BABEŞ-BOLYAI UNIVERSITY CLUJ-NAPOCA

FACULTY OF PHYSICS

OPTICAL COHERENCE TOMOGRAPHY - A MODERN DIAGNOSTIC APPROACH IN OPHTHALMOLOGY

- DOCTORAL THESIS SUMMARY -

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Contents

INTRODUCTION

The optical coherence tomography (OCT) is a new imaging method for used for medical diagnosis. The OCT is a high-resolution, non-invasive technique, which uses electromagnetic waves in the near infrared field, called non-ionizing optical radiation. OCT derives from the low coherence optical interferometry and was first applied in the biomedical field for measuring the length of the eye globe [1].

OCT makes cross sections or tomographic sections of the internal microstructure in biological tissues. It is an extraordinary imaging technology, because it allows *in situ* real time measurement of the tissue structure at 5-15 μm resolution and 1-2 size ranges higher than that of conventional medical imaging technologies (ultrasound scans, magnetic resonance, CT scan).

All previous information regarding this new imaging technique fully justifies the interest for the topic chosen in this doctoral thesis. In daily ophthalmology medical practice, OCT investigations have become almost compulsory to increase the diagnosis accuracy. In 2006, the Review Ophthalmology Investigations Center (Centrul de Investigaţii Oftalmologice Review) purchased a Stratus OCT 3000, Carl Zeiss Meditech Inc, the first one of this kind in Romania. Thus, it is only natural to wish that, starting with a good knowledge of its physical operating principles, we scientifically analyze the results obtained since then in the medical practice, as well as how this type of investigation has changed the clinical approach of different ocular pathologies examined. It may be imperative to re-write certain chapters in medicine, considering the new data on ocular tissues gathered using this instrument. There is a great necessity in the medical world to publish the new physiopathological features and aspects described in various pathologies using the OCT, and the interest for this new method is increasing.

Key words: optical coherence tomography – OCT; time-domain OCT; Optic Nerve Head – ONH; Retinal Nerve Fiber Layers – RNFL; Retinal Thickness Macular – RTM

PART I:

CURRENT STATE OF KNOWLEDGE IN THE FIELD OF OPTICAL COHERENCE TOMOGRAPHY (OCT) AND ITS USE IN OPHTHALMOLOGY

CHAPTER I

OPTICAL COHERENCE TOMOGRAPHY – OCT

1. Basics about OCT
2. Optical fundamentals of function in OCT
3. Light source of the OCT
4. Technical data about the construction and the use of an OCT
5. Specific problems about recording and processing OCT images

I.1. Basics about OCT

The theoretical operating bases have been established by the mathematicians D. Huang and M. R. Hee [1]. In principle, the optical coherence tomograph is based on a Michelson interferometer, built using the following elements: light source, scanning system and detector (Figure 1 – scanning the human eye globe). These elements fulfill almost all the essential functions of the equipment. A beam is directed to the measured sample, and the other one towards the reference mirror, thus the light spread by the sample (in our case by the eye bottom) and that reflected by the reference mirror shall be overlapped by passing through the beam splitter and shall interfere. The beam resulting from the interference is collected using the detector.

Initially, the first OCT images were performed in the "*time-domain*" mode. The "*time-domain*" systems can acquire around 400 type A scans per second, using the 6 radial scans with intervals of 30 degrees. There is a risk of omitting certain pathologies affecting the areas between the scans. The "*spectral-domain*" technology, however, performs around 20,000-40,000 scans per second, continuously, on the scanned area (without any un-scanned tissue intervals). Thus, the accuracy increases, the resolution is better and lower risk of artifacts due to omission of scanning certain tissue parts and omission of certain pathologies. The resolution of most *time domain* OCTs is 10-15 microns, while the newest ones, of *spectral-domain* type, have an improved resolution, of almost 3 microns.

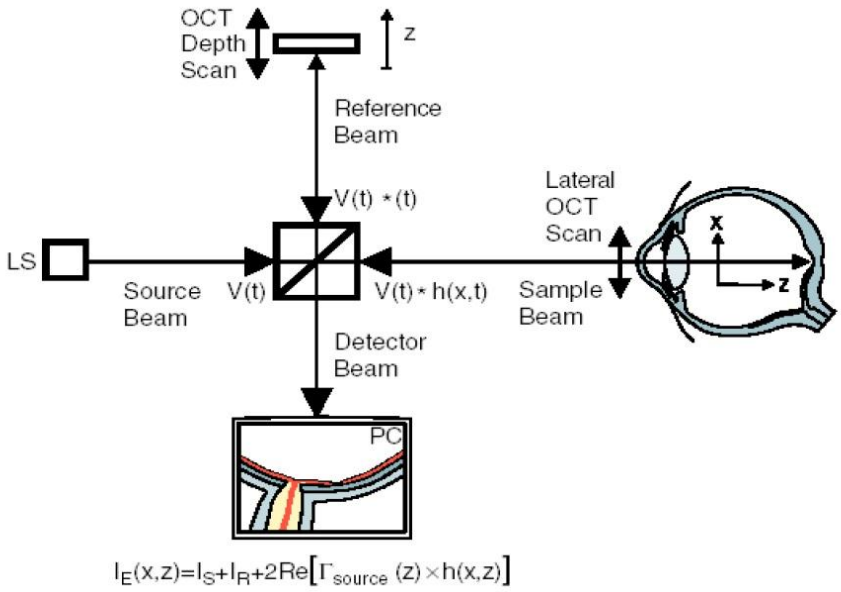

Figure 1. Scheme of the optical coherence tomograph [2]

I.2. Optical fundamentals of function in OCT

Compared to the speed of ultrasound propagation (331 m/s in the air and 1430 m/s in water), the speed of light is extremely high (approximately 3108 m/s in the air and 2,25 108 m/s in water). Therefore, the time gap between two waves (reference wave and reflected wave) coming from the same source after they cross distances that are different in terms of a few tens of microns, cannot be directly measured, unless using interferometry techniques. One method to measure the delay between two light waves is interferometry through low coherence, which accomplish the optical coherence in the domain of reflectometry. Low coherence interferometry was first developed in the field of communications, to measure the optical reflections coming from the faults or connections of the optical fibers [3]. Later, the first applications in biology were performed on one-dimensional samples in the optical field, to determine various ocular structures [2].

The first OCT installation was implemented using, as source, a femtoseconds pulse laser with a wide emission spectra [1], which implies a low coherence length. The low coherence visible light features a continuous series of small pulses with a duration equal to the coherence length. The lower side of Figure 2 shows the difference between a high coherence visible light and a low coherence one. The commercial OCT devices use low coherence light sources – such as superluminescent diode (SLD).

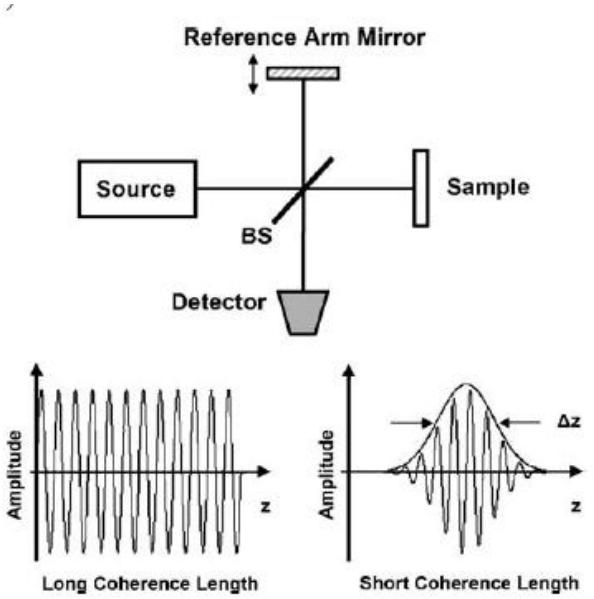

Figure 2. Low coherence interferometry [4]

The delay between the two light beams is usually measured with a **Michelson interferometer** (Figure 2, upper side). Using a low coherence length light source and a Michelson interferometer, the interference fringes are seen only when the length of the path between the two arms of the interferometer is adapted to the coherence length of the radiation emitted by the source. The visible light reflected by the measured sample is disturbed by the one reflected in the mirror of the reference arm of the interferometer (of the known wavelength). The interference of the two reflected light beams (one by the sample, and the other one by the interferometer mirror) happens only when the difference between the lengths of the optical paths crossed by the two beams has the same range as the wavelength of the used radiations (the near infrared). Thus, the coherence condition of the optical radiation source is fulfilled.

It is known that a random signal can be mathematically described either using a time function (f(t)=time evolution) or a frequency function (F(v) – or the signal's spectra) and the operation connecting the two types of signal is the Fourier transform. Thus, buy using the Fourier transform, the original technology of the TD-OCT method (time-domain OCT) allowed the evolution towards SD-OCT (spectral domain OCT).

I.3. Light source of the OCT

Most OCT systems use superluminescent diode (SLD) as source of visible light with large emission spectrum, but low coherence [3].

