



# The use of zonal analysis of peripapillary choroidal thickness in primary open-angle glaucoma

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## Abstract

**Purpose** To evaluate automatic peripapillary choroidal thickness (PPCT) measurements in a wide area around the optic disc and various established zones in primary open-angle glaucoma (POAG) patients and age- and sex-matched healthy controls using a new swept-source optical coherence tomography (SS-OCT) device.

**Study design** Single center cross-sectional observational study.

**Methods** A total of 135 POAG patients and 86 healthy subjects were consecutively enrolled. An optic disc  $6.0 \times 6.0$  mm three-dimensional scan OD was obtained using the SS-OCT Triton. A  $26 \times 26$  cube-grid centered in the optic disc was generated to automatically measure choroidal thickness. Seven choroidal zones were established (superior temporal, central, and nasal; inferior temporal, central, and nasal, and the optic nerve head) and compared between healthy controls and POAG patients.

**Results** PPCT was significantly thinner in the central superior, nasal superior, and nasal inferior zones of the POAG subjects. Choroidal thickness in the central superior zone was  $124.61 \pm 54.95$   $\mu\text{m}$  in POAG group vs  $156.17 \pm 80.89$   $\mu\text{m}$  in healthy controls ( $p = 0.029$ ); in the nasal superior zone,  $133.84 \pm 58.89$   $\mu\text{m}$  in the POAG

group vs  $168.34 \pm 73.45$   $\mu\text{m}$  in healthy controls ( $p = 0.012$ ); and in the nasal inferior zone,  $113.45 \pm 49.93$   $\mu\text{m}$  in the POAG group vs  $137.47 \pm 65.96$   $\mu\text{m}$  in healthy controls ( $p = 0.049$ ).

**Conclusion** Compared with healthy subjects, glaucoma patients present with peripapillary choroidal thinning, especially in the central superior, nasal superior, and nasal inferior zones. The new SS-OCT could be a useful tool to evaluate choroidal thinning, and it could be an additional support to facilitate glaucoma diagnosis.

**Keywords** Peripapillary choroidal thickness · Optical coherence tomography · Primary open-angle glaucoma · Choroid

## Introduction

The main theories regarding glaucoma pathogenesis stress the importance of optic nerve head (ONH) vascularization. The peripapillary choroid provides the main blood supply to the prelaminar region of the ONH [1]. As perfusion anomalies contribute to glaucoma [2], several studies suggest that peripapillary choroidal thickness (PPCT) could potentially serve as a clinical indicator for diagnosing glaucoma [3–5].

In many cases, however, ONH analysis is difficult due to features such as a tilted position, a complex distribution of ONH margins, or the presence of drusen or myopic crescents. In these and other situations, supplementary tests such as PPCT analysis could greatly benefit the clinician [6].

The choroid is a dynamic structure, and a thinner choroid is associated with older age [7, 8], higher intraocular pressure (IOP) [9], higher myopia and longer

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axial length [10, 11]. Efforts to introduce PPCT into the routine clinical arsenal of glaucoma diagnosis, however, have been impeded by measurement difficulties and a relative lack of knowledge about the normal distribution of PPCT [12].

Automated choroidal segmentation over a relatively wide section of PPTC allows for a quantitative and accurate approximation of the actual topography of this area. A better understanding of the normal PPCT distribution will help to elucidate the role of PPCT in glaucoma pathogenesis and facilitate diagnosis [13, 14].

Currently, the differences between normal and glaucomatous eyes are measured from a radial scan surrounding the ONH with a fixed diameter of 3.6 mm at 12 discrete locations (30° apart), rather than on a grid created from many points on the peripapillary choroid [15, 16]. The latest swept-source optical coherence tomography (SS-OCT) technology, however, allows for the measurement of a 26 × 26 cube-grid area of the peripapillary choroid and could provide valuable information about the actual disposition and distribution of a wide area of choroidal tissue surrounding the ONH.

The main aim of this study was to improve our knowledge regarding the thickness distribution of different zones around the ONH by comparing a population of control healthy eyes with a population of glaucomatous eyes, and to define the choroidal thickness distribution in both groups. We then compared the average thicknesses of different topographic zones between glaucomatous and normal eyes to explore the differences and to discuss the potential role of PPTC measurements in routine clinical practice.

