Enhanced Depth Imaging Optical Coherence Tomography: A Primary Modality for Evaluating Nevi Changes

O Papel Essencial da Tomografia de Coerência Ótica-*Enhanced Depth* Imaging na Avaliação de Alterações de *Nevus Coroideus*

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ABSTRACT

INTRODUCTION: Our purpose was to analyse the enhanced depth imaging (EDI) - optical coherence tomography (OCT) ability to measure change in thickness and identify high-risk features in choroidal nevi over time.

METHODS: Prospective observational study of patients with choroidal nevi in a tertiary hospital. Comprehensive eye examination and multimodal imaging were performed for each nevus, including spectral domain EDI-OCT and B-scan ultrasonography (US) at baseline (0) and one year after (1). Main outcome measures were US and EDI-OCT lesion thickness and change in thickness in micrometre, and nevi features (pigmentation, location of the epicentre, distance to the optic disc margin, shape, largest basal diameter, presence of drusen and orange pigment).

RESULTS: Ninety nevi (86 patients) were included. Three were considered suspicious lesions, one with transformation into melanoma. The median maximum thickness on EDI-OCT at baseline was 581.50 ± 411.75 µm, one year later was 619.50 ± 457.25 µm (p<0.001). The median absolute change in thickness was 28.50 ± 106.50 µm. Sixty-six nevi (73.3%) were never identified on US, behaving as flat. The median maximum thickness on US was 1180.00 ± 660.00 µm at baseline; 1160.00 ± 790.00 µm one year later (p=0.658). The median absolute change in thickness was 195.00 ± 320.00 µm. The US nevi maximum thickness was significantly different from the EDI-OCT in each timing (US-0 1180.00 ± 660.00 µm *vs* EDI-OCT-0 581.50 ± 411.75 µm, p<0.001; US-1 1160.00 ± 790.00 µm *versus* EDI-OCT-1 619.50 ± 457.25 µm, p<0.001). The absolute and arithmetic change in thickness significantly differed between US and EDI-OCT (p<0.001 for both). All the 66 consistently flat nevi in US were identified and measured in EDI-OCT (mean thickness 262.58 ± 116.17 µm baseline, 272.29 ± 127.48 µm at one year). Of the 14 lesions with a thickness increase in EDI-OCT of more than 10%, nine (64.2%) were not identified in US.

CONCLUSION: EDI-OCT can consistently measure nevi thickness and its change over time, and identify high-risk features. US failed to identify and measure most nevi, including the ones with significant thickness increase in EDI-OCT. EDI-OCT should replace US in evaluating flat nevi, and might become the primary modality to comprehensively analyse high-risk nevi.

KEYWORDS: Choroid Neoplasms/diagnostic imaging; Nevus, Pigmented / diagnostic imaging; Tomography, Optical Coherence; Ultrasonography.

RESUMO

INTRODUÇÃO: Analisar a capacidade da tomografia de coerência ótica (OCT) – *enhanced depth imaging* (EDI) de medir alterações na espessura e identificar características de alto-risco em nevus coroideus ao longo do tempo.

MÉTODOS: Estudo observacional prospetivo de nevus da coróide num hospital terciário. Avaliação oftalmológica completa e metodologia de imagem multimodal incluindo *spectral domain*-EDI-OCT e ecografia modo-B (US) foram realizados no momento de inclusão (0) e um ano depois (1). Os indicadores primários foram espessura e sua alteração em micrómetros na US e EDI-OCT, e suas características (pigmentação, localização do epicentro, distância à margem do disco ótico, forma, maior diâmetro basal, presença de drusen e pigmento laranja).