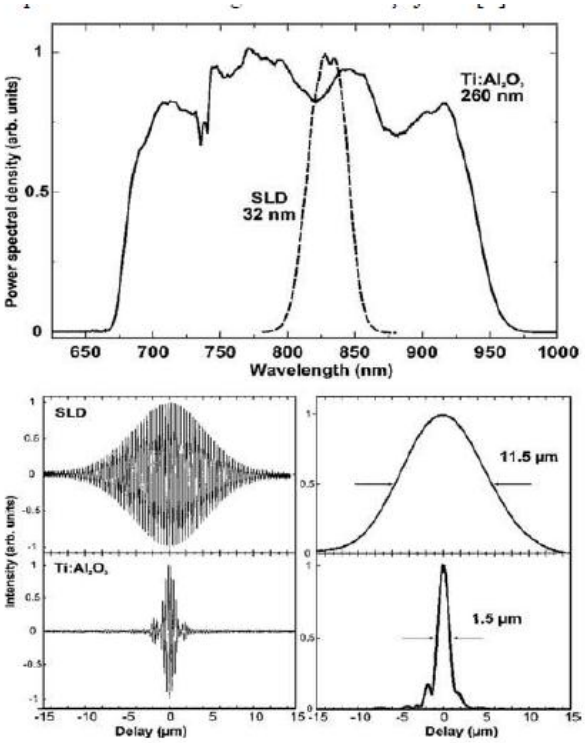

Figure 3. Comparison between the spectral density (upper), interference signals (lower, on the left, and the profile (lower on the right) for the visible light emitted by the Ti-Sapphire laser and the SLD diode [9]

High resolution OCT images, at 0.5-2 μm and 5 μm were obtained at 800 nm and 1.3 μm, using the sources Ti:Al2O3 and Cr4+:Mg2SiO4, respectively. A comparison between the spectral power and the autocorrelation function of the SRD with central wavelength of 800 nm and short pulse (≈5.5fs) Ti:Al2O3 is presented in Figure 3. Thus, there is a successful improvement of the axial resolution, with a size range, by using the titanium ultrashort pulse laser sources: sapphire. Recently, the optical fiber lasers containing rare-earth doping elements proved to be much more compact and more efficient light sources for OCT. These lasers have a spectral region with broadband width between 1.1 and 1.6 μm and a resolution up to 2 μm [6,7,8].

I.5. Specific problems about recording and processing OCT images

The light beam used for scanning is directed towards the intended structure. The delay and the amplitude of the beam reflected by various elements of the scanned microstructures are measured non-invasively.

The optical coherence tomograph was used in our studies to scan the posterior pole of the eye, the macula of retina, and the optic nerve (Figure 4).

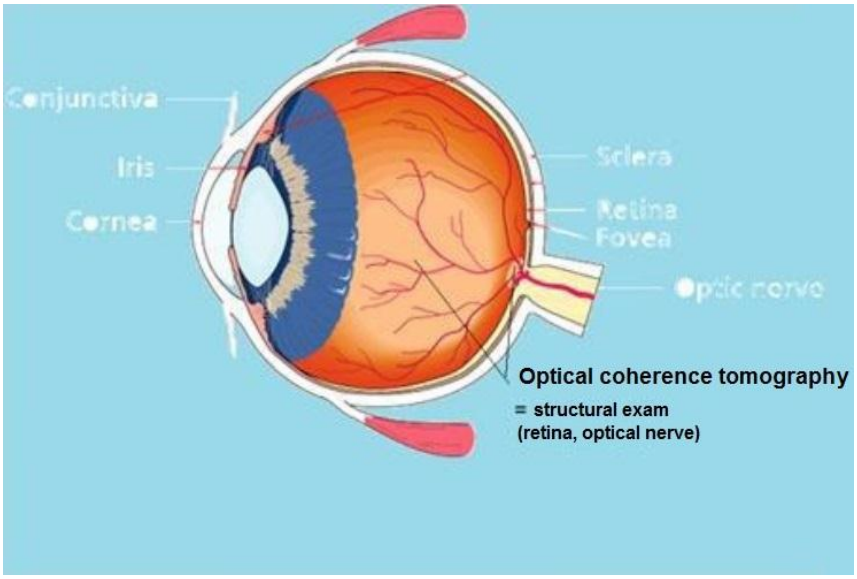

Figure 4. Section through the eye globe [10] with specification of the areas scanned by OCT at the level of the posterior pole of the eye

Parameters of the OCT images:

1. The spatial resolution of the images defines the performance of the OCT system. It refers to the **axial and longitudinal resolution (Δz)** and the **transverse resolution (Δx)**, each of them being accomplished by completely different physical mechanisms [4,9].

- **The axial resolution of the images** depends on the *coherence length of the light source,* which determines the **Δz** resolution or accuracy, by which the distance can be measured. It does not depend on focusing. In ophthalmology, this allows the OCT images to reach extremely high axial resolutions, even if the pupil diameter is limited.

- **The transverse resolution** of the images complies with the same principles as the transverse resolution in the conventional optical microscopy. It is expressed using the dimensions of the diffraction circle obtained when focusing a ray beam.

2. The pixel density: The image must have a *pixel density that is high enough* to allow the visualization of the small details at a given resolution.

3. Detection sensibility: In order to obtain images through high quality OCT, it is necessary to obtain ***extremely high detection sensibilities;*** this is proportional with

the amount of power available in the signal and inversely proportional with the detection bandwidth.

CHAPTER II

MEDICAL CONSIDERATIONS ABOUT OCULAR STRUCTURES EXAMINED BY OCT

The eye, due to transparent media, was among the first human structures scanned with OCT in vivo. In the ophthalmology medical practice, scans of both the *anterior pole* (cornea, iris, crystalline lens) and *posterior pole* (retina, optic nerve) *of the eye* are used.
The information obtained from the optical coherence tomography can be **qualitative** and **quantitative**. In the case of *qualitative* measurements, we obtain information referring to *what* the structure of the retina, of the optic nerve and of the macula *look like*. On the other hand, the *quantitative* measurements provide information on thickness and volume of the scanned eye elements.
The most important structural elements observed while scanning the posterior pole of the eye globe are (Figure 5): the optic disc, or papilla (**O.N.H.** = Optic Nerve Head), the peripapillary optic fiber layer (**R.N.F.L.** = Retinal Nerve Fiber Layers) and macula (**R.T.M.** = Retinal Thickness Macular).

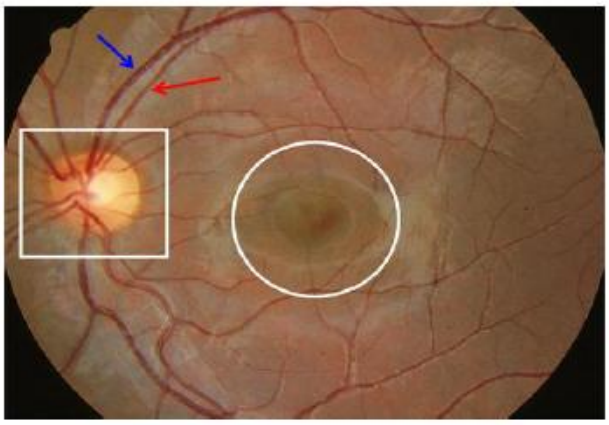

Figure 5: Normal eye bottom; the structural elements of interest are: optic disc (white square), macula with fovea centralis (white circle), arterioles (red arrow), venules (blue arrow)

Figure 6 shows how they are scanned, the scan lines for the optic disc (a / upper-left) and macula (c / bottom) are yellow; the peripapillary optic fiber layer is scanned in a circular way – the yellow and green circles in the image (b / upper-right).

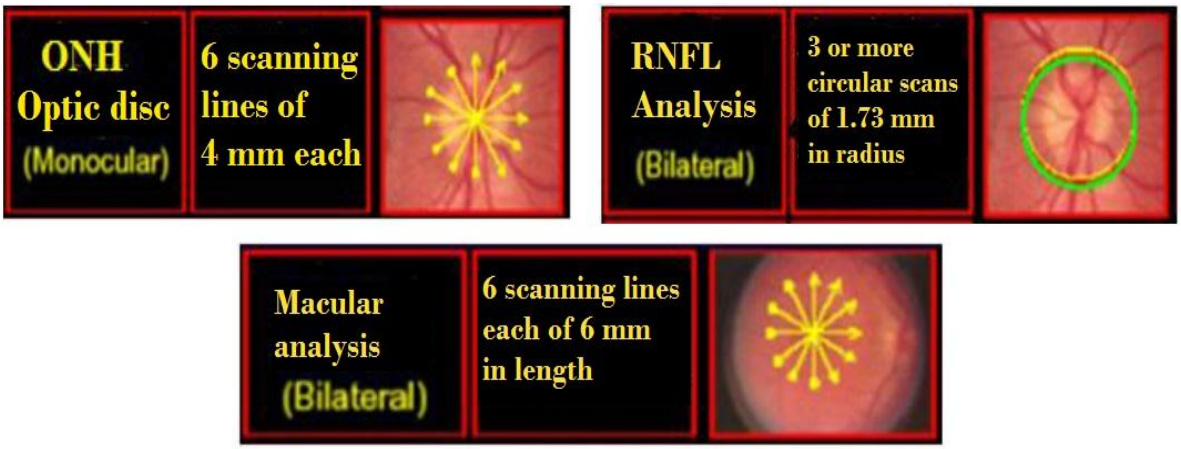

Figure 6. Acquisition methods (12) ONH (a), RNLF (b) and macula (c) respectively

PART II

ORIGINAL CONTRIBUTIONS TO THE MODERN DIAGNOSTIC APPROACH OF THE OCULAR PATHOLOGY USING OCT

CHAPTER III
BASICS FOR THE OCT EXAM OF THE OCULAR POSTERIOR SEGMENT AND ALGORITHMS FOR INTERPRETATION OF THE OCT DATA

I considered necessary to make a **synthesis** *of the published studies* up to the moment when I began this thesis, in order to have the basis on which I would add my own "bricks", to develop the medical knowledge, which is continuously changing and evolving. After a few definitions that are necessary to understand the OCT "language" (Figure 7), I moved on to establishing the basic knowledge related to the structures of interest at the posterior pole of the eye: the number of nerve fibers, the peripapillary

