lebanon	20 (100%)	23 (58%)
	Syria	0	17 (42%)
Gender	Male	11 (55%)	26 (65%)
	Female	9 (45%)	14 (35%)
Age at diagnosis (months)	0-12	14 (70%)	19 (48%)
	13-24	2 (10%)	12 (30%)
	>24	4 (20%)	9 (22%)
Tumor location	Unilateral	9 (45%)	19 (48%)
	Bilateral	11 (55%)	21 (52%)
Family history of retinoblastoma	Positive	2 (10%)	4 (10%)
	Negative	18 (90%)	36 (90%)

diode laser at 810 nm (Iridex, Mountain View, CA), focused with a 20- or 28-diopter lens. Intravitreal chemotherapy (Melphalan 30 μg) was delivered for eyes with vitreous seeding in Group C or D that were resistant to chemotherapy.[9] Injections were given every 2-3 weeks until resolution of vitreous disease, to a maximum of six injections.

External-beam radiation therapy (EBRT) was used for eyes with poor clinical response or to salvage a potentially seeing eye in patients with one remaining eye. Enucleation was recommended for Group E or D eyes with no visual potential or for those who showed no response to treatment, or eyes with tumor progression despite chemotherapy.

For patients with unilateral disease where enucleation showed high-risk histological features (ie, massive choroidal invasion, extra scleral extension, or optic nerve invasion beyond the lamina cribrosa), adjuvant chemotherapy was administered as above.

Following end of treatment, patients were monitored with periodic EUA and clinical examination as per standard practice.

2.3 | Clinical data collection

This study was approved by the Institutional Review Board at the American University of Beirut Medical Center. Data were collected for all patients diagnosed with retinoblastoma between January 1, 2002 and June 30, 2017, including nationality, age at diagnosis, tumor group information, laterality, treatment, response to therapy, and vision and clinical outcome. Follow-up data were included until December 31, 2018. Descriptive analysis was performed to describe the demographics and clinical information. Frequency, median, and range were calculated for continuous variables, while number and frequency were used for categorical variables. OS was defined as the time interval from date of diagnosis to either death from any cause or last follow-up, using Kaplan-Meier estimates.

3 | RESULTS

3.1 | Patient numbers and characteristics

Between January 2002 and December 2011, prior to establishment of a formal retinoblastoma program, a total of 20 patients with newly diagnosed retinoblastoma were treated at the CCI, thus averaging two patients per year. After establishment of the retinoblastoma program in 2012, the numbers increased, with a total of 52 patients evaluated for retinoblastoma between June 2012 and June 2017, thus averaging 10 patients per year. Over this period, six patients were excluded due to having received prior therapy and three patients for having extraocular disease at presentation. Three other patients were diagnosed not to have retinoblastoma but simulating disorders: Coats disease, exudative retinopathy, and persistent fetal vasculature (PFV). Thus, a total of 40 eligible subjects were treated between January 2012 and June 2017, averaging eight newly diagnosed patients per year. Patient demographics and clinical details for the two time periods are presented in Table 1, and show an increase in patients referred from neighboring countries in the latter period.

The tumor staging details of patients diagnosed before and after establishment of the retinoblastoma program are shown in Table 2. In the latter period, 21 eyes (34%) had early disease (Groups A-C) at the time of diagnosis. Notably, diagnosis of early disease was made in the setting of an advanced disease in the second eye in 12 patients (12 eyes, 57%), screening due to family history of retinoblastoma in two patients (three eyes, 14%), and abnormal red visual reflex detected by the parents in four patients (six eyes, 29%). In the previous period (January 2002-June 2012), 26% had undocumented tumor group and stage, making it difficult to compare across periods. However, while 13% of eyes were enucleated prior to referral to our center in the

TABLE 2 Tumor classification (International Intraocular Retinoblastoma Classification)

Group	Number of eyes (%)	
	January 2002-June 2012, total *N* = 31	July 2012-June 2017, total *N* = 61
A	2 (6%)	0 (0%)
B	5 (16%)	13 (21%)
C	0	8 (13%)
D	6 (19%)	14 (23%)
E	6 (19%)	23 (38%)
Enucleated prior to referral without group information	4 (13%)	3 (5%)
Not available	8 (26%)	0 (0%)

earlier period, the number was only 5% between July 2012 and June 2017, reflecting earlier referral prior to surgical intervention.

