Optical Coherence Tomography (OCT) in Retinoblastoma Management: Experience of the Portuguese National Reference Center

Tomografia de Coerência Óptica (OCT) no Seguimento de Retinoblastoma: Experiência do Centro de Referência Português

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ABSTRACT

INTRODUCTION: Patients under 5 years old with retinoblastoma require close monitoring under anesthesia to ensure early detection of new tumors. They undergo monthly observations after diagnosis and during the first 6 months after treatment, then observations are gradually spaced in time until the age of five. Optical coherence tomography (OCT) is a relatively new exam in monitoring retinoblastoma patients. The advantages include pre-clinical diagnosis of new tumors when located in the posterior pole and evaluation of retinal layers in eyes submitted to intra-arterial chemotherapy. We aimed to review the role of handheld OCT in evaluating eyes affected by retinoblastoma and to report our experience using this device.

METHODS: The observational case series included children with retinoblastoma followed at Centro Hospitalar e Universitário de Coimbra from January 2022 to August 2022 who underwent an OCT session during their routine observations under anesthesia. We collected data regarding patients' age at presentation, family history, RB1 mutation status and International Intraocular Retinoblastoma Classification. The OCT images were analyzed for primary tumor characterization, relapse tumors and associated findings, and correlated to the fundus image on Retcam®.

RESULTS: We included 23 eyes of 19 children that had a total of 44 OCT exams. The median number of OCT scans per eye was 2 (range 1-6). The mean age at presentation of retinoblastoma was 9.37 months old. After reviewing the images, we were able to identify all 4 types of tumor remnants in our series. One patient had a new relapsed tumor that was detected primarily with OCT and treatment was initiated accordingly. In nine eyes, it was impossible to scan the primary tumor due to peripheral localization in the fundus due to advanced stages.

CONCLUSION: Hand-held OCT allows direct visualization of the retina and ensures a closer follow-up of young children with retinoblastoma, leading to the earlier diagnosis of relapses and the ability to treat them with less aggressive options, which may preserve more vision. The use and experience with OCT are increasing in all specialized centers that treat retinoblastoma. Hence, its usefulness will continue to grow and, in the future, there will be more clues to help diagnose retinoblastoma even sooner.

KEYWORDS: Disease Management; Retinoblastoma; Tomography, Optical Coherence.

RESUMO

INTRODUÇÃO: Doentes com retinoblastoma e idade inferior a 5 anos requerem monitorização sob anestesia para garantir a deteção precoce de recidivas. No nosso centro, são observados mensalmente após o diagnóstico e nos seis meses que sucedem o tratamento. Seguidamente, as observações são progressivamente espaçadas no tempo até aos 5 anos de idade.

A tomografia de coerência óptica (OCT) é um exame relativamente novo no seguimento de doentes com retinoblastoma. A versão portátil deste aparelho permite diagnóstico pré-clínico de novos tumores no polo posterior e avaliação das camadas da retina submetidas a quimioterapia supra-seletiva intra-arterial. Neste artigo procuramos descrever a nossa experiência com este aparelho e rever a sua utilidade no seguimento de doentes com retinoblastoma.

MÉTODOS: Estudo observacional que incluiu crianças com retinoblastoma seguidas no Centro Hospitalar e Universitário de Coimbra desde janeiro 2022 até agosto 2022 que realizaram pelo menos uma sessão de OCT durante a observação de rotina sob anestesia. As imagens de OCT foram analisadas para caracterização do tumor primário, recidivas e achatados associados, e foram correlacionadas com a imagem do fundo ocular.

RESULTADOS: Incluímos 23 olhos de 19 crianças que realizaram um total de 44 sessões com OCT. A mediana de *scans* de OCT realizados por olho foi de 2 (intervalo de 1 - 6). A média de idade ao diagnóstico foi de 9,37 meses. Um doente apresentou uma recidiva tumoral que foi confirmada com OCT e o tratamento foi iniciado em seguida. Em 9 olhos não foi possível analisar a massa primária pela localização periférica ou devido a estadios tumorais mais avançados.