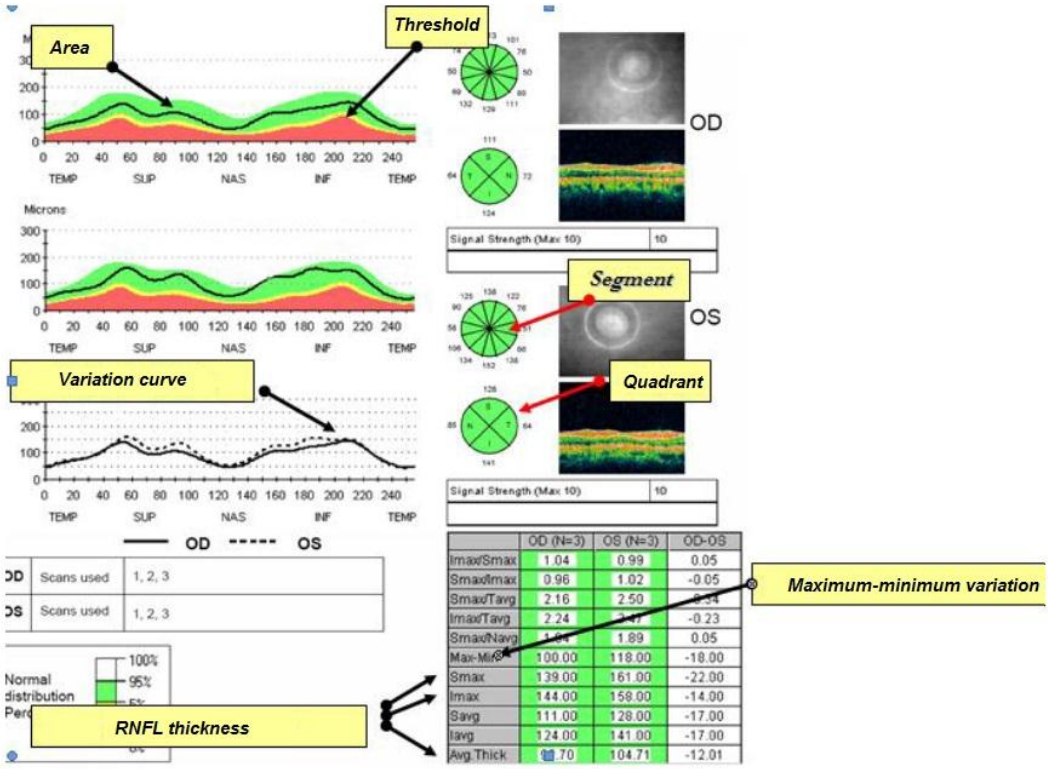

Figure 7: Terms used in designing the algorithm for the interpretation of data provided by the OCT RNFL protocol (in yellow) [14]

optic fiber layer (RNFL), the optic nerve head or optic disc (ONH), the macula (RTM). We kept the English abbreviations because the device's software uses them and they are

very well known, being the same in the entire specialized literature, and have already entered our usual medical practice language.

A. Definitions:

1. **Reference point:** represents the starting point of the defined parameter, considered for all the calculations
2. **Area:** represents the variation interval of the defined parameter
3. **Threshold:** represents the limit where the defined parameter crosses to another area
4. **Distribution probability:** represents the number of probabilities distributed to events.

B. Defined parameters:

III.1. The number of the optical fibers within the optic nerve:

1. **The reference point:** is 1,36 millions of fibers (existing in the optic nerve at birth) [11]
2. **Area:** [3]

   Green: is 1,36 mil – 0,94 mil, with variation limit < 30% (between 70-100%), within safety limits, considered normal [4]

   Yellow: is 0,94 mil – 0,8 mil fibers (loss percentage of 30-38%) and represents the transition from the yellow threshold (alert) to the red one (high pathological probability)

   Red: is <0,8 mil fibers (loss percentage >40%) and represents a clear pathological area
3. Threshold: **Yellow**: when the limit of 0,94 mil fibers is reached (loss percentage>30%)

   Red: when the limit of 0,8 mil fibers is reached (loss percentage exceeds 40%)

	Area			Threshold: Yellow	Yellow area - alert
	Green - safety				
Number of nervous fibers (max-min)	**1,36 mil (max.)**	**0,94 mil (min)**	**Number of nervous fibers (Max-Min)**	**0,94 mil**	**0,94 mil – 0,8 mil**
Variation (%)	100% »» 70%		**Loss (%)**	**≥30**	**≥30-40%**

Table 1: Establishing the areas and thresholds of the number of nervous fibers

4. **The distribution probability** of the healthy population related to the number of nervous fibers

Remark: Probability is expressed using **the standard average** of the population (%)
Events are expressed using the **areas** determined by the number of nervous fibers.

	Area	
Normal distribution (%)		**95%**
		4%
		1%

Table 2: Normal distribution (%) of the population depending on the number of nervous fibers [4]

5. **Statistical loss:** during life, the average loss is 5000 fibers /year until the age of 40 (≤4% per decade), after that, an average loss of 7000 fibers /year is accepted (≥5% per decade) [12]

Age (in decades - years)	**0 »»10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**
Decrease percentage / decade	**≤4%**	**≤4%**	**≤4%**	**≤4%**	**≤5%**	**≤5%**	**≥5%**	**≥7%**
Min. no. of nervous fibers	1,36mil »»1,31 mil	1,26 mil	1,2 mil	1,15 mil	1,08 mil	1,01 mil	0,94 mil	0,94 mil »»0,84 mil
Warning !!	**Cumulated: the losses can exceed 30% (at the age of 70 they reach the yellow threshold)**							Yellow area

Table 3: The relation between age and number of nervous fibers

III.2. Peripapillary optic nerve layers = RNFL:

1. **Reference point:** [11]

is 136 ym (corresponding to 1,36 mil fibers existing in the optic nerve at birth)

Remark: The diameter of the nervous fibers of the RNFL – type C amyelinic axons – is 1 ym on average (variation 0,8-1,4 ym) – the formal correspondence was made of 1 ym / nervous fiber

2. **Area:**

White: is the alert area, with thickness higher than the level of white threshold

Green: is 136-94 ym thickness, with variation limit <30% (between 70-100%), within safety limits, considered normal

Yellow: is 94ym – 84 ym thickness (loss percentage 30-38%) and represents the transition from the yellow threshold (alert) to the red one (high pathological probability)

Red: is from <80 ym thickness (loss percentage ≥40%)

3. **Threshold:** **Yellow:** when the limit of 94 ym thickness is reached (loss percentage >30%)

   Red: when the limit of 80 ym thickness is reached (loss percentage >40%)

   White: when it exceeds the upper limit of the green area

Area				Threshold: Yellow	Yellow area - alert	Red
	Green - safety					
Average thickness of RNFL (max-min)	**136 ym (max.)**	**94 ym (min)**	**Average thickness of RNFL (Max-Min)**	**94 ym**	**94 ym – 80 ym**	**80ym**
Variation (%)	100% »» 70%		**Loss (%)**	**≥30**	**≥30-40%**	**≥40%**

Table 4: Establishing the areas and thresholds of the RNFL average thickness [1,4]

4. **Distribution probability**: of the healthy population in relation with the RNFL thickness

Remark: Probability is expressed using **the standard average** of the population (%)
Events are expressed using the **areas determined by** the RNFL thickness.

	Area	5%
Normal distribution (%)		90%
		4%
		1%

Table 5: Normal distribution (%) of the population depending on the RNFL thickness [4]

5. **Statistical loss:** during the lifetime, the decrease of RNFL/decade, on average, can be ≤4% per decade until the age of 40, ≥5% per decade until the age of 70, and then ≥7% per decade for over 70 years old [12].

		Age (in decades)						
		20	30	40	50	60	70	80
Loss (%)		≤4%	≤4%	≤4%	≤5%	≤5%	≥5%	≥7%
Average RNFL thickness		>126 ym	120 ym	115 ym	108 ym	101 ym	94 ym	94 ym »» 84 ym
Sector distribution	Smax	190	180	170	160	148	138	128
	Imax	190	180	170	160	148	138	128
	Savg	156	140	133	126	118	110	93
	Iavg	156	140	133	126	118	110	93
	Tavg.	112	106	100	94	87	81	76 »» 52
	Navg.	138	131	124	117	108	102	93 »» 56

Table 6: Relation between age and RNFL thickness

III.3. Optic nerve head = ONH

Optic disc:

1. **Average area of the disc:** classification: [13]
   - **Small discs,** with average area < 1,9 mmp
   - **Medium discs,** with average area ~ 2,3 mmp (±0,4 mmp)
   - **Large discs,** with average area > 2,8 mmp

RIM (the disc "frame"): [13, 14]

1. **Average RIM area:** normal value expressed in percentage is ~ 70% of the disc's size

   Remark! The threshold values for the RIM area are:

	Threshold (mmp)	
	Yellow	Red
RIM area	<1,16mmp	<0,924 mmp
Percentage	<50 %	<40%

Table 7: The threshold values of the RIM area [12]

2. **RIM integrated volume:** is a global indicator; the values of the green area begin at 0,28 mmc

   Remark! The threshold values for the RIM integrated volume are:

RIM integrated volume (mmc)	Yellow	Green
	<0,28 mmc	>0,28 mmc

Table 8: The threshold values of the RIM integrated volume

Cup (optic disc "excavation")

1. **Relations cup/disc**: they are of three types
    1. Ratio between horizontal cup/disc diameters: with normal values 0,3-0,5
    2. Ratio between vertical cup/disc diameters: with normal values 0,3-0,5
    3. Ratio between cup/disc areas: with normal values <0,465

III.5. Personal recording sheets for the OCT analyze in current ophthalmological practice

The ophthalmological diagnosis represents an extremely complex activity, requiring the correlation of anamnesis, clinical and paraclinical data, corresponding to each case. In order to optimize the analysis of the data collected through OCT examination, some work sheets have been created, to facilitate a correct approach, and represent a guideline in the large amount of information that must be correctly analyzed. [14,15,16]

OD

RTM quadrant (area of the retina)	RTM sector	RTM defect	
		p<5%	p<1%
Fovea	Faveola		
	F avg.		
Internal ring	S int		
	N int		
	I int		
	T int		
External ring	S ext		
	N ext		
	I ext		
	N ext		
Sum of defects (Σ%)			
Avg thickness (at 6 mm)			
Avg thickness (at 3,4 mm)			

OS

RTM quadrant (area of the retina)	RTM sector	RTM defect	
		p<5%	p<1%
Fovea	Faveola		
	F avg.		
Internal ring	S int		
	N int		
	I int		
	T int		
External ring	S ext		
	N ext		
	I ext		
	N ext		
Sum of defects (Σ%)			
Avg thickness (at 6 mm)			
Avg thickness (at 3,4 mm)			

Table 9: Sheet for collecting data on the RTM [14]

Conclusions: In the quantitative interpretation of the data base, we succeeded to:

- Identify normal reference levels for macular and papillary thicknesses
- Define the safety areas (green), alert areas (yellow), and lesion areas (red), with specified particularities
- Adapt the physiological loss of neuronal fiber to the age level.