Thus, establishment of the retinoblastoma program correlated with increased referral of patients from both Lebanon and the region, with a lower rate of prestaging enucleation, but with no demonstrable effect on earlier detection of early-stage disease.

3.2 | Coordination of treatment delivery

More than 40% of patients treated after 2012 received chemotherapy at the referring institution, with close coordination with our unit for monthly eye EUA and focal laser therapy. This required dedicated time by a nurse coordinator for timely follow-up with the referring physician for patient clearance for travel, treatment timing coordination, sharing of treatment planning, multidisciplinary meeting coordination, documentation of chemotherapy received at the local hospital, and facilitation of the needed reports for families to travel across the border. In addition, the coordinator helped interface with social services to tackle social and financial barriers to travel or treatment delivery. For our patient load, this necessitated 40% dedicated time for one nurse coordinator, and included communication by email, phone, and instant messaging applications.

3.3 | Treatment and globe outcome

Patient and eye outcomes for both periods are detailed in Table 3, separately for patients with bilateral and unilateral tumors, respectively. For patients with bilateral retinoblastoma, upfront enucleation was performed for 26% of eyes in the latter period compared to 41% in the earlier period. Another 19% and 18%, respectively, were later enucleated after receiving one or more cycles of chemotherapy, due to failure of adequate response, poor visual potential, or uncontrollable recurrences. In the latter period, high-risk histopathologic features were noted in four enucleated eyes (22%) in this group of patients, while these data were not available to us for the former period. In the recent period, five eyes (four patients) were advised enucleation but family refused and left to seek another opinion. Thus, eye salvage rate was similar in both periods (43% on retinoblastoma program vs 41% in earlier period). Notably, radiation therapy was used for two eyes (5%) after failure of first-line therapy on the retinoblastoma program, compared to four eyes (18%) in the former period.

When analyzing outcome of bilateral tumors by stage, we found that, in the earlier period, all 10 eyes with Group D or E disease were eventually enucleated, while all seven eyes with Groups A and B disease were salvaged. Of five eyes with undocumented group, two were

TABLE 3 Treatment and outcome

Laterality		Bilateral retinoblastoma		Unilateral retinoblastoma	
Year of diagnosis Total number of eyes		January 2002-June 2012 *n* = 22	July 2012-June 2017 *n* = 42	January 2002-June 2012 *n* = 9	July 2012-June 2017 *n* = 19
Number of eyes (%)	Upfront enucleation	9 (41%)	11 (26%)	7 (78%)	14 (74%)
	Delayed enucleation	4 (18%)	8 (19%)	2 (22%)	3 (16%)
	Refused enucleation/left for other treatment	0	5 (12%)	0	0
	Radiation therapy	4 (18%)	2 (5%)	4 (44%)	0
Number of patients (%)	Bilateral vision	1 (9%)	4 (19%)	1 (10%)	2 (10%)
	Unilateral vision	7 (64%)	9 (43%)	9 (90%)	17 (90%)
	Blind	3 (27%)	3 (14%)	0	0
	No information (left treatment)	0	4 (19%)	0	0
	Died of disease	0	1 (5%)	0	0
Ocular survival (percentage saved eyes)		41	43	0	10
2-Year overall survival (Kaplan-Meier estimate)		100%	95%	100%	100%
Median follow-up in months (range)		39 (20-73)	32 (1-77)	47 (3-67)	35 (5-65)

salvaged. Similarly, after establishment of the retinoblastoma program, only one of 24 eyes with Group D and E tumors was salvaged, compared to 17 of the 18 eyes presenting with Group B or C disease. One eye with Group B disease eventually underwent enucleation after multiple relapses and chemoresistant disease.

Importantly, one patient developed meningeal metastases within 3 months after end of treatment and died of disease progression; this patient had had upfront enucleation prior to being referred to our center, and histopathologic evaluation was not available for review.