RESULTADOS: Foram incluídos 90 nevus de 86 doentes. Três foram considerados lesões suspeitas, um com transformação para melanoma. A mediana da espessura máxima no EDI-OCT de base foi 581,50 ± 411,75 μm, a um ano 619,50 ± 457,25 μm (p<0,001), e a mediana de alteração absoluta de espessura 28,50 ± 106,50 μm. Sessenta e seis nevus (73,3%) nunca foram identificados na US. A mediana da espessura máxima no US de base foi 1180,00 ± 660,00 μm, a um ano 1160,00 ± 790,00 μm (p=0,658), e a mediana de alteração absoluta 195,00 ± 320,00 μm. A espessura máxima medida na US foi significativamente diferente da do EDI-OCT, em cada avaliação (US-0 1180,00 ± 660,00 μm *versus* EDI-OCT-0 581,50 ± 411,75 μm, p<0,001; US-1 1160,00 ± 790,00 μm *versus* EDI-OCT-1 619,50 ± 457,25 μm, p<0,001). A alteração absoluta e aritmética de espessura foi significativamente diferente entre aparelhos (p<0,001 para ambos). Os 66 nevus nunca identificados na US foram identificados e medidos com EDI-OCT. Dos 14 nevus com um aumento de espessura no EDI-OCT superior a 10%, 9 (64,2%) não foram identificados na US.

CONCLUSÃO: O EDI-OCT mede de formar consistente a espessura dos nevus e a sua alteração com o tempo, e identifica características de alto-risco. A US não conseguiu identificar e consequentemente medir a maior parte dos nevus, mesmo perante aumentos significativos na espessura no EDI-OCT. Recomendamos a substituição da US pelo EDI-OCT na avaliação de nevus ecograficamente planos, e a adoção do EDI-OCT como modalidade primordial na avaliação de nevus de alto risco.

PALAVRAS-CHAVE: Neoplasias da coroide/diagnóstico por imagem; Nevo Pigmentado/diagnóstico por imagem; Tomografia de Coerência Ótica; Ultrassonografia.

INTRODUCTION

Choroidal nevi are the most common benign tumor of the ocular fundus, with a prevalence of 6.5% in the adult white population.[1] Given the concern of nevus malignant transformation into uveal melanoma, with its morbidity and mortality, a strong development has been made to establish objective criteria predictive of transformation.

The features classified as risk factors have been updated with the advance of multimodal imaging. Initially, Shields *et al* identified mainly clinical features: symptoms of vision loss, floaters and photopsia, presence of subretinal (SRF) and orange pigment in fundus examination, lesion margin smaller than 3 mm of the optic disc in fundus photography, and tumor thickness greater than 2 mm in B-scan ultrasonography (US).[2] Later, ultrasonographic hollowness was added,[3] highlighting the value of US. As more advanced imaging emerged, optic coherence tomography (OCT) allowed subclinical detection of subtle features in choroidal lesions, such as change in thickness, presence of SRF, and pigment epithelial detachment, which may not be visible with fundus examination and US alone.

The last update made by Shields *et al* of the six features that may signify nevi at risk of malignant transformation comprises thickness greater than 2 mm on US, SRF over nevus or up to 3 mm from the nevus margin on OCT, symptoms of visual acuity loss of 20/50 or worse by Snellen visual acuity, orange pigment on fundus auto-fluorescence (AF), melanoma acoustic hollowness on US, and tumor diameter greater than 5 mm on fundus photography.[4]

Spectral-domain OCT (SD-OCT) detects retinal and retinal pigment epithelial (RPE) changes secondary to choroidal tumors, however, the findings are limited to the anterior side of the nevus.[5] The enhanced depth imaging (EDI) adjustment of SD-OCT brought high-resolution cross-sectional imaging of choroidal lesions, with proper visualization of structures deep into the RPE, allowing a complete characterization of intrinsic features.[6,7]