## Materials and methods

### Study subjects

One hundred thirty-five right eyes of 135 glaucoma patients between 60 and 80 years of age who visited our department during the recruitment period were consecutively enrolled in this cross-sectional observational study. Given the influence of age on choroidal thickness [7, 8], and to homogenize study sample, we established an age range for recruitment. All patients were enrolled prospectively in the Glaucoma Diagnostic protocol at Miguel Servet University Hospital, Zaragoza, Spain. Eighty-six age- and sex-matched healthy subjects who visited our department during the recruitment period were selected and enrolled as the control group. Written informed consent was obtained from all participants after explanation of the nature and potential consequences of the research. The study protocol followed the tenets of the Declaration of

Helsinki, and ethics approval was obtained from the Clinical Regional Ethics Committee of Aragón (CEICA).

Inclusion criteria consisted of a clinical diagnosis of POAG at a previous visit at least 1 year earlier. The diagnosis of POAG was based on characteristic optic nerve damage on slit-lamp examination (defined as a definite notch in the neuroretinal rim or absence of the neuroretinal rim not due to another known cause) with corresponding visual field (VF) defects, an open-appearing anterior chamber angle, and increased IOP (> 21 mmHg). A glaucomatous VF defect was defined as the presence of three or more significant ( $p < 0.05$ ) nonedge continuous points with at least 1 at the  $p < 0.01$  level on the same side of the horizontal meridian in the pattern deviation plot, and classified as “outside normal limits” on the Glaucoma Hemifield Test, confirmed on two consecutive VF examinations.

Subjects were excluded if they had vision loss secondary to another eye condition, any laser procedure in the previous 2 months, previous filtration surgery or previous cataract surgery. Other exclusion criteria included extreme refractive errors, such as high myopia (− 6.0 or higher), hyperopia (+ 6.0 or higher), or astigmatism ( $\pm 3.0$  or higher), acute angle closure glaucoma, and evidence of macular pathologies, vascular or inflammatory diseases, or optic nerve neuropathies other than glaucoma. As we used refractive error as a comparison variable, pseudophakic eyes were also excluded. Participants with clinically significant lenticular opacity using the LOCS III classification were also excluded [17]. The exclusion criteria for lenticular opacity were nuclear color/opalescence greater than NC2 and NO2, respectively, cortical cataract greater than C2, and posterior subcapsular cataract greater than or equal to P1.

### Ophthalmological examination

All subjects underwent a complete ophthalmologic examination, including measurements of best-corrected visual acuity (BCVA) (using a Snellen chart at 4 m) and IOP (using a calibrated Goldmann applanation tonometer), slit-lamp examination of the anterior segment, and fundus evaluation. The Humphrey 24-2 Swedish Interactive Threshold Algorithm Standard perimeter (Zeiss Meditec, Dublin, CA, USA) was used to evaluate the VF. Only reliable VFs, defined as those with < 20% fixation errors and < 33% false positives or false negatives were used. VF and OCT examinations were performed within a 2-month period.

## Optical coherence tomography measurement

All participants included in the current study had SS-OCT measurements obtained using Deep Range Imaging (DRI) OCT Triton (Topcon Corporation, Tokyo, Japan), software IMAGEnet 6 version 1.19, through dilated pupils. An optic disc of  $6.0 \times 6.0$  mm three-dimensional scan was obtained. This scan combines automatically morphometric optic disc parameters (such as disc area and vertical cup-to-disc ratio) and various peripapillary parameters, including retinal nerve fiber layer and choroidal thicknesses. The subjects were seated and properly positioned. All DRI-OCT images were obtained by a single well-trained technician. The DRI-OCT Triton includes the new SMART-Track™ tool, which enhances tracking, corrects for motion, and guides the operator to reduce potential errors when acquiring images. Only eyes with good-quality scans were included in the analysis. Good-quality SS-OCT images were defined as those with signal strength  $\geq 40$  (maximum = 100), and without motion artifacts, involuntary saccades, or overt misalignment of de-centration.