CONCLUSÃO: O aparelho de OCT portátil permite a visualização direta da retina e assegura uma monitorização mais precisa das crianças com retinoblastoma. Este instrumento tem a capacidade de antecipar o diagnóstico de recaídas, permitindo o tratamento local precoce e menos agressivo, que potencialmente preservará mais visão. O OCT está a ser usado de uma forma crescente por todos os centros que tratam retinoblastoma, pelo que a sua utilidade vai aumentar e serão encontradas mais alterações típicas que nos poderão auxiliar nunca diagnóstico cada vez mais precoce.

PALAVRAS-CHAVE: Gestão da Doença; Retinoblastoma; Tomografia de Coerência Óptica.

INTRODUCTION

Retinoblastoma is the most common intraocular tumor in children.[1] Currently, the survival rate of this malignancy can range between 90% and 99% with the current standard of care.[2]

Patients under 5 years old with retinoblastoma require close monitoring under anesthesia and a complete fundoscopy to ensure early detection of new or relapsed tumors and to detect and manage side effects from treatments.[3] At our center, they have monthly observations after diagnosis and during the first 6 months after treatment. Subsequently, observations are slowly spaced in time according to disease progression, maintaining a follow-up of every 6 months under anesthesia until the age of five. At this time, when collaboration of the children is considered enough to perform a complete evaluation, visits are scheduled in regular appointments.

Optical coherence tomography (OCT) is a well-known instrument that improved the diagnosis and management of many retinal conditions in the last 3 decades.[4-7] However, its use in young children was precluded due to insufficient collaboration to perform the exam.

Hand-held OCT is a new device that allows for scanning patients who are unable to cooperate, specifically children, under anesthesia.[8] In the specific case of retinoblastoma patients, it has permitted a greater comprehension of this malignancy. In fact, it has increased our ability to assess precise tumor growth,[9] relationship to the fovea,10 and optic nerve infiltration,[11] detect subclinical relapsed tumors,[9,12] and evaluate therapy response and scarring.[13] Soliman *et al*[14] previously determined that OCT improved the accuracy of clinical evaluation in retinoblastomas, guiding decisions and disease management. This relatively new tool has also rendered possible *in vivo* analysis of retinoblastomas, granting precise localization of this tumor to a specific anatomic layer of the neurosensory retina, namely, the inner nuclear layer (INL).[15]

However, this device is only available at highly specialized ocular oncology centers. Here, we sought to review the role of handheld optical coherence tomography in evaluating eyes affected by retinoblastoma and to report our single-center experience using this device.

METHODS

This study is a retrospective observational case series that included children with retinoblastoma followed at Centro Hospitalar e Universitário de Coimbra from January 2022 to August 2022. This study followed the Declaration of Helsinki and was approved by the institutional research ethics board.

We reviewed the records of all children that had an OCT session during their routine observations under anesthesia and all were included in the present study. We excluded eyes of children bilateral retinoblastomas that were enucleated without an OCT scan. We collected data regarding patient's age at presentation (months), laterality (unilateral, bilateral or trilateral), family history, *RB1* mutation status, International Intraocular Retinoblastoma Classification (IIRC),[16] tumor location (anteroposterior location) and associated findings (subretinal seeds, vitreous seeding, cystoid macular edema, subretinal fluid and retinal detachment), active treatment duration (in months) and primary modality (intravenous chemotherapy [IVC] or selective intra-arterial chemotherapy [IAC]) and number of relapses. The OCT images were reviewed and analyzed for primary tumor characterization, associated findings, new relapsed tumors, scarring type, and were correlated to the fundus image.

Scarring type in the OCT scans was defined based on the Wills Eye Institute classification: type 0 - no tumor or retinal scar visible; type I – tumor remnant completely calcified (cottage cheese scar); type II – tumor remnant without calcification (fish flesh scar) – type III – combination of type I and II; type IV – chorioretinal scar.[17]

We also analyzed the OCT scans for signs related to neurosensorial retina origin, according to previous reports, and identified the shark fin sign and the fish tail sign.[15] Shark fin sign corresponds to folding of external nuclear layer in the lateral tumor margins, whereas fish tail sign appears as splaying of the inner nuclear layer by tumor margins.

Throughout the study, we used the system Bioptgen Envisu C2300 (Bioptigen, Inc./Leica Microsystems, Morrisville, NC). The scans were obtained using standardized methodology to ensure good reproducibility.