According to Shields *et al*, thickness greater than 2 mm accounted for the highest hazard ratio in terms of growth

and tumor transformation.[4] In the MOLES score system, which estimates malignancy in choroidal lesions, thickness greater than 2 mm is considered as significant and accounts for two points, and enlargement is considered definite when confirmed by sequential imaging, accounting for two points in the severity score.[8] Hence, thickness is established as one of the most important features to assess, which leads to the question of how to accurately measure nevi thickness. US repeatedly failed to identify a significant percentage of choroidal nevi,[9] lacks consistency and tens to overestimate nevi thickness.[7,9,10] On the other hand, EDI-OCT has been proven to objectively measure small choroidal nevi undetectable on US.[7,9,10] Jonna *et al* EDI-OCT classification of ultrasonographically flat lesions demonstrated that type 4 nevi - the elevated ones - were at higher risk of growth.[11] Around 28% of type 4 nevi were never identified on US in our previous study[9] confirming that these lesions are more precisely measured with EDI-OCT as the posterior border is better delimited.[9,11,12]

Bearing in mind the above-mentioned significant US inability to identify a considerable percentage of nevi, including nevi at higher risk of growth, a reliable methodology to evaluate nevi is needed. After proving that EDI-OCT measures and characterizes with more precision both flat and non-flat nevi thickness,[9] the next required step is to analyse its ability to assess change in thickness over time, compared to US, along with other high-risk morphological changes.

METHODS

A prospective observational study was performed, involving patients with choroidal nevi followed at the Ophthalmology Department of Central Lisbon Hospital and Universitary Centre, Lisbon, Portugal, between January 2022 and September 2023, with a minimum of one year of follow-up. Because the study involved the collection of anonymised data and had no impact on the protocol of clinical follow-up of these patients, ethics approval was waived.

The patients were evaluated at two different timings, the first considered as baseline (0), and a second time point one year later (1). At each time, a comprehensive eye exam with dilated fundus examination, fundus photography, 10MHZ probe B-US (Aviso S, Quantel Medical™, Paris, France; axial resolution 150 µm, lateral resolution 300 µm), SD-OCT, EDI SD-OCT and AF using the Heidelberg Spectralis system (Heidelberg Engineering, Heidelberg, Germany) were performed. EDI was performed using a technique similar to the one described by Spaide *et al*.[6] B-US was performed by one experienced operator, and representative images were archived. Exclusion criteria included: patients who did not complete the one-year follow-up period, patients who did not undergo complete multimodal imaging and chorio-retinal lesions not suggestive of choroidal nevi.

Demographic characteristics recorded included age, sex, skin color, age at diagnosis, and the presence of a significant decrease in visual acuity (loss of 20/50 in Snellen or half of the baseline visual acuity). The number of choroidal nevi and laterality were documented. Clinical and multimodal imaging findings were recorded at baseline and one year later. Explicitly, the clinical features included degree of pigmentation (pigmented, non-pigmented), location of the epicentre of the nevus (superotemporal, inferotemporal, superonasal, inferonasal, macular), distance to the optic disc margin (in disc-diameters), shape (round, oval, irregular), largest basal diameter (in disc-diameters), presence of drusen and presence of orange pigment (lipofuscin). AF analysis included whether pigment was visible or not.

At each timing, B-scan ultrasonography performed for each nevus divided the nevi into two groups whether the nevus was identified on B-scan or not (behaving as flat nevi). The largest basal dimension and its perpendicular basal dimension, nevi maximal thickness and hollow echogenicity were recorded.

EDI SD-OCT lesion thickness, the presence of drusen, the presence of SRF or intra-retinal fluid and posterior shadowing were recorded at each time. Lesion thickness was measured with calipers, with a method equivalent to the one described by Shah *et al*.[7] Lesion thickness including choroid was measured in micrometre from the sclerochoroidal junction to the outermost boundary or base of the RPE. Lesions were classified into 5 groups (invisible lesion, hyperreflective lesion, discrete lesion, posteriorly bowed lesion or elevated lesion) based on EDI-OCT appearance, as described by Jonna *et al*.[11] All EDI-OCT imaging was interpreted, graded and confirmed by two independent reviewers with ocular oncology experience, and in cases of disagreement, a third independent senior doctor intervened.