Following data acquisition, a  $26 \times 26$  cube-grid centered in the optic disc was generated to automatically measure choroidal thickness. This grid included 676 cubes of  $200 \mu\text{m}$  around the ONH, including the 88 central cubes corresponding to the ONH area that were not analyzed; thus the DRI-OCT Triton displays choroidal thickness for a total of 588 peripapillary cubes (Fig. 1a). The Bruch membrane and choroidal-scleral interface were delineated with the segmentation algorithm implemented by Topcon.

After two experts carefully examined all images, three eyes were excluded due to improperly defined choroidal

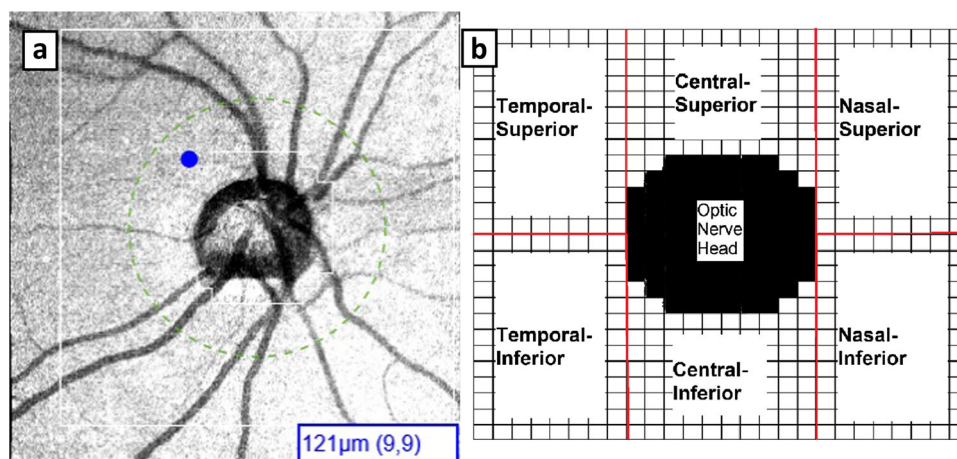
boundaries, two eyes were excluded due to poor DRI-OCT image quality, and one eye was excluded during the examination due to poor fixation.

## Statistical analysis

For the statistical analysis, the PPCT OCT grid was divided into the following seven zones: superior temporal, superior central, superior nasal, inferior temporal, inferior central, inferior nasal, and the ONH (Fig. 1b). Study zones were set according to their position around the ONH; the central superior zone included 86 cubes directly positioned above the ONH, and the central inferior zone included the 86 points below the ONH. The four squares beyond the ONH were labeled as temporal superior, temporal inferior (104 cubes each), nasal superior, and nasal inferior (104 cubes each).

Once established, the mean PPCT value for each study zone was obtained for the healthy control and glaucoma groups. The ONH was not examined and therefore not included in the statistical analysis. Only right eyes were selected for the statistical analysis.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 20.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the sample distribution of the variables. BCVA decimal values were converted to the LogMAR equivalent using the following formula [18]:  $\text{LogMAR} = -\text{Log}(\text{Decimal Acuity})$ . For quantitative data following a parametric distribution, differences between groups were compared using Student's *t* test. For qualitative data, a Chi square test was used for comparison. A



**Fig. 1** Peripapillary choroid grid. **a** Image of the  $26 \times 26$  cube-grid centered in the optic disc of a right eye obtained with deep range imaging (DRI) optical coherence tomography (OCT) Triton (Topcon Corporation, Tokyo, Japan). This grid includes 676 cubes of  $200 \mu\text{m}$  around the optic disc: the 88 central cubes corresponding to the optic disc area are not measured, and the DRI-OCT Triton automatically

displays choroidal thickness in each of the 588 peripapillary cubes. **b** Schematic representation of the peripapillary choroidal thickness zones defined in this study (superior temporal, superior central, superior nasal, inferior temporal, inferior central, and inferior nasal) bounded by a red line

logistic regression analysis was performed to know the diagnostic power of the mean choroidal thickness in each of the areas studied. The Pearson correlation coefficients between PPCT in the different areas analyzed with age, IOP and spherical equivalent were calculated. A  $p$ -value of less than 0.05 was considered statistically significant.