Scanning protocol included acquisition of volumetric scans built with non-averaged OCT scans (1000 A-scans x 100 B-scans per volume), and the accumulation of 100 individual B-scans produced a C-scan fundus image.

In each session, the child under anesthesia would be evaluated first by indirect ophthalmoscopy, then the OCT scan was performed and lastly the fundus image was recorded using Clarity Retcam 3. The OCT scan must be performed prior to the recording of the fundus image, because the gel used during this procedure diminishes the quality of the scan. We followed the technique previously described in another study.[14] Scans were obtained with the child in supine position at 12 o'clock, and the scanner was aimed through the pupil, pivoting it above the cornea. To achieve better image quality, we manually adjusted the reference arm setting according to the patients age and eye's axial length, optimized the focus according to the child's refraction and frequently hydrated the cornea with balanced salt solution.

Data was tabulated using Microsoft Excel 2016. Measures of central tendency were calculated using its built-in functions. Given the small sample size, we were not able to perform other statistical analysis.

RESULTS

We included 23 eyes of 19 children that had a total of 44 OCT sessions. In this sample, the mean age at presentation of retinoblastoma was 9.37 months old (median 6 months, range 2 – 34). Most were male (14/19, 74%) with bilateral tumor involvement (13/19, 68%). In 14 cases, *RB1* mutation was present (one unilateral case presented a *RB1* mutation with 11% mosaicism). No patient died or was lost to follow-up during this study. The described demographics are in line with what was described in our center between 2015 and 2020.[18]

Table 1 describes each patient, numbered from 1 to 19 and details treatment modality, duration of treatment and phase of treatment when the eye was scanned with OCT.

In the eyes included in this report, 6 were classified as group A, 1 as group B, 5 as group C and the other 12 eyes were classified as group D. No eyes classified as group E were included. The primary treatment modality was intravenous chemotherapy (IVC) in 10 eyes and selective intra-arterial chemotherapy (IAC) in 7 eyes. Of the 10 eyes primarily submitted to 10 IVC, 7 belonged to patients younger than 6 months, which require bridging therapy; the other 3 eyes had advanced disease at diagnosis, which demands primary IVC treatment. Focal treatment with laser was the primary option in 5 eyes, all classified as stage A. Importantly, 3 of the patients that had an eye classified as group A, were submitted to IVC prior to focal laser therapy because the other eye had an advanced tumor. The other 2 eyes belong to patient 17, that had a positive family history and was followed since birth, which allowed early detection and treatment. The left eye of patient 6 was later enucleated due to relapsed tumor and suspicion of invasion of the optic nerve. The median treatment duration was 19 months (range 1 – 39). The median number of OCT scans per eye was 2 (range 1-6). Only 7 eyes were in active phase of treatment during the OCT sessions.

During this follow-up period, 12 eyes experienced at least one relapse.

While analyzing the OCT image scans, we were able to identify all 4 types of tumor scarring defined by the Wills Eye Institute classification.

In Fig. 1A, we can see on example of type I, which corresponds to calcification of tumor. This pattern, also known as cottage cheese scar, was identified in 6 patients.

In Fig. 1B, we present the only case presenting type II tumor remnant, which is non-calcified.

Type III scar, which corresponds to a mixed pattern between the previous 2 types, was identified in 3 patients. We present in Fig. 1C a case illustrating this.

Table 1. Characterization of each patient that had an OCT scan session during their follow-up.