Absolute and arithmetic change in nevi maximal thickness on US and on EDI-OCT were calculated. Change in clinical aspects (degree of pigmentation, shape, presence of drusen and presence of orange pigment) and any change in US and EDI-OCT features (such as presence of sub/intra-retinal fluid, drusen and posterior shadowing) were analysed.

For each nevus, baseline and one-year US and EDI-OCT nevi thickness were compared; as well as absolute and arithmetic change in nevi thickness between US and EDI-OCT.

Demographics and clinical characteristics were described by frequencies (percentages) for categorical variables, and means (standard deviation) or medians (interquartile range) for continuous variables, according to normality. Wilcoxon matched-pairs signed-rank test was used for comparisons. A p value <0.05 was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 16.0 (SPSS, Inc., Chicago, USA).

RESULTS

From 105 identified nevi, a total of 90 nevi in 86 patients were included, representing the study sample. Fourteen nevi were excluded for not having an EDI-OCT scan over the nevus, and one for being thicker than the EDI-OCT scan capacity.

The mean patient age at nevus diagnosis was 70.56 ± 10.76 years (range 36-93 years), with 97.8% being Caucasian. Demographic data are detailed in Table 1.

Table 1. Demographic characteristics of patients.	
Age at diagnosis, years [mean ± SD (range)]	70,50 ± 10,81 (36-93)
Gender, n(%)	
Male	33 (36.7)
Female	57 (63.3)
Race, n(%)	
Caucasian	88 (97.8)
Non-Caucasian	2 (2.2)
Eye, n(%)	
Right	43 (47.8)
Left	47 (52.2)
Nevus number/patient, n(%)	
One	86 (95.6)
Two	4 (4.4)

All the 90 nevi were pigmented nevi. Three (3.3%) were considered suspicious lesions by the presence of more than one high-risk feature at baseline assessment. One of the suspicious lesions was classified as melanoma during the study period. The follow-up interval ranged from 1 to 3 months for suspicious lesions, to annually for others. Clinical features are detailed in Table 2.

Sixty-six of all nevi (73.3%) were never identified on US, behaving as flat nevi, 3 were identified only at baseline, and 1 only on the one-year US. For the identified nevi, the median largest basal dimension in US was 4880.00 ± 2890.00 µm at baseline and 4680.00 ± 2900.00 µm, one year later (p=0.554). The median maximum thickness on US was 1180.00 ± 660.00 µm at baseline, and 1160.00 ± 790.00 µm one year later (p=0.658), the median absolute change in thickness was 195.00 ± 320.00 µm, and the median arithmetic change in thickness was -45.00 ± 39.00 µm. Five nevi (5,6%) had hollow echogenicity.

The maximum thickness on EDI-OCT at baseline was 581.50 ± 411.75 µm, one year later was 619.50 ± 457.25 µm (p<0.001). The absolute change in thickness was 28.50 ± 106.50 µm, and the arithmetic change in thickness was 25.00 ± 84.75 µm (minus146 – 592 µm).

The nevi maximum thickness measured in US was significantly different from the one measured by EDI-OCT in each timing (US-0 1180.00 ± 660.00 µm versus EDI-OCT-0 581.50 ± 411.75 µm, p<0.001; US-1 1160.00 ± 790.00 µm versus EDI-OCT-1 619.50 ± 457.25 µm, p<0.001). The absolute and arithmetic change in thickness significantly differed between US and EDI-OCT (p<0.001 for both). EDI-OCT and US thickness analysis are resumed in Table 3.