## Results

A total of 221 right eyes were analyzed for statistical purposes: 135 from glaucoma patients and 86 from healthy controls. Mean age of the POAG patients was  $70.35 \pm 6.13$  years (range 60 to 80 years) and that of the healthy controls was  $68.88 \pm 4.11$  years (range 60 to 80 years). Seventy-three (54%) of the 135 subjects in POAG group and 45 (52%) of the 86 subjects in control group were men. Mean spherical equivalent was  $-0.08 \pm 1.64$  D in the POAG group and  $0.07 \pm 2.76$  D in the control group, and there was no significant difference. There were no statistically significant differences in age, sex, and spherical equivalent between groups ( $p = 0.118$ ; 0.627, and 0.088, respectively). The study population characteristics are summarized in Table 1.

The peripapillary choroid was thicker in the superior sector in absolute terms; statistical comparison between inferior and superior zones, in each of the temporal, central, or nasal position zones revealed significant differences between the superior and inferior areas in control healthy eyes as well as in glaucomatous eyes (Table 2).

Comparison between control and POAG eyes showed a thinner choroidal layer in every zone in the glaucoma group. The central superior, nasal superior, and nasal inferior zones were significantly thinner in the POAG eyes (Table 3). The choroidal thickness in the central superior zone was  $124.61 \pm 54.95$   $\mu\text{m}$  in the POAG group and

$156.17 \pm 80.89$   $\mu\text{m}$  in the healthy controls ( $p = 0.029$ ); in the nasal superior zone,  $133.84 \pm 58.89$   $\mu\text{m}$  in the POAG group vs  $168.34 \pm 73.45$   $\mu\text{m}$  in the healthy controls ( $p = 0.012$ ); and in the nasal inferior zone,  $113.45 \pm 49.93$   $\mu\text{m}$  in the POAG group vs  $137.47 \pm 65.96$   $\mu\text{m}$  in the healthy controls ( $p = 0.049$ ). None of the zones analyzed showed a statistically significant value in the logistic regression equation. Slight significant correlations were found between each of the six PPCT areas with age (values ranged from  $-0.204$  to  $-0.266$ ). We did not find any significant correlation between PPCT and IOP or spherical equivalent.

## Discussion

Using automated choroidal segmentation software in a wide area around the ONH, we found the thinnest PPCT in the inferior sectors of the optic discs in both glaucoma and control eyes; however, in general the POAG group showed thinner choroidal layer pattern compared with the control group, especially in the nasal and central superior sectors. Until OCT technology provided the possibility of accurately measuring choroidal thickness, histology was the only valid approach to determine the boundaries of the choroidal layer. Different microscopic studies have provided controversial results: some reporting a decrease in the choroidal thickness of glaucomatous eyes [19], while others reporting the opposite, probably due to methodological differences [20].

The first OCT analysis evaluating choroidal thicknesses in eyes with and without glaucoma was focused within the macular area, and again discrepancies over choroidal thinning in glaucomatous eyes are reported [21–24]. It seems that studying the foveal, temporal, nasal macular, or

**Table 1** Descriptive and clinical data for 135 primary open-angle glaucoma (POAG) eyes and 86 healthy control eyes

Parameters	POAG (average $\pm$ SD)	Control (average $\pm$ SD)	$p$ value
Number of eyes	135	86	–
Age (years)	$70.35 \pm 6.13$	$68.88 \pm 4.11$	0.118
Sex (male/female)	73/62	45/41	0.627
Spherical equivalent (D)	$-0.08 \pm 1.64$	$0.07 \pm 2.76$	0.088
BCVA (LogMAR)	$0.07 \pm 0.14$	$0.028 \pm 0.12$	0.001*
IOP (mmHg)	$16.35 \pm 2.96$	$17.67 \pm 3.14$	0.051
Disc area ( $\text{mm}^2$ )	$2.00 \pm 0.43$	$1.88 \pm 0.33$	0.357
VCDR	$0.74 \pm 0.18$	$0.48 \pm 0.22$	<0.001*
MD (dB)	$-8.52 \pm 6.57$	$-0.89 \pm 1.12$	<0.001*
Corneal pachymetry ( $\mu\text{m}$ )	$537.35 \pm 35.32$	$523.90 \pm 41.25$	0.669

POAG primary open-angle glaucoma, SD standard deviation, D diopters, BCVA best corrected visual acuity, IOP intraocular pressure, VCDR vertical cup-to-disc ratio, MD mean deviation, dB decibels