The study we performed creates the premises for other medical research, as it clarify the quantitative interpretation of the OCT data. In table 9, one of the sheets is shown as example.

CHAPTER IV

QUALITATIVE STUDIES ON CERTAIN SEMIOLOGICAL OCT FEATURES IN SOME OCULAR PATHOLOGIES

IV.1. OCT importance in cone dystrophy diagnosis [18, 19]

Cone dystrophy can occur in various genetic diseases that affect certain specific loci (over 500 genes responsible, which are known and described until now) on all chromosomes, except 21, 22 and Y, according to OMIM (Online Mendelian Inheritance in Man) [17]. The situations when patients were examined through OCT as well are rare, thus the information provided is useful for the ophthalmological practice. It is important to know the OCT aspect of these patients, especially because until now the diagnosis was by exclusion, being difficult to increase the objectivity on the loss of cone cells in the fovea, and the patients were often considered as simulating.

Clinical case: The patient S.D., 20 years old, female, came to the Review Ophthalmological Center accusing a decrease of visual sharpness at both eyes and light photophobia. The symptoms first occurred during childhood and had a slow, progressive evolution. No ocular pathologies in the family (AHC).

TioAO = 14.6mmHG., biomicroscopy: normal anterior pole of the eye: eye bottom: apparently normal aspect; slightly blurred foveolar reflex. Corresponding OCT – Figure 8 – absence of cones.

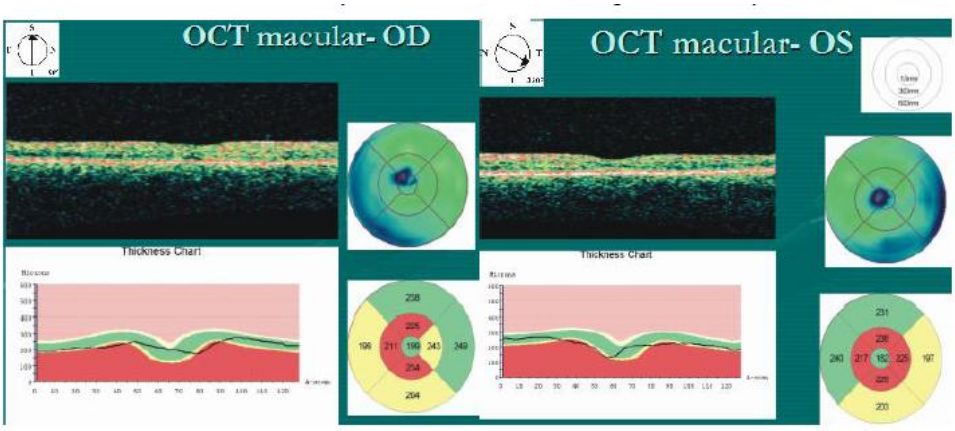

Figure 8: Macular qualitative scan – cone dystrophy

IV.2. OCT particularities in two familial cases of pigmentary rethinopathy [21]

Pigmentary retinopathy is a genetic disabling disease [20], determining the degradation of sight to the extent that it makes it almost impossible to work on a job having the minimum visual requirements, according to the law of labour medicine in our country, and almost automatically determines patients to be classified into a certain group of visual disability. It is thus extremely important to correctly diagnose this pathology and know its particularities.

The particularities of two clinical cases are presented. The first one is M.I., female, aged 47, and the second one is S.A., male, aged 23, which are 2nd degree relatives. They both accuse a decrease in visual sharpness at both eyes, especially in crepuscular light. OCT was useful in the diagnosis, by describing the qualitative and quantitative aspects of the posterior pole structures of the eye. At the limit area – retinal and choroidal atrophy, hyper-reflective in the neuroepithelial cells (Fig. 9). The macular OCT shows, at both patients, that there is a strong decrease of the photo-receptors (hypo-reflective) especially in the area of the internal and external ring, complying with the foveal area (Figure 10).

No edema wass found on the neuro-epithelium corresponding to that of the ONH and RNFL.

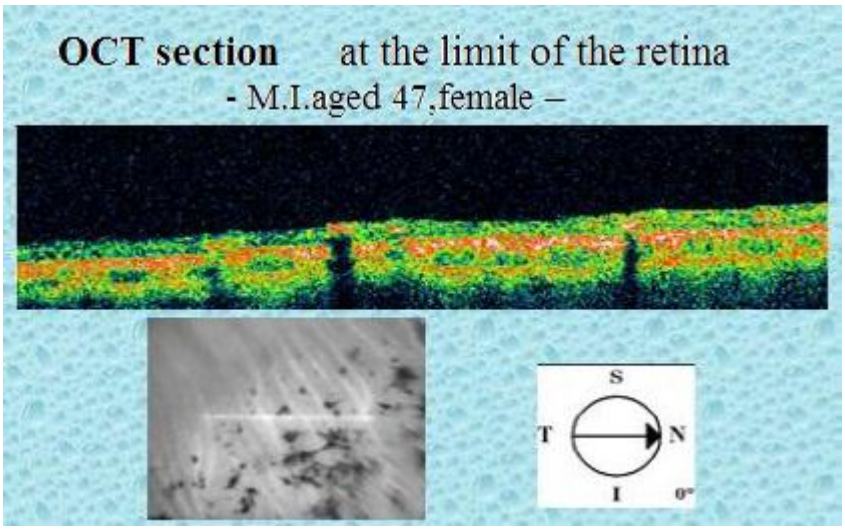

Figure 9: OCT – "line" – qualitative aspect at the limit of the retina case I

OCT scanning of the papilla has emphasized physiological, central, reduced, excavation, overall prominence in relation with the retinal plane and increase of rim's volume at both patients, which defines the moderate papillary edema, extended at the level of adjacent neuro-epithelium. Figure 11 presents the qualitative and quantitative aspect of ONH scanning protocol for case I.

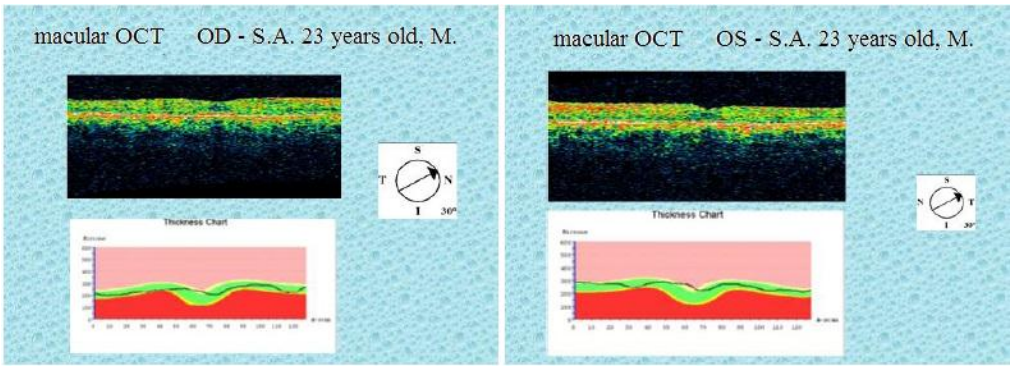

Figure 10: Macular OCT – qualitative and quantitative aspects

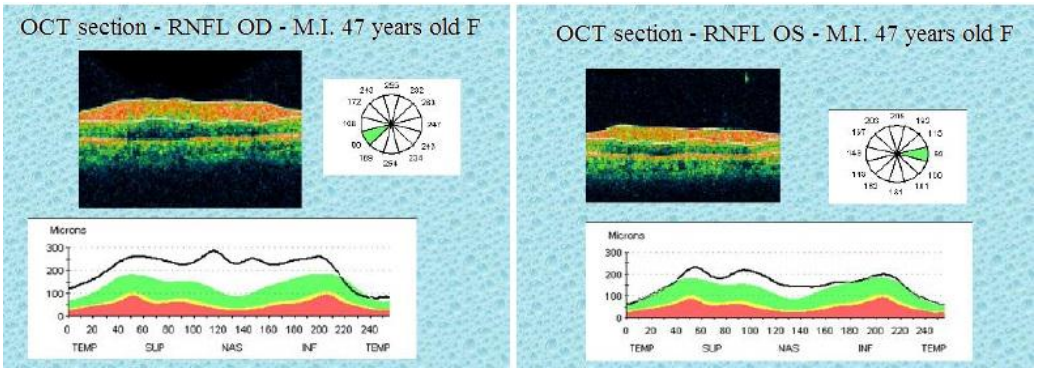

Figure 11: RNFL OCT – qualitative and quantitative aspect for case I

IV.3. Central detachment of retinal epithelial pigment layer in a patient treated with Tamoxifen [22]

Aggressive treatments required to maintain the vital functions at certain patients determine various side effects, among which those at eye level, have entered our field of interest. In our practice, we identified a side effect which hasn't been reported yet, up to now, in the specialized literature, as being related to the chemotherapy treatment using tamoxifen, at patients suffering from breast cancer (**Figure**).

Clinical case: Patient D.E., female, aged 65, has come for a consultation in 2006, accusing diplopia, for about a month. She declares antecedents with APP: right breast neoplasm, operated in 2005. At the time of the examination, she was undergoing treatment with Tamoxifen.