As for visual outcome, as detailed in Table 3, 73% and 62% of patients diagnosed with bilateral tumors in the earlier and latter period, respectively, had documented useful vision. Numerical visual acuity (Snellen acuity) was recorded for verbal patients treated on the retinoblastoma program (latter period). Of the four patients retaining both eyes, one patient had 20/30 visual acuity in both eyes (originally Group B), and the remaining three are still nonverbal. Of the nine patients retaining one eye, four attained 20/20 vision (originally two were Group B and two were Group C), two eyes had 20/50-20/60 vision (originally Group C), and the remaining three patients are still nonverbal).

For patients with unilateral retinoblastoma, both periods showed high rates of enucleation due to advanced disease at presentation (Table 3). Of the 17 enucleated eyes in patients treated since 2012, high-risk histopathologic features were noted in four (24%), who then received adjuvant chemotherapy. This information was not available for patients treated before 2012. Notably, radiation therapy was used in four patients (44%) with unilateral retinoblastoma in the earlier period, but in none (0%) of those treated on the program (Table 3).

As for visual outcomes, the one eye with Group D disease that was salvaged had 20/40 visual acuity after chemoreduction, focal treatment, and intravitreal chemotherapy. All patients had 20/20 visual acuity in the normal fellow eye.

3.4 | Genetic testing

After June 2012, genetic germline testing (peripheral blood sample) was performed for 20 of the 21 patients with bilateral retinoblastoma, and positive RB1 gene mutation/deletion was detected in 17 (85%) patients. For patients with unilateral retinoblastoma, germline genetic testing was done in 10 patients (53%), all of whom were younger than 2 years at diagnosis, and a positive RB1 gene mutation/deletion was detected in three (30%) patients.

3.5 | Direct costs of treatment

Treatment for all patients at our center—specifically imaging, EUA, focal therapy with laser or other modalities, and enucleation—was supported in full by the retinoblastoma program fund. In the absence of such funding, the majority of patients would not have been able to access these specialized modalities. Through this fund, the average direct cost of treatment for a child with unilateral retinoblastoma for the first year was $7995 (range $3446-$15 891), with an average yearly cost for the ensuing 2 years being $2650 (range $200-$6942) and $1136 (range $200-$4838), respectively. For a child for bilateral retinoblastoma, the average cost for the first year was $21 035 (range $8204-$40 549), and the average yearly cost for the next 2 years was $14 751 (range $200-$47 134) and $7422 (range $200-$26 029), respectively.

4 | DISCUSSION

Management of retinoblastoma in less developed countries can be particularly challenging due to the relative rarity of the disease, the need for interdisciplinary management and close real-time coordination among subspecialists, as well as the need for specialized ophthalmologists trained in focal/laser therapy, and orbital/oculoplastics specialists. Additional important barriers include the costly and sometimes unavailable appropriate operational setup to image and deliver focal therapy to the retina. These factors prompt the need to centralize such care to tertiary hospitals, with establishment of solid referral networks that ensure maintenance of expertise, delivery of care to populations in need, and reduction in service redundancy.

Formalizing a multidisciplinary retinoblastoma program initially aimed at standardizing care locally at our cancer center in a multidisciplinary fashion. Once the program was established, there was an increase in referrals from other centers in Lebanon, Syria, and more recently Iraq, validating the impact and value of these otherwise unavailable services in many hospitals in underdeveloped and developing countries. The number of patients evaluated increased from an average of two per year to an average of 10 per year. Three patients were diagnosed with benign mimicking conditions (Coats disease, PFV, and exudative retinopathy), two of whom had been scheduled for chemotherapy at the referring institution, and therefore their referral completely altered their management plan. Indeed, Shields et al reported simulating eye conditions in up to 22% of patients referred for management of retinoblastoma,[10] underscoring the importance of centralized expert evaluation of these rare conditions.

In addition to ensuring the availability of the needed clinical subspecialty expertise in the multiple involved disciplines, a central component of this program was the establishment of a nurse coordinator role for this program. This ensured continuous coordination with the referring oncologists under whose care the child receives chemotherapy, with the central retinoblastoma team where the evaluations, focal therapy, and treatment planning are discussed. The coordinator was also essential in tracking problems and treatment delays related to patient travel across borders, financial burdens of transportation, and social barriers to follow-up that need to be addressed for each family to reduce abandonment potential.