Name	Sex	Laterality	RB1 mutation status	Eye	Age (mo)	Nº scans	Scar Classification	Treatment status during OCT	IIRC	Primary treatment modality	Treatment duration (mo)	Nº of relapses
Patient 1	M	Bilateral	Present	OD	6	2	-	Out	B	IVC	39	1
Patient 2	M	Unilateral	Mosaicism	OS	12	1	-	Out	D	IAC	21	1
Patient 3	F	Bilateral	Present	OS	7	1	-	Out	C	IVC	4	1
Patient 4	F	Unilateral	Absent	OS	34	2	I	Out	D	IAC	4	0
Patient 5	M	Bilateral	Present	OD	2	4	II	Out	C	IVC	35	4
Patient 6	M	Bilateral	Present	OD	13	2	III	Active	D	IAC	17	1
				OS	13	2	I	Active	D	IACa	15	1
Patient 7	M	Bilateral	Present	OD	4	2	I	Out	D	IVC	4	0
				OS	4	2	-	Out	A	IAC	10	1
Patient 8	M	Bilateral	Present	OS	0	6	IV	Active	C	IVC	15	2
Patient 9	M	Bilateral	Present	OS	3	2	I	Active	D	IVC	13	2
Patient 10	M	Bilateral	Present	OD	10	2	III	Out	D	IAC	5	0
Patient 11	M	Unilateral	Present	OS	4	2	III	Out	D	IVC	14	1
Patient 12	M	Bilateral	Present	OD	18	1	-	Active	D	IVC	28	1
				OS	18	1	-	Out	D	IVC	7	0
Patient 13	F	Unilateral	Absent	OD	4	1	-	Out	C	IVC	21	2
Patient 14	F	Unilateral	Absent	OS	7	1	-	Out	D	IAC	5	0
Patient 15	M	Bilateral	Present	OD	3	2	I	Active	A	FT	3	0
Patient 16	M	Bilateral	Absent	OD	4	1	-	Out	A	FT	3	0
Patient 17	M	Bilateral	Present	OD	4	2	-	Out	A	FT	4	0
				OS	5	2	-	Out	A	FT	1	0
Patient 18	M	Bilateral	Present	OS	26	2	I	Active	A	FT	4	0
Patient 19	F	Unilateral	Absent	OS	11	1	-	Out	C	IAC	4	0

OCT – optical coherence tomography; IIRC –vInternational Intraocular Retinoblastoma Classification; OD – right eye; OS – left eye; IVC – intravenous chemotherapy; IAC – intra-arterial chemotherapy.; mo – months

[a] The left eye of patient 6 was later enucleated due to relapsed tumor and suspicion of invasion of the optic nerve.

Finally, type IV tumor remnant, the chorioretinal flat scar, was identified in only one patient, presented in Fig. 1D.

We were able to identify the shark fin sign in 2 patients and the fish tail sign in one patient. Fig. 2A and 2B demonstrate these findings.

During one of the visits of patient 8, we noticed an alteration on fundoscopy of the known macular lesion. The OCT scan revealed a new thickening of the macular layers, which confirmed a relapsed tumor. The patient restarted IAC and the tumor was reassessed. In the following OCT scans, we were able to see a regression of the previous thickened pattern – Figs. 3A, 3B and 3C.

In three patients, we noticed a thickening near the optic nerve, which we assumed to be a retinoblastoma in correlation to fundus image – Fig. 4.

In patients 1, 16 and 17, we were not able to acquire a direct OCT scan from the primary lesion, considering its peripheral position.

In patient 2 OCT scan quality due to bad image capture, along with the peripheral location of the lesion also deterred from analysis of the primary tumor.

In 6 patients, the quality of the image was not sufficient to analyze the retinal layers due to advanced tumors. In one of these cases, namely patient 16, the lesion was accompanied with exudation in the posterior pole. In all but these 6 cases, we were able to assess the integrity of the retinal structures, such as the fovea appearance, on the OCT scan. We also verified that none of the patients submitted to IAC had negative effects on the integrity of these structures.

DISCUSSION

A number of reports regarding use of hand-held OCT in retinoblastoma follow-up have been published after the introduction of this technique by Scott *et al* in 2009.[8]

Although conventional OCT is a widely used exam in ophthalmology, previously to this hand-held technology, it was a difficult image modality to implement in small children.

Formerly, the distinction between suspect lesions and Retinoblastoma was only based on clinical opinion and B-ultrasound image. With OCT, we can achieve the visualization of the internal retinal and lesion architecture,