Particularity of the case: Retinal pigment epithelium detachment, centered, remitted after interrupting the medication – Figure 12.

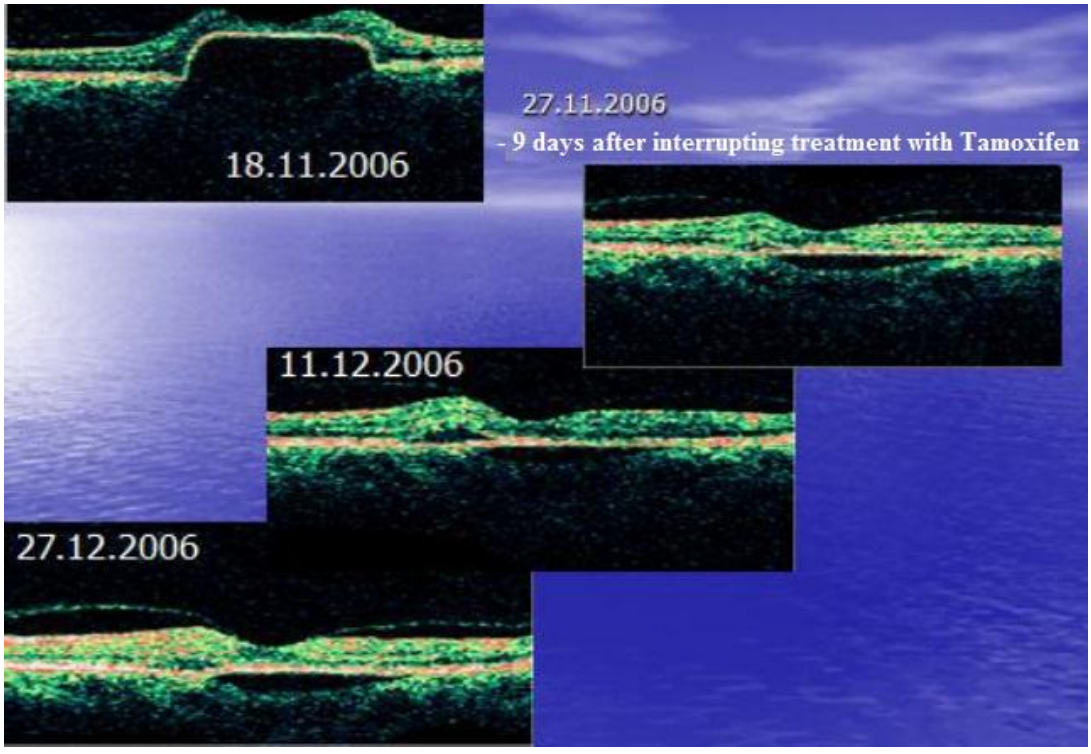

Figure 12: Synthesis of the macular modifications in the presented case

IV.4. Optic nerve drusen - diagnosis and association with glaucoma

The papillary drusen is a congenital anomaly of the optic nerve head: in etiopathogenesis, it represents the deposit of certain mucoprotein globules and muco-poly-carbohydrates that calcify in time, progressively, determining clinical aspects that papillary are interpreted in different ways: hyaline bodies at the level of the disc, pseudo-edema, optic pseudoneuritis. [23, 24]

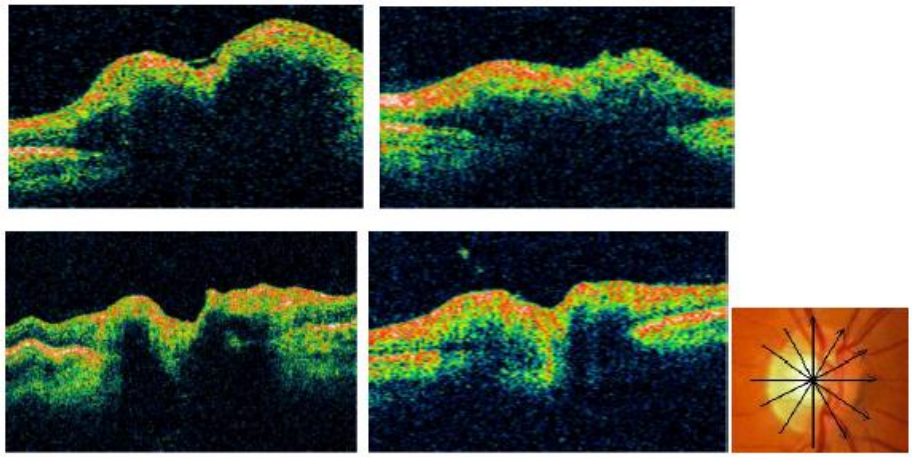

Figure 13: Optical coherence tomography – ONH qualitative aspect, at patients suffering from papillary drusen

The OCT of the optic nerve head shows the prominence of the papilla at all patients (Figure 13); the ONH volume can be measured and observed in time, to evaluate the evolution.

IV.5. Optic nerve pathology in children –modern investigation methods –

Ophthalmological consultations at children are usually performed for refraction vices., strabismus, various causes of red eye or screenings. The possibility of optic nerve pathology is rarely considered, and additional examinations are necessary for diagnosis. A few clinical cases are presented (Figure 14) with significant elements to prove the utility of the OCT in establishing the final diagnosis. [25, 26, 27]

The edematous aspect of the optic nerve may conceal a papillary drusen, and its diagnosis through auto-fluorescence or eye ultrasound avoids performing neurological complex examinations.

The patient suffering from papillary drusen requires periodical control, to measure Pio, visual field and RNFL.

The measurement of the optical fiber layer thickness and the RIM integrated volume, together with the clinical data, can confirm or clear juvenile glaucoma: if the values are "borderline", observing these parameters in time may document the stability or the loss of optical fibers.

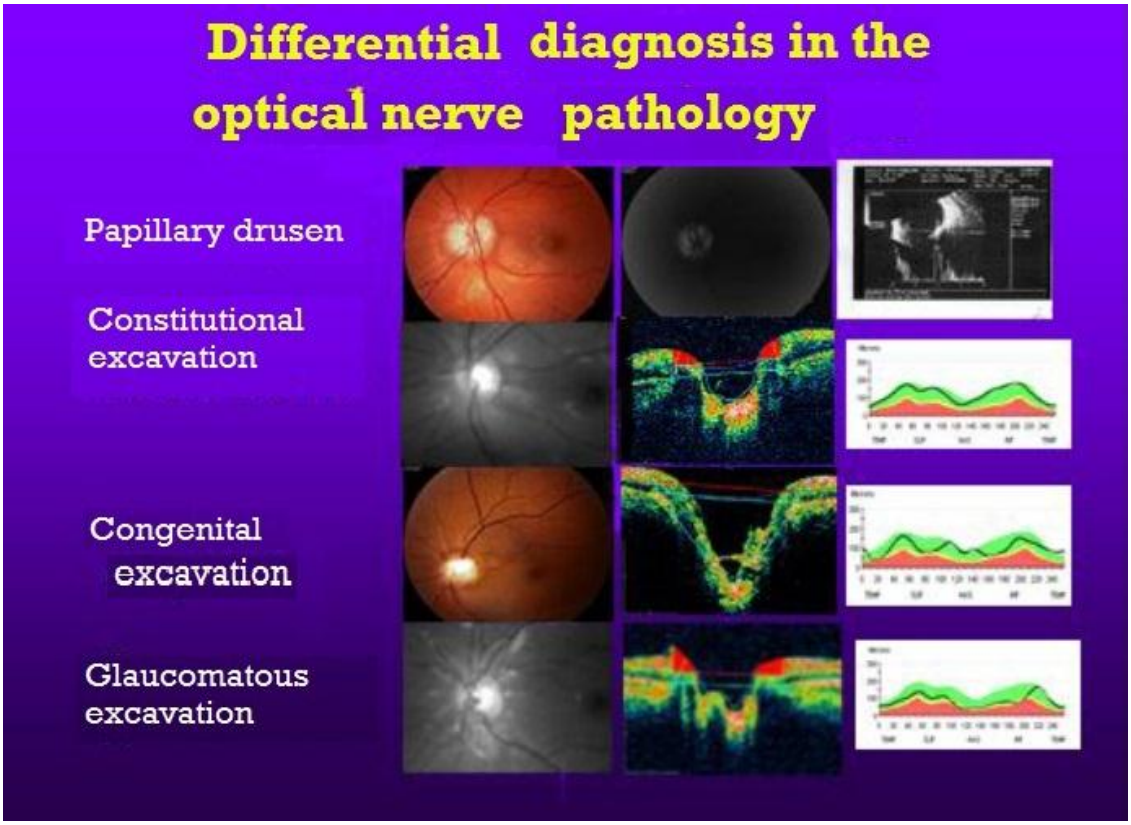

Figure 14: Aspects of the FO, OCT RNFL and ONH, useful ultrasound in the pathology of the optic nerve

IV.6. Complementarity between OCT and angiofluorography in ocular pathology

The combination of *structural* and *functional* information is used in many clinical medical disciplines to **increase the diagnosis accuracy.** The new ophthalmological examination possibilities can be also combined when wishing to understand a more complex pathology. In the presented paper we considered aspects as AFG and OCT in a few groups of ophthalmological disorders. We performed an observation and retrospective study of the selected cases, depending on the association of the two types of examinations used, out of the group of patients consulted in the period of 2006-2008.