We dedicated funds to cover the expenses of imaging, eye EUA, focal laser therapy, enucleation, and gene testing. This greatly contributed to improving accessibility to these expensive procedures, as otherwise high levels of abandonment would likely have occurred. Acquiring the RetCam device allowed close monitoring of critical cases, external consultation, collaboration, and objective reporting. Notably, the direct cost of treatment reached over $40 000 per year for some

patients with bilateral retinoblastoma, which is very expensive for families in low- and middle-income countries, and would not be accessible in the absence of national health care coverage plans or other sources of funding.

In our series, 55-65% of patients were males, which is similar to other reports where male:female ratio ranges from 1.1:1.0 to 2.2:1.0.[11,12] However, less than 50% of our patients had unilateral disease, which differs from the literature where unilateral disease accounts for up to 60% of cases.[13] One possible explanation could be that patients with bilateral tumors are more likely to be referred to oncologists, whereas patients with unilateral disease may have been managed by enucleation only by an ophthalmologist. Approximately, 80% of our patients were younger than 2 years, similar to reports from other countries, where most bilateral disease is diagnosed by 15 months and unilateral disease by 24 months of age.[14]

Our program was accessible only for patients with newly diagnosed intraocular disease, and therefore the three patients who presented with extraocular disease were excluded. However, intraocular tumors presented relatively advanced, with the vast majority (66%) of eyes having Groups D and E disease. As for eyes with early disease, two-thirds were discovered in the setting of the second eye having an advanced intraocular tumor. This is similar to reports from other lower income and middle-income countries, where advanced intraocular presentations are much more common than in high-income countries.[3,15]

Our rates of globe salvage were very low for eyes with Groups D and E disease. While Group E eyes are rarely salvageable, up to 25-40% of Group D eyes may be saved as reported elsewhere.[16–19] This difference may be due to several factors, including the higher use of EBRT as a salvage modality.[20] In our setting, EBRT was recommended only for patients who had meaningful residual visual acuity, while all eyes that lacked visual acuity were recommended enucleation, to avoid risks associated with radiation such as second malignancies, or further tumor progression in a nonseeing eye. Recent reports regarding efficacy of intra-arterial chemotherapy in globe preservation suggests that use of this modality may improve salvage rates in carefully selected groups of patients.[21,22]

Importantly, high-risk pathologic features were present in 21% of enucleated eyes in the bilateral group, and 24% in the unilateral group. The numbers are similar to those reported from other studies,[3,23,24] and continue to underline the need for prompt management for patients with extensive intraocular disease, prior to dissemination beyond the eye globe.[25]

Four patients with bilateral disease who were advised enucleation abandoned treatment. While we could not find any documented cases of patients who had refused treatment in the prior era, such information may have been missed due to the retrospective nature of the review for that period. Alternatively, the higher use of radiation therapy in the previous era may have reflected patient refusal of enucleation, although that cannot be ascertained. Thus, as noted in other settings,[26] enucleation recommendation remains a primary reason for treatment refusal in retinoblastoma, especially in patients with bilateral disease.

Gene testing in our program showed that 85% of patients with bilateral disease had identifiable deleterious mutations in RB1, which is similar to numbers reported elsewhere.[27] While financial coverage of gene testing in unilateral tumors was offered only for those younger than 2 years, 30% of those were found to have RB1 gene mutation, underscoring the importance of considering hereditary retinoblastoma in patients with unilateral disease.

In conclusion, in our series of patients, even within a multidisciplinary setting, most patients with retinoblastoma still present with advanced intraocular disease, and eye salvage rates were poor for patients with Group D and E tumors. Future efforts should aim at promoting earlier diagnosis, possibly through enhancing screening in primary health care and possibly caregivers. Newer approaches to treatment of advanced intraocular disease need to be investigated and utilized to improve ocular outcome.

Importantly, our report shows that formalization of a multidisciplinary retinoblastoma program with associated financial support helped facilitate access to treatment for patients beyond the number initially expected. Such a model of establishment of a specialized team for multidisciplinary care of patients with rare tumors that require complex treatment (such as retinoblastoma), for regional collaboration and referral across borders, can be utilized to help maintain expertise to improve outcomes in under-resourced countries.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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