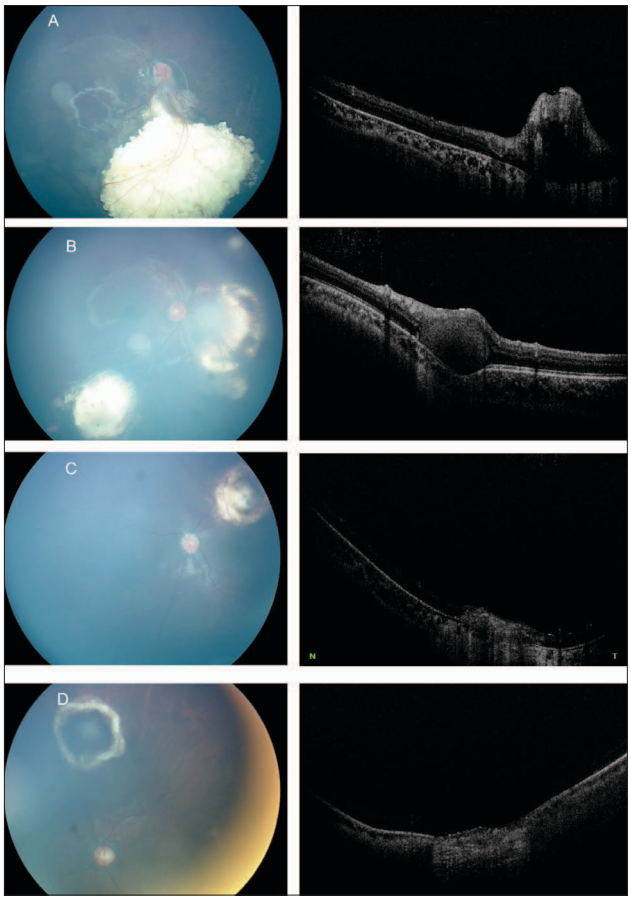

Figure 1. Different types of tumor remnants. 1A – Patient 7 OS: type I calcified tumor remnant, also known as cottage cheese scar; 1B – Patient 5 OD: type II non-calcified tumor remnant, also called fish flesh scar; 1C – Patient 7 OD: type III mixed tumor remnant; 1D – Patient 18: type IV chorioretinal scar. OS – left eye. OD – right eye.

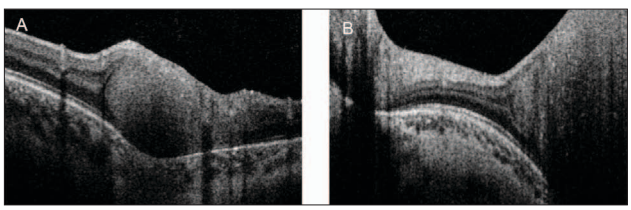

Figure 2. Neurosensorial retinal layers and relationship to tumor. 2A – Fish-tail sign (white arrow) and shark fin sign (yellow arrow); 2B – Fish-tail sign (white arrow).

which allows better decision-making regarding treatment and follow-up. In fact, Soliman *et al*[14] found that the use of hand-held OCT was confirmatory of diagnosis in 83% of cases and altered the previous clinical decision in 17% of cases, improving diagnosis acuity and retinoblastoma staging. In our series, we also changed the pre-OCT clinical decision in patient 8 and started treatment, after finding a relapsed tumor. Traditionally, a suspect area on the fundus image would be closely monitored every 2-3 weeks and designated as new tumor if growth was confirmed.[19] The OCT allows, in selected cases, to begin a less aggressive