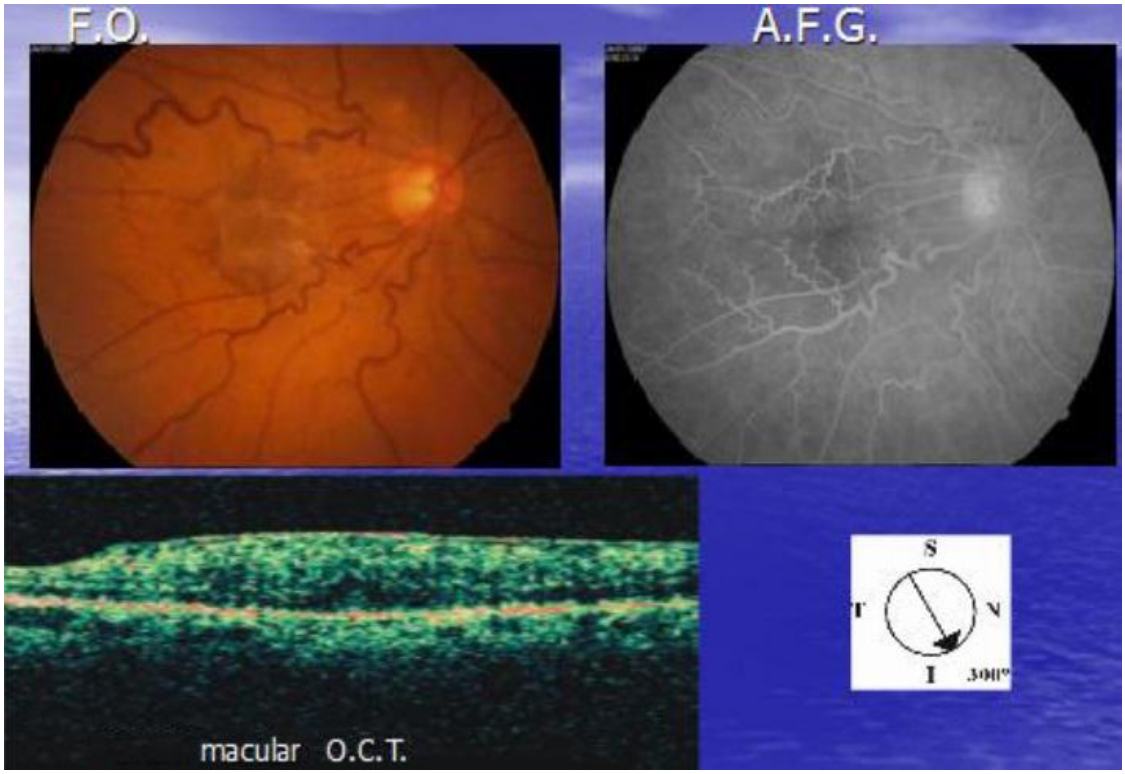

Figure 15: Retinal photography, macular AFC and OCT: patient T.A., aged 65, female, vitreoretineal interface syndrome (epimacular membrane)

The role of imaging exams: [28, 29, 31, 32]

- Combining *physiopathological* information offered by AFG with the *structural* ones obtained through OCT allows **creating a more complete image** of the studied pathology (Figure 15)
- This association of exams (AFG+OCT) can be used to the **diagnosis, prognosis and evolution assessment** of more complex eye disorders, especially in case of maculopathy or disorders of the optic nerve [34]
- They increase the accuracy of the **diagnosis.**
- They allow a better classification/ **staging** of the disease
- **Therapeutic** decision/option
- Storing information / quantification of defects
- **Documentation** / observing **evolution**
- AFG – additional information, as compared to FO and OCT examinations
- OCT can replace AFG in certain situations and it is preferably non-invasive and rapid

- In the diabetic macula edema, only OCT can emphasize the type of edema (diffuse, focal, cystoid, etc) and can help in observing it most effectively [30, 33].

IV.7. OCT - method for the quantification of the optic nerve fibers loss in chiasmal syndromes

We presented the case of a patient suffering from optic chiasmal compression syndrome due to a pituitary tumor, with prevalent visual issues. We analyzed: RNFL thickness and the optic disc RIM (ONH method) as well as the macular thickness (RTM method) – with an time-domain OCT, model Zeiss Stratus 3000 and we assessed the visual field – using automated static perimetry – the Oculus Centerfield perimeter.

We revised and synthesized the published data regarding the visual field defects and the RNFL OCT measurements in optic chiasmal compression. We made a synthetic table, with various associations between clinical data and paraclinical data from hypophyseal tumors, as well as visual field defects and OCT measurements of the optic nerve at these patients.

Using the automated static perimetry, we found bitemporal hemianopsia at the analyzed patient. At both eyes, OCT indicated a general reduction of the RNFL thickness (axone loss in all the four quadrants), but especially in the nasal segment, with “band” atrophy of the optic nerve. The data observed in the case of our patient correspond to the previously published one, considering the dimensions of the tumor and the type of chiasmatic compression. There is an axonal loss at these patients, characterized by a “band atrophy” of the optic nerve, caused by the compression of the optic chiasma (Figure 16). The optical coherence tomography is able to identify this type of lesion of the RNFL and it is an objective test, which can be reproduced, and should be introduced in the compulsory screening protocols for hypophyse tumors, together with computer perimetry. [35, 36]

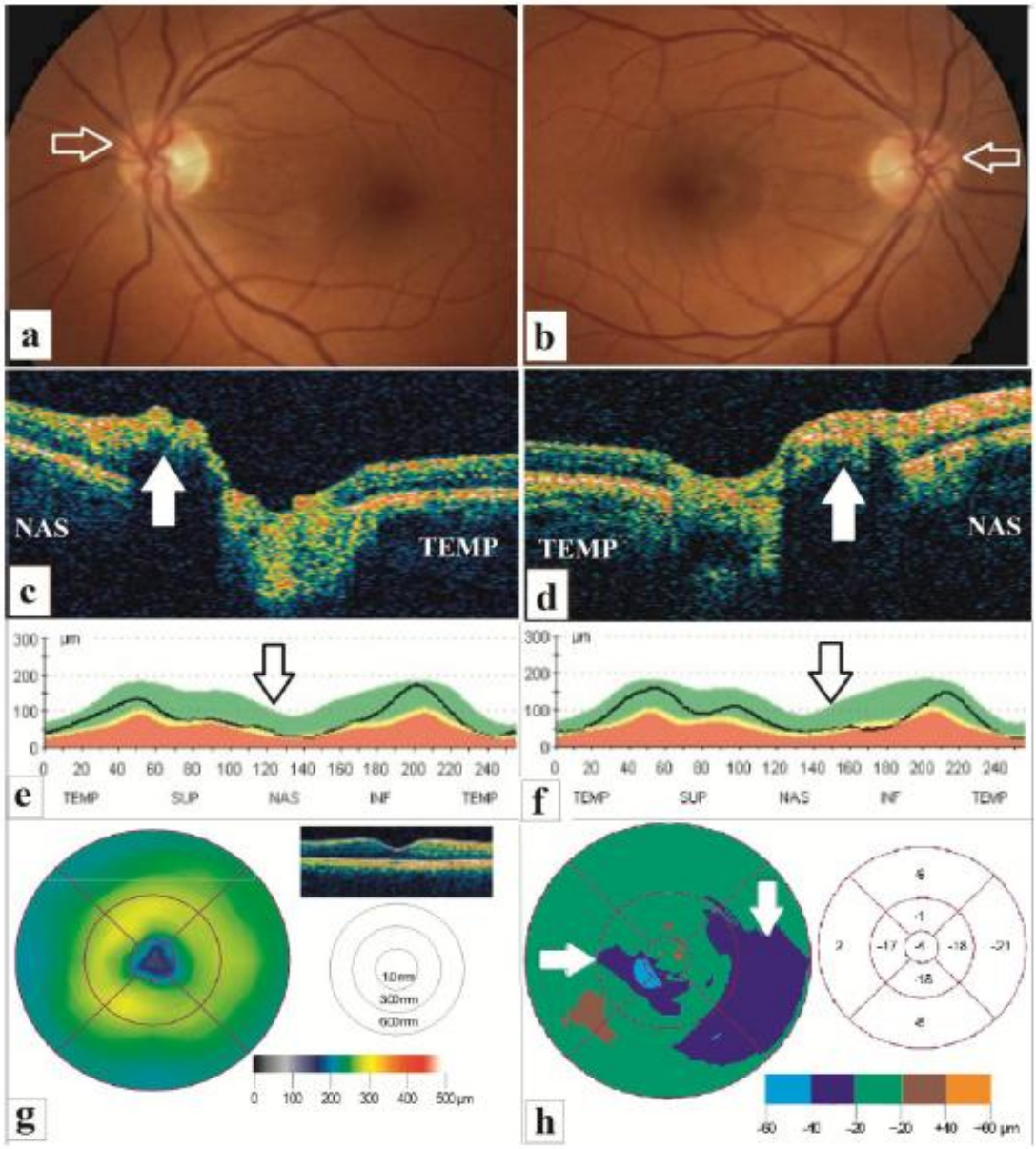

Figure 16:

a, b – **retinal photographs** OS and OD; white arrows indicate a small prominence of the nasal part

c, d – OCT ONH OS and OD, horizontal temporo-nasal line; white arrows indicate a small prominence in the nasal sector;

e, f – OCT RNFL average thickness OS and OD (microns – black line), compared to the statistically normative data base (coloured), in various quadrants: TEMP temporal, SUP superior, NAS nasal, INF inferior; black arrows indicate the reduced thickness in the inferonasal quadrant;

g, h – macular OCT with color codes (bottom right); **g – macular map** (left), **macular line** (upper right) and a diagram containing 1,3 and 6mm diameters scanning circles centered on the fovea; **h** – report **analyzing the thickness differences** in evolution, with colour codes on the map (left); the blue area (indicated by white arrows(shows the decrease of macular thickness during the control after the treatment.

CHAPTER V

STATISTICAL QUANTITATIVE STUDIES ABOUT THE VALUE OF OCT IN SCANNING OCULAR STRUCTURES

V.1. OCT- RNFL particularities in myopic patients

Myopia is more frequent in the domain of refraction defects distinguished among the population, medium and high myopias being associated also with modifications of the retina and choroid.