Table 2. Clinical features of choroidal nevi at baseline and 1 year later.	
Visual acuity decrease, n (%)	
Yes	6 (6.7)
No	84 (93.3)
Location, n (%)	
Macular	2 (2.2)
Infero-nasal	13 (14.4)
Supero-nasal	11 (12.2)
Infero-temporal	37 (41.1)
Temporal	2 (2.2)
Supero-temporal	25 (27.8)
Shape, n (%)	
Irregular	33 (36.7)
Oval	23 (25.6)
Round	34 (37.8)
Drusen, n (%)	
Present	43 (47.8)
Absent	47 (52.2)
Orange pigment, n (%)	
Present	15 (16,7)
Absent	75 (83.3)
Subretinal fluid, n (%)	
Present	11 (12.2)
Absent	79 (87.8)
Papillary margin distance (DD), n (%)	
0	5 (5.6)
> 0 and ≤ 1	16 (17.8)
> 1 and ≤ 2	32 (35.6)
> 2 and ≤ 3	22 (24.4)
> 3 and ≤ 4	13 (14.4)
> 4	2 (2.2)
Mean largest dimension, DD [mean ± SD (range)]	2.06 ± 1.49 (0.50 – 10.00)

Table 3. Nevus thickness comparison between ultrasonography and EDI-OCT.			
Features	**US**	**EDI-OCT**	***p* value**
Median baseline thickness µm ± IQR	1180.00 ± 660.00 (450-2400)	581.50 ± 411.75 (207-1548)	**<0.001**
Median lesion thickness at 1 year µm ± IQR	1160.00 ± 790.00 (400-3400)	619.50 ± 457.25 (199-1938)	**<0.001**
Median absolute change of thickness µm ± IQR	195.00 ± 320.00 (0-1040)	28.50 ± 106.50 (1-592)	**<0.001**
Median arithmetic change of thickness µm ± IQR	-45.00 ± 39.,00 (-840-1040)	25.00 ± 84.75 (-146-592)	**<0.001**

Based on EDI-OCT findings, each choroidal lesion was classified into one of the distinct EDI-OCT patterns, that remained stable in all cases: no nevi was not visible on EDI-OCT imaging (classified as type 0); 53 of 90 nevi (58.9%) demonstrated hyperreflectivity confined within normal choroidal thickness (type 1); 11 of 90 nevi (12.2%) had anteriorly bowed hyperreflectivity cascading at discrete lesion edges with dark posterior shadowing (classified as "discrete", type 2); 3 of 90 nevi (3.3%) had a flat surface but with a "posterior bowing" with scleral excavation (classified as type 3); and 23 of 90 nevi (26.4%) had an elevation of the surface of the nevus (classified as "elevated", type 4). OCT features and patterns are detailed in Table 4. Fig. 1 shows representative fundus photos and EDI-OCTs of the 4 different subtypes identified.

Table 4. Enhanced Depth Imaging OCT features of choroidal nevi at baseline and one-year later.

Features	
EDI SD-OCT Pattern n (%)	
Type 0 = Not visible	0 (0.0)
Type 1 = Hyperreflective but confined within normal choroidal thickness	53 (58.9)
Type 2 = Discrete (waterfall appearance at lesion edges)	11 (12.2)
Type 3 = Posteriorly bowed	3 (3.3)
Type 4 = Elevated	23 (25.6)
Posterior shadowing n (%)	
Present	65 (72.2)
Absent	25 (27.8)
Drusen n (%)	
Present	41 (45.6)
Absent	49 (54.4)
Sub/intraretinal fluid n (%)	
Present	9 (10.0)
Absent	81 (90.0)

All the 66 consistently flat nevi on US were identified and measured in EDI-OCT, with a mean thickness of 262.58 ± 116.17 µm (99.00-696.00 µm) at baseline and 272.29 ± 127.48 µm (106.00-790.00 µm) one year later (p<0.001). The two nevi identified only at baseline US (with thickness of 500 and 770 µm), had a baseline EDI-OCT thickness of 364 and 988 µm and thickness increase of 3 and 17 µm, respectively. The nevus only identified at the 1-year US (thickness of 870 µm),