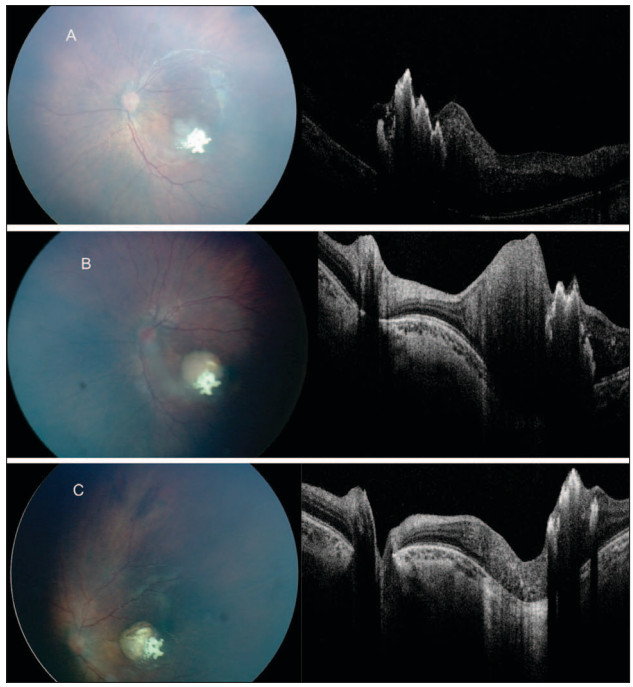

Figure 3. Patient 8 relapse timeline. 3A – Fundoscopy image reveals calcified macular lesion, also present on the OCT scan (white arrow), that had remained stable during follow-up; 3B – We noticed a slight alteration of the lesion on fundoscopy, and the OCT scan revealed a thickening of the neurosensorial retinal layers close to the macular lesion and the optic disk (white arrow); 3C – After IAC, the tumor appearance on fundoscopy remained similar, but the lesion flattened and gained some calcification on the OCT scan (white arrow).

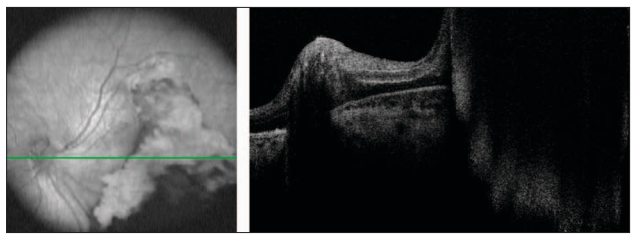

Figure 4. Patient 9 OCT revealed thickening of the peripapillary area (white arrow).

treatment earlier, possibly improving the survival rate and visual function preservation.[12]

Importantly, OCT of small retinoblastomas permitted a better understanding of the tumor origin. In fact, we were able to identify in smaller tumors the shark fin and the fish tail signs, which correspond to the folding of the ONL and OPL in the lateral tumor margins and to splaying of the INL on the tumor margin, respectively. These findings corroborate the postulated theory that the INL was, in most cases, the tumor origin.[4,15]

We were also able to evaluate important anatomic marks in most patients, such as the fovea and the optic disk. When considering peripapillary tumor, it can be difficult to distinguish between tumor and papilledema.[11] Additionally, we can closely monitor the integrity of the retinal structures submitted to IAC. Hence, OCT improves the safety of this therapy.

Furthermore, we consider this report to be an innovative study, as it characterizes this technique in our population, which has never been done before. In addition, up to date, there have been few published reports regarding single reference center experience.

Yet, it is essential to note that hand-held OCT has important limitations. Firstly, it is difficult to correlate lesion activity with the tumor appearance on the scan, especially when the scar is classified as type II or III, unless by OCT scan stability.[13]

Other limitations, also present in this series, were the scanning of peripheral lesions, and the evaluation of advanced lesions, that can absorb the optical signal and with elevations that exceed the scan capacity.[20]

Further, it is a time-consuming exam, with frequent need to repeat imaging, which increases time under anesthesia. The OCT scanner dimensions can also interfere with acquiring the scans, as it frequently can conflict in space with the facial mask.

The hand-held OCT requires a skilled medical image specialist, and has an important learning curve. Our experience with this instrument has been increasing, and it has permitted improvement in the follow-up of retinoblastoma patients. Considering the small sample of patients included in the study, we were not able to draw conclusions supported by statistical analysis. Nonetheless, we believe reporting our experience is valuable and we were able to demonstrate several cases where OCT added new information about tumor status.

CONCLUSION

Hand-held OCT allows for direct visualization of the retina and assures a closer follow-up of young children with retinoblastoma. It has the capacity to anticipate the diagnosis of relapses, allowing the initiation of precocious local and less aggressive treatment, which might preserve more vision. Our experience with OCT is improving and it constitutes a valuable tool to improve the follow up of retinoblastoma patients. The use of hand-held OCT is increasing in all specialized centers that treat retinoblastoma. Hence, its usefulness will continue to grow and, in the future, there will be more clues to help diagnose retinoblastoma even sooner.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

MQD: Conception, design, analysis and interpretation of data, drafting the article.

JP, MM and GC: Design, analysis interpretation of data and revising the article.

All authors approved the version to be published.

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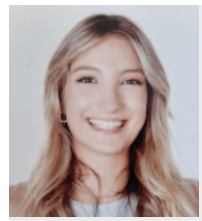

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