One of the severe eye diseases associated with myopia is the progressive degeneration of the retinal ganglion cells in glaucoma, being quite difficult to diagnose at myopic patients. [37]

The optical coherence tomography (OCT) – as a non-invasive complementary examination method, has recently imposed, in the ophthalmological practice, a structural detailed analysis of the macula, peripheral retina, optic nerve with the ganglion nervous fibers (RNFL). This measurement is very sensible for the detection of glaucomatous defects (early).

Conclusions:

- There are RNFL thickness variations depending on the ocular refraction, namely a negative linear correlation between RNFL and SE
- There is circumpapillary redistribution of the optic fibers a myopic patients: less temporal, more superior and inferior type
- RNFL thicknesses are inversely correlated with age
- Reduced RNFL thickness in myopic eyes must be carefully examined, because it can be confused with glaucomatous defects
- Since there isn't any refraction vice correction included in the OCT RNFL measurements with the associated normative database – it requires much ATTENTION when interpreting the results
- The equation that can be applied in practice, deduced in our study, is y=138.205+/-3.445x , where y = RNFL thickness, x=SE

V.2. Specular endothelial mycroscopy, Pentacam and Ocular Response Analyser - correlations with OCT

The eye structures are the results of combining the genetic information send from certain loci, belonging to each of the 22 human chromosomes. There are 705 distinct genetic syndromes known, including eye anomalies. Looking in the OMIM catalogue [17] on their full characteristics of these genes, it is easily observed that none of the organs, apparatus or systems of the human organism remains uninfluenced by at least one of them. The same gene simultaneously encodes a certain eye feature as well as certain morphological or functional feature of other organs, inside the human organism.
There is quite little data communicated or published regarding the corneal endothelial cells (healthy or ill). There certainly are genetically determined similarities between the features of the endothelial cells and other features of the eye structures.
In our study group, we intended to observe and analyze the structural particularities of certain corneal diseases and the correlation with the other eye structures. The study group included 201 patients – 402 eyes, of which:

- 10 patients – 20 eyes – with endothelial corneal dystrophy
- 10 patients – 20 eyes – with ectatic corneal disorders (keratoconus – 8 patients, pellucid marginal degeneration – 2 patients)

The devices used to collect data on these patients were:

- **the optical coherence tomograph (OCT),**
- **Nidek endothelial specular microscope** (SEM),
- **Ocular Response Analyzer (O.R.A.**- device for measuring the intra-ocular pressure).

  The calculation of the statistical correlations were made using the SPSS program.

Conclusions [38]:

- Various characteristics of the eyes are inter-dependent
- It is useful to know what type of correlations there are among the eye structures, in order to know what the patient is predisposed to and to recommend the minimum necessary examinations, for a certain diagnosis
- Men have a 10% higher density of endothelial cells (average 2438 vs. 2274) and 10% more reduced polymegathism (average 50 vs. 56), compared to women

- The structure of the corneal endothelium is less correlated to age, while CRF, CH, anterior chamber volume and RNFL, RIM – significantly decrease with age, from the statistical point of view
- There are interesting significant correlation between cell density (↓), and the diameter of the optic disc (↑), between polymegathism (↑) and the rim area/volume (↑) (larger corneal endothelial cells, with higher polymegathism at persons with big optic disc and rim)
- The central corneal thickness, CCT (average 606 vs 553 μ) and corneal reflectivity are ~15% higher than at normal people, in case of dystrophic cornea
- The density of endothelial cells (15%<) (average 2084 vs 2331 cell/mm2), pleomorphism (average 28 vs 36) and the anterior chamber volume (40%<) are lower in corneal dystrophies, than at normal people

In the ectatic corneal disorders, DMP = Pellucid Marginal Dystrophy):

- CCT is lower (on average 466 vs. 557 μ) than in normal people
- PIO, CH and CRF are significantly smaller than in healthy people
- Anterior corneal topography is pathognomonic and sets the diagnosis

V.3. Optic nerve fibers loss (OCT findings) and visual function alteration (measured with computerized perimetry)

Glaucoma is a frequent pathology, under-diagnosed in the current practice and difficult to recognized in early stages. The loss of optic fibers and alterations specific to the visual field are important elements for the diagnosis. There is published data [39, 40] according to which the structure defects of the optic nerve (RNFL defects) precede the functional ones (VF defects).

We intended to make an OCT-VF global comparative analysis, OCT-VF sector analysis, as well as to identify the elements influencing them. We performed a retrospective study, observing 141 patients, analyzing 282 eyes (table 10). We used all the equipment we had available: Visucam Zeiss, Stratus OCT, OCTOPUS perimeter (Octo A 100), ORA tonometer. We performed the OCT-RNFL scan to the patients and the visual field (VF) – "glaucoma fast threshold" protocol. We established correspondences between the RNFL sectors and the VF sectors, as in Figure 17.

Circumpapillary retinal quadrants		Matching results RNFL-VF		Mismatching results RNFL-VF	
		No. of patients	Percentage of patients	No. of patients	Percentage of patients
OD	Superior	92	**65**	49	35
	Nasal	115	**81**	26	19
	Temporal	101	**71**	40	29
	Inferior	76	53	65	47
OS	Superior	90	**64**	51	36
	Nasal	106	**75**	35	25
	Temporal	105	**74**	36	26
	Inferior	71	50	70	50

Table 10: Matching between VF and RNFL, studied by circumpapillary quadrants, at each eye

Conclusions:

The VF-RNFL matches are maximum in the superior, nasal and temporal circumpapillary sectors. The match increases, considering that the RNFL modifications precede the VF ones (Table 3). The global defects are less important than the sector ones (lower correspondence between methods for the global situation) [15]

OCT changes how the patients are approached in practice:

- *Suspects of glaucoma*: either the disease is confirmed or their health
- *Glaucomatous patients*: can be monitored with high accuracy
- *Uncertainties decrease* in diagnosis and observation
- The patient's *trust increases* towards the doctor

1. Correspondence between RNFL and PNF Map

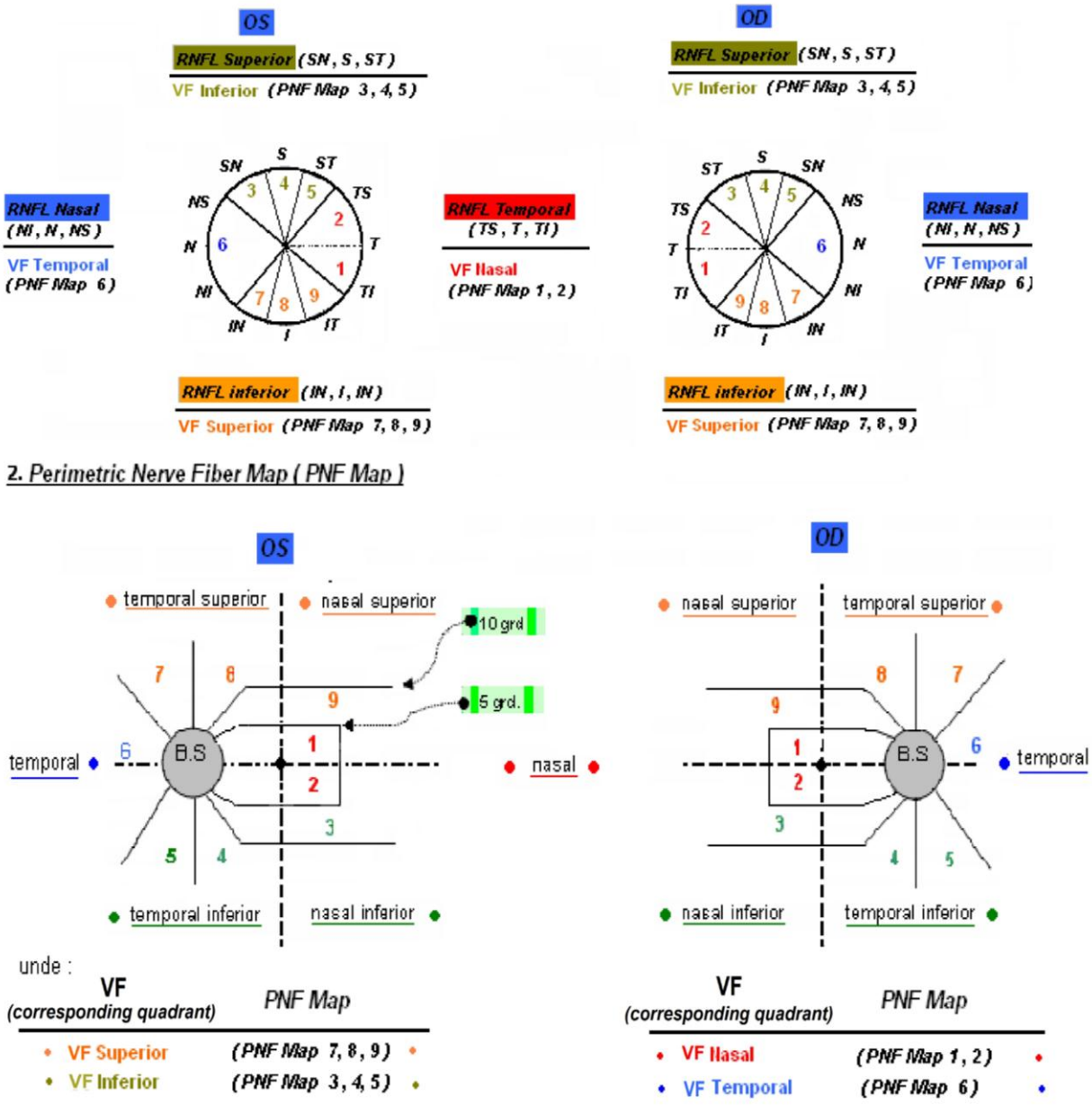

Figure 17: Sectors of visual fields (map of perimeter nervous fibers = PNF MAP) established to correspond to the measured RNFL sectors [40]

V.4. Automated quantification of glaucoma risk with Effort Staging System Scale (ESS), demonstrated by OCT