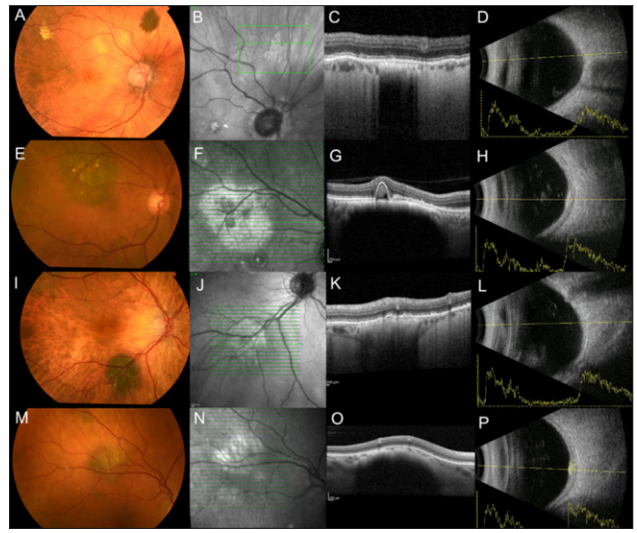

Figure 1. Enhanced depth imaging (EDI) – OCT Type 1-4 and multimodal imaging of choroidal nevi.

A-D, Type 1 "hyperreflective" lesion. A – pigmented lesion without drusen or orange pigment; B – the lesion seems pale on infrared (IR); C – the lesion is hyperreflective but confined within normal choroidal thickness on EDI-OCT; D – flat appearance on US;
E-H, Type 2 "discrete" lesion. E – pigmented nevus with drusen; F – the lesion seems white on IR, with drusen and darker focal areas; G – the lesion seems discrete (anteriorly bowed hyperreflectivity cascading at lesion edges) on EDI-OCT, with one pigmented epithelium detachment; H – hyperechogenic appearance on US;
I-L, Type 3 "posteriorly bowed" lesion. I – pigmented nevus with drusen; J – the lesion seems pale on IR; K – the lesion looks posteriorly bowed on EDI-OCT; L – flat appearance on US;
M-P, Type 4 "elevated" lesion. M – mildly pigmented lesion with drusen; N – the lesion is pale on IR; O – elevated lesion on EDI-OCT; P –hyperechogenic lesion with high anterior reflectivity on US.

had an insignificant EDI-OCT increase of 2.82% (from 350 to 362 µm). Of the 23 EDI-OCT type 4 lesions, 7 (29.2%) were not identified on the US, with a mean baseline EDI-OCT thickness of 655.65 ± 358.06 µm (312.00-1548.00 µm) and 718.74 ± 433.55 µm (315.00-1938.00 µm) one year later (p<0.001).

EDI-OCT nevus classification was associated with a decrease in visual acuity (p=0.003) and the presence of intraretinal fluid or SRF on OCT (p=0.001). Six of the seven nevi (85.7%) with a decrease in visual acuity were classified as EDI-OCT type 4, and their characteristics were: two macular, one nasal-superior and four temporal-inferior; two with a choroidal neovascular membrane; one with hard exudates; and one with an RPE detachment. Seven of the 10 nevi (70%) with intra or SRF were classified as EDI-OCT type 4. The relationship between EDI-OCT nevus classification and clinical characteristics of the choroidal lesions is detailed in Table 5.

Table 5. EDI-OCT findings correlated with known high-risk features.