\*  $p < 0.05$ , Student  $T$ -test (except for sex, Chi square test)

**Table 2** Mean and standard deviation of peripapillary choroidal thickness in control and glaucoma subjects, comparison between inferior and superior zones

	Inferior (average $\pm$ SD)	Superior (average $\pm$ SD)	<i>p</i> value
Control group			
PPCT Central Zone ( $\mu\text{m}$ )	112.01 $\pm$ 68.90	156.17 $\pm$ 80.89	<0.0001*
PPCT Temporal Zone ( $\mu\text{m}$ )	148.04 $\pm$ 73.32	169.47 $\pm$ 77.58	0.0025*
PPCT Nasal Zone ( $\mu\text{m}$ )	137.04 $\pm$ 65.96	168.34 $\pm$ 73.45	<0.0001*
Glaucoma group			
PPCT Central Zone ( $\mu\text{m}$ )	91.93 $\pm$ 43.75	124.62 $\pm$ 54.95	<0.0001*
PPCT Temporal Zone ( $\mu\text{m}$ )	130.17 $\pm$ 63.93	142.88 $\pm$ 67.17	0.0003*
PPCT Nasal Zone ( $\mu\text{m}$ )	113.45 $\pm$ 49.93	133.84 $\pm$ 58.89	<0.0001*

Zone ONH corresponds to the optic nerve head and was not included in the analysis

SD standard deviation, POAG primary open-angle glaucoma, PPCT peripapillary choroidal thickness

\*  $p < 0.05$ , Student paired samples *t*-test

**Table 3** Mean and standard deviation of choroidal thickness in the established zones in control and glaucoma subjects, and statistical comparison between groups

Parameters	POAG (average $\pm$ SD)	CONTROL (average $\pm$ SD)	<i>p</i> value
PPCT zone CS ( $\mu\text{m}$ )	124.61 $\pm$ 54.95	156.17 $\pm$ 80.89	0.029*
PPCT zone CI ( $\mu\text{m}$ )	91.93 $\pm$ 43.75	112.01 $\pm$ 68.90	0.097
PPCT zone TS ( $\mu\text{m}$ )	142.88 $\pm$ 67.17	169.47 $\pm$ 77.58	0.052
PPCT zone TI ( $\mu\text{m}$ )	130.17 $\pm$ 63.93	148.04 $\pm$ 73.32	0.168
PPCT zone NS ( $\mu\text{m}$ )	133.84 $\pm$ 58.89	168.34 $\pm$ 73.45	0.012*
PPCT zone NI ( $\mu\text{m}$ )	113.45 $\pm$ 49.93	137.47 $\pm$ 65.96	0.049*

Zone ONH corresponds with the optic nerve head and was not included in the analysis

POAG primary open-angle glaucoma, SD standard deviation, PPCT peripapillary choroidal thickness, CS central superior, CI central inferior, TS temporal superior, TI temporal inferior, NS nasal superior, NI nasal inferior

\*  $p < 0.05$ , Student's *t*-test

average macular choroidal thicknesses is not the best approach for evaluating glaucomatous changes [15, 16].

PPCT examination seems to be the most useful approach to diagnosing glaucoma [3–5]. But relationship between PPCT and blood supply is still controversial in the available literature. In the Beijing Eye Study [2], the findings do not indicate a significant association between PPCT and blood pressure (BP). Gupta et al. [12], using novel automated choroidal segmentation software in an Asian population did not find any association between BP and PPCT either. However, in a recent review performed by Goharian and Sehi [25], the conclusion was that alterations in BP and ocular perfusion pressure could affect choroidal thickness. Tan et al. [26] report that arterial BP had an effect on subfoveal choroidal thickness. New studies are necessary to elucidate the relationship between BP, choroidal thickness and IOP. These studies need to conduct different measurements during the same day of these factors while keeping strict control of vascular factors. With regard to the profile of the PPCT, our finding of the thinnest PPCT in the inferior region is consistent with other studies. Thus, we believe this area with a thinnest choroid may represent consequently an area of lower blood supply (as the

peripapillary choroid is the main source of ONH nourishment), which may predispose the inferior region of the optic nerve to glaucomatous ischaemic damage [27, 28].