EDI-OCT Type	Visual acuity decrease n(%)	Median diameter in Fundus photograpy (DD±IQR)	Orange pigment by AF n(%)	Subretinal fluid by OCT n(%)	US Hollow n(%)	Median US thickness (µm±QR)		Median OCT thickness (µm±IQR)	
						Baseline	1 year	Baseline	1 year
1	1 (1.9)	1.00 ± 1.00	5 (9.4)	2 (3.8)	2 (3.8)	0.97 ± 0.5	0.75 ± 0.4	222.0 ± 144.0	222.0 ± 160.0
2	0 (0)	2.00 ± 2.00	4 (36.4)	1 (1.9)	1 (1.9)	0.92 ± 0.5	0.90 ± 0.5	305.0 ± 90.0	331.0 ± 133.0
3	0 (0)	1.50 ± 0.50	0 (0)	0 (0)	0 (0)	-	-	319.0 ± 111.0	312.0 ± 104.0
4	6 (26.1)	3.00 ± 1.50	6 (26.1)	7 (30.4)	2 (8.6)	1.26±0.65	1.20±0.69	569.0 ± 379.0	600.0 ± 408.0

All three suspicious lesions, classified as type 4 on EDI-OCT, were associated with other high-risk features of growth of transformation, such as a decrease in visual acuity (100%), thickness greater than 2 mm on US (67%) and SRF (100%). Their mean thickness at one year in EDI-OCT was 846.00 ± 189.50 μm, with an absolute change of 106.00 ± 108.89 μm.

The lesion that transformed into melanoma had a thickness increase of 1000 μm in US and 183 μm in EDI-OCT in one year. Of the 14 lesions with a thickness increase in EDI-OCT of more than 10%, nine (64.2%) were still not identified in US. Their EDI-OCT median thickness at baseline was 305.00 ± 410.50 μm and one year later was 356.00 ± 521.50 μm (p=0.001). Three of those (21.4%) presented decreased visual acuity, orange pigment and subretinal fluid.

DISCUSSION

Nevi thickness is known to be the parameter associated with the highest risk of growth or malignant transformation,[2-4] so it is easy to understand why it is so important to have a consistent and precise measurement methodology of nevi. To meticulously monitor a nevus, three steps are mandatory, each ultimately depending on the success of the previous one. First: identifying the nevus; second: measuring it; and third: assessing its changes over time. In our study, the US failed to identify, measure and assess change in thickness in most nevi.

Regarding the first step - identifying the nevus - 66 (73.3%) of 90 nevi were never identified on the US, being considered flat nevi. All the consistently flat nevi on the US were identified and measured in EDI-OCT. In summary, in almost three-quarters of cases a doctor could not rely on the US to identify nevi, and without identifying the nevus the two other steps cannot be achieved with this methodology. US is known for a lack of sensitivity, especially for smaller lesions, as the axial and lateral ultrasonography resolutions are approximately 150 and 450 μm, respectively.[13] On the other hand, EDI-OCT corroborated the known capacity of detecting and measuring infra-millimetric lesions.[9,14] Only far peripheral nevi could not be scanned with EDI-OCT.

As for the second step – measuring the nevus – the US overestimated choroidal nevi thickness compared to EDI-OCT, which agrees with previous studies.[7,9,10] It also suggests the known lack of consistency among measurements and a lack of accuracy.[7,10] Without being able to delineate the posterior limit of the nevi, measurements tend to be less reliable, compared with SD-EDI-OCT.

Concerning the third step – assessing thickness changes over time - the median absolute change in thickness was significantly different between US and EDI-OCT (US 195.00 ± 320.00 μm; EDI-OCT 28.50 ± 106.50 μm), showing the expected overestimation of US, and a significant difference in resolution between the two imaging. Regarding thickness variation, US measurements ranged from minus 840 to plus 1040 μm within one year, meaning that a nevus could diminish up to 840 μm on a subsequent examination (compared to a range of variation of minus 146 to plus 592 μm on EDI-OCT). These findings might corroborate US lack of consistency. Relying on the US in the 2 cases in which nevi were identified at US baseline but not one year later, one might think that the nevi disappeared, when in fact EDI-OCT proved the nevi to remain there, with even an increase in thickness. Likewise, the nevus that US only identified after one year, should be explained by a significant increase in thickness, which was not the case as proved by EDI-OCT. It is known that more than 10% of thickness increase is the described cut-off value that should denote some additional risk of growth and transformation[11] and require a tighter periodical vigilance. In 64.2% of lesions with an EDI-OCT thickness increase of more than 10%, that change went unnoticed on US, since the nevi were never identified in the first place, demonstrating our point that without steps one and two, the third step cannot be confidently achieved.