The development of enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) enables a more accurate measurement of choroidal thickness, but provides conflicting results [29] as well. A recent meta-analysis conducted by Lin et al. [30], demonstrates average PPCT in open-angle glaucoma (OAG) as significantly reduced compared with healthy subjects, especially in the superior and nasal sectors, the same as our results. They included different studies performed with various OCT instruments (spectral domain and SS-OCT). Contrary to this, previous meta-analysis conducted by Wang and Zhang [31] and Zhang et al. [32] show no correlation between PPCT and OAG, but both only included studies using EDI-OCT technology, without SS-OCT. A recent publication performed by Song et al. [33] with SS-OCT, found that the global and all 12 clock-hour PPCT, with the exception of the 10 o'clock sector, were thinner in OAG (even after adjusting for age, axial length and disc area). However, macular choroidal thickness did not remain thinner in

glaucoma group after adjusting for age, axial length and spherical equivalent.

The discrepancies among authors may be related to the dynamic and variable nature of the choroid and some methodological and operative aspects like manual segmentation or the limited amount of locations evaluated. For example, spectral domain-OCT evaluates the 12 central degrees around the optic nerve through a 3.4-mm lineal-circle scan to produce a total of only 100 points [34].

New technologies such as SS-OCT provide the opportunity for better delimitation of the retinal layers, as well as a much improved method for measuring a large number of points (588 cubes) in a wider peripapillary area ( $5.2 \times 5.2$  mm, 20 central degrees) that provides topographic information of the choroidal shape and distribution. Theoretically, with these tools, we could obtain useful information especially in glaucoma patients with a tilted or aberrant optic disc. Further investigations focused on the association between the type of glaucomatous disc damage and the pattern of PPCT, are required to better understand the role of the choroid in glaucoma.

Our study has several limitations. First, we did not collect data on axial length; however, we demonstrated that there was no significant difference in the refractive error among the groups. The axial length and refractive error variables are related, but not interchangeable, as the axial length tends not to change after the second decade of life, except in cases with some pathology. Instead, the refractive error may fluctuate or change due to different factors and, for this reason; we excluded pseudophakic eyes [35]. The results from a recent study by Ikuno and Tano [36] using OCT, however, suggest that refractive error and axial length have a similar relationship with OCT measurements. Second, the choroid can be influenced by circadian changes [26], and we did not perform OCT examinations at the same time in all participants; however, all the OCT scans were acquired in the morning (between 09:00 and 12:00). Third, we only measured choroidal thickness in the right eyes of each participant, and inter-eye differences were not assessed. Fourth, the POAG patients were not divided according to severity, and it would be interesting to investigate whether there is an association between PPCT and glaucoma severity or normal tension glaucoma; or between PPCT and peripapillary retinal nerve fiber layer thickness.

Finally, we have not confirmed the reliability of the automated PPCT measurements obtained with the new SS-OCT (there is only one study that analyzed repeatability of retinal and choroidal thickness with SS-OCT in neovascular age-related macular degeneration) [37]; and it is necessary to investigate the accuracy of this software in other studies. Intradevice repeatability of peripapillary retinal nerve fiber layer thickness and different retinal

measurements using the same SS-OCT device (DRI-OCT Topcon) are good, with intraclass correlation coefficients (ICCs)  $\geq 0.9$  for all sectors in control subjects [38, 39]. Ikuno et al. [40] studied the reliability and reproducibility of manual normal choroidal thickness measurements on EDI-OCT; and interobserver correlation was found to be 0.970 and intervisit correlation was 0.893. So, it's expected that reliability of automated choroidal thickness measurements with SS-OCT will be good.

The present study demonstrates that peripapillary choroidal tissue is thickest superiorly and thinnest inferiorly, both in controls and glaucoma patients. Significant associations were detected between choroidal thickness along different zones of the retinal tissue around the optic disc, and the presence of glaucomatous changes; although these associations were statistically significant in three zones (i.e., central superior, nasal superior, and nasal inferior), the remaining zones were also thinner in glaucomatous eyes. Our findings suggest that glaucoma degeneration affects the choroidal tissue, especially in the superior and nasal areas around the optic nerve.

More studies based on new technology that explores peripapillary thickness in different areas of the choroid, with a careful recording of vascular variables, would clarify the actual role of this evaluation of PPCT in clinical practice.

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