Nevi that are flat on US might not be benign and carry no worrisome. Besides the above-discussed thickness increase of more than 10%, we may consider other nevi features that are believed to help signal nevi at risk of growth or transformation. The EDI-OCT type 4 – "elevated" is one of those features. In our study, 23 nevi had elevation of the surface of the nevus, and 29.2% of those were never identified on US. Type 4 EDI-OCT was also associated with other high-risk features such as a decrease in visual acuity and SRF, emphasizing the importance of a thorough monitorization of these lesions. Regarding suspicious lesions (with more than one high-risk feature), all were classified as type 4 and had SRF. Thus, the SD-EDI-OCT benefit goes beyond the ability to identify, measure and assess thickness change, as it includes other very important features such as identifying SRF (not always identified in clinical examination) and identifying type 4 lesions.

Despite the overall SD-EDI-OCT superiority in evaluating nevi features, US continues to hold an important position in nevi assessment. We continue to suggest US analysis at baseline for every nevus. From then, if the lesion is not identified, no other US should be done by default, until changes in EDI-OCT or clinical features are noted. For nevi identified on US but too peripheral to have an EDI-OCT scan performed, or too thick exceeding the scan display, regular default imaging evaluation should be done only by US. For every nevus identified both with EDI-OCT and US, if no high-risk feature is present, we recommend a monitorization with EDI-OCT only, since it is more reliable and accurate. If any high-risk feature is identified, both exams should be done periodically, not only to measure change in thickness but also to assess the shape of the lesion, hollow echogenicity and possible associated complications.

The strengths of our study include the prospective design, a considerable sample size and a comprehensive and consistent clinical and imaging protocol. The limitations of our study encompassed the exclusion of far peripheral lesions, due to the inability to scan with EDI-OCT, and the exclusion of lesions thicker than the EDI-OCT screen display, which could represent high-risk lesions interesting to analyse. EDI-OCT widefield or ultra-widefield could be valuable by reaching peripheral lesions. It is our intention to prolong the present study, to assess the changes over a longer period.

CONCLUSION

As a parameter with one of the highest risk of growth or malignant transformation, a consistent and precise nevi thickness methodology is needed. For it to happen, three steps are mandatory: identifying the nevus, measuring it and assessing its changes over time. US failed at the first step, not being able to identify most nevi, including ones with significant increases in thickness and other high-risk features. EDI-OCT successfully fulfilled the three steps. EDI-OCT should replace US in evaluating flat nevi, and we advocate its adoption as the primary modality to comprehensively analyse high-risk nevi.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

BC: Responsible for gathering the data, presenting the results, and creating the manuscript.

PG: Responsible for the statistical analysis and the manuscript revision.

NRA: Contributed for the data collection.

AM: Supervised this project and contributed with her expertise to its conclusion.

All the authors read and approved the final manuscript. All the authors had full access to all the data and take full responsibility for the integrity of the data and the accuracy of the data analysis; all were responsible for conceiving this research.

BC: Responsável pela recolha dos dados, apresentação dos resultados e elaboração do manuscrito.

PG: Responsável pela análise estatística e pela revisão do manuscrito.

NRA: Contribuiu para a recolha de dados.

AM: Orientou este projeto e contribuiu com a sua experiência para a sua conclusão.

Todos os autores leram e aprovaram o manuscrito final. Todos os autores tiveram acesso total a todos os dados e assumem total responsabilidade pela integridade dos dados e pela exatidão da análise dos mesmos; todos foram responsáveis pela conceção desta investigação.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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