This chapter shows the necessity of determining two parameters: the intraocular compensated pressure (IOPcc) and that of corneal hysteresis (CH). These two mechanical risk factors, from a physiological point of view, are extremely important because: IOPcc – is the loading factor or the stress factor, while CH – as unloading factor or protection factor. The risk of lesion occurrence in the retinal fiber layer (RNFL) – implicitly the risk of glaucoma – is determine by any unbalance between these factors. [42, 43]

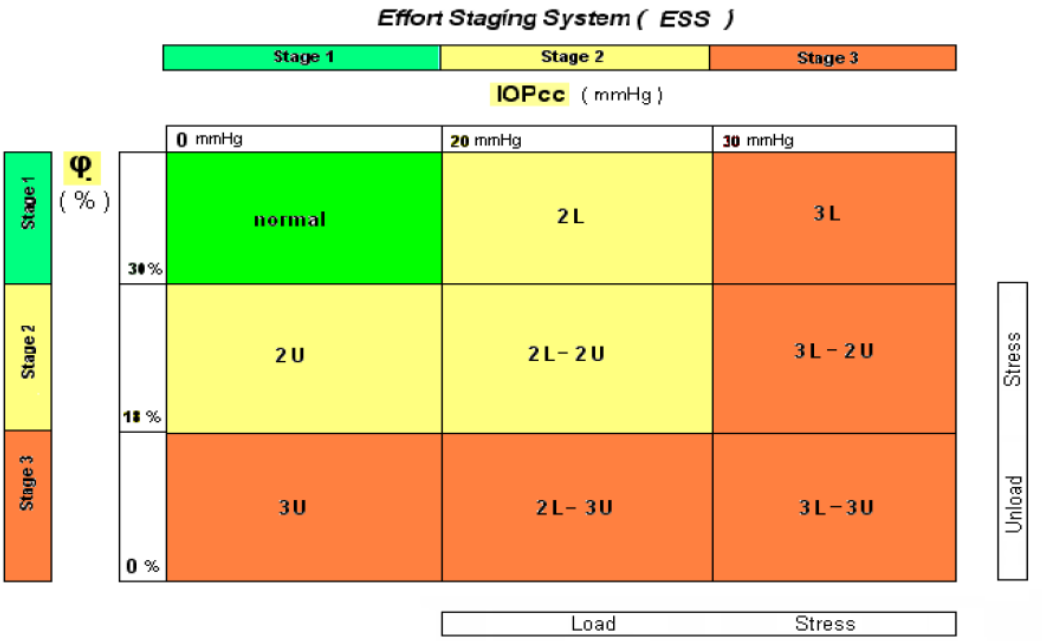

Figure 18: ESS scale (Effort Staging System)

The ESS scale method (Figure 18) improves the possibility to classify examine patients as being normal, or belonging to one of the risk categories: borderline, or pathological. The two examined parameters: IOPcc and the specific amortization ability φ are useful in the daily clinical practice, being reliable indicators of this disease.

The ESS scale represents an objective and quantifiable instrument for the classification of patients suspect of glaucoma. Thus, we can perform an objective assessment of the

eye stress; for example – increased IOPcc associated with a high specific amortization ability do not represent such a severe condition, as opposed to a high IOPg associated with lower specific amortization ability.

V.5. Statistical study of our OCT database

Daily ophthalmological practice means also to divide a large amount of data collected from patients into categories. Current patient symptoms, records of personal data, several different measurements performed during the medical exam, all these for a group of patients that come every day, make up a huge medical database, that the doctor must use. For a higher performance, strategies must be elaborated, this being the reason why there have been attempts to automatically assign patients to different risk categories, such as the ESS scale, previously presented. It is important to know the most important elements and how the collected data is correlated, in order to establish a diagnosis algorithm.

The statistical analysis was made using SPSS 13, where we imported the database file (given in Figure 19), modules for descriptive statistics, bi-various correlations, linear and multiple regression, steps regression, ROC curves, AUC (aria under curve). We also made calculations for Sensibility (percentage of disease positive tests), Specificity (percentage of health negative tests), Positive Predictive Value, Negative Predictive Value, Positive Likelihood Ratio, considering some of the ORA parameters as possible tests in the prediction of fibers loss (average on quadrants).

The 4343 eyes that we have studied belong to a group of patients aged between 8 and 95, with an average of 53.17 years.

Conclusions: [44, 45, 46, 47]

The following are important in the daily medical practice, to make our work easier and to optimize the criteria for assignment to a risk group and for the final diagnosis:

- Introducing automatization methods to categorize patients depending on the measured parameters
- Considering the age as the main element predicting the thickness of the optic fiber layer

	A	B	C	D	E	F	G	H	I	J	K	L	N	O	P	Q	R	S	T	U	V
1	Sex	Varsta	Fibre-S	S N/P	Fibre-N	N N/P	Fibre-T	T N/P	Fibre-I	I N/P	Fibre-Avg	Avg N/P	FIBRE N/P	Fibre 123	Pg	Pc	CRF	CH	ϕ	SCALA	SCALA 123
2	Female	80	295	2	219	2	271	2	314	2	274.7	2	2	1	15	16	10.1	10	0.32	1	1
3	Female	23	342	2	223	2	222	2	282	2	267.3	2	2	1	14	13	11.9	12.6	0.44	1	1
4	Female	67	291	2	271	2	198	2	310	2	267.2	2	2	1	23	24	11.7	9.2	0.20	5	2
5	Female	58	267	2	244	2	306	2	238	2	263.8	2	2	1	24	16	18.7	17.1	0.35	1	1
6	Female	57	275	2	290	2	163	2	327	2	263.7	2	2	1	18	19	10.1	9.3	0.26	5	2
7	Male	60	280	2	310	2	119	2	244	2	238.2	2	2	1	16	17	9.8	9.5	0.30	1	1
8	Female	60	303	2	222	2	177	2	211	2	228.4	2	2	1	22	22	12	10	0.23	5	2
9	Female	22	278	2	168	2	185	2	280	2	227.8	2	2	1	12	13	9.1	10.3	0.45	1	1
10	Female	66	94	1	431	2	41	1	304	2	217.5	2	1	1	16	19	8.5	7.8	0.24	5	2
11	Female	78	124	2	126	2	370	2	218	2	209.6	2	2	1	21	24	9.7	7.6	0.18	8	3
12	Female	55	227	2	153	2	222	2	217	2	204.8	2	2	1	19	21	9.5	8.2	0.22	5	2
13	Female	22	258	2	201	2	117	2	232	2	202	2	2	1	13	15	9.3	9.8	0.37	1	1
14	Male	59	226	2	125	2	287	2	162	2	199.9	2	2	1	18	18	10.7	10	0.28	4	2
15	Female	58	199	2	209	2	197	2	179	2	196	2	2	1	25	22	14.8	12.3	0.25	5	2
16	Male	58	230	2	170	2	161	2	211	2	193.2	2	2	1	9.6	10	9.2	11.1	0.58	1	1
17	Female	57	234	2	94	2	130	2	290	2	187.2	2	2	1	14	12	12.6	13.4	0.47	1	1
18	Female	31	187	2	164	2	149	2	232	2	182.9	2	2	1	16	12	13.6	14.1	0.45	1	1
19	Female	70	244	2	171	2	88	2	227	2	182.5	2	2	1	26	24	14.6	11.6	0.22	5	2
20	Female	34	216	2	117	2	212	2	157	2	175.5	2	2	1	21	22	11.3	9.5	0.23	5	2
21	Male	62	229	2	146	2	174	2	151	2	174.8	2	2	1	18	20	9.3	8.3	0.23	5	2
22	Female	31	202	2	136	2	123	2	211	2	169.3	2	2	1	18	13	15.1	15.1	0.42	1	1
23	Male	62	229	2	147	2	133	2	151	2	165.1	2	2	1	18	19	10.2	9.4	0.27	4	2
24	Female	55	192	2	131	2	154	2	184	2	165.1	2	2	1	15	16	10.2	10.3	0.34	1	1
25	Male	63	197	2	140	2	93	2	227	2	164.4	2	2	1	11	14	7.2	8.3	0.38	1	1
26	Female	72	228	2	113	2	117	2	186	2	161.3	2	2	1	7.5	8.1	8.8	11.4	0.76	1	1

Figure 19: Database used in the statistical calculations

(first part/beginning, shown in print-screen)

- Calculating the corneal dumping coefficient (ω) and enclosing them in the ESS scale as elements for the optimization of categorizing patients with glaucoma risk
- Considering IOPcc a better predictor for the RNFL loss than IOPg, especially at higher values of IOP and especially at ages over 40
- The ages is statistically significantly correlated (in the studied batch) better with the average RNFL thickness, but also with that by quadrants, in the following order: S, I, N, T
- The lowest correlations, but still statistically significant, are those of CRF with age and RNFL thickness (globally and by quadrants)
- correlations of IOPcc, CH and ω with RNFL are generally stronger that correlations of IOPg
- the best predictors for glaucoma, with negative correlation, are the associations: age+IOPc, age+CH, Age+ ω, but they are still responsible only for 11% of the RNFL variability (Fiber avg), if we consider the entire batch
- the association age + corneal dumping coefficient (ω) as well as the association age – IOPcc have the highest predictive value, similar to the patient subgroups studied and prove to be responsible for 22-23% of the variation of fiber thickness at IOPg over 24-25 mmHg
- age can predict >30% of RNFL modification at patients over 40, with values of IOPg over 30 mmHg (R square 0.32)
- the association age - ω increases the possibility of predicting the RNFL variation (R square 0.39) at the same batch of patients, and is the best predictor found in the study
- the calculation of ROC curves and corresponding AUC (aria under curve) show that, among the parameters that best fit the diagnosis elements of glaucoma are: age, CH, IOPcc, ω, ESS scale

CHAPTER VI

FINAL CONCLUSIONS

The studies presented are part of the overall effort of reorganization, on the new bases, of medical knowledge, providing, after a necessary deepening of the OCT knowledge, both the original scheme of interpretation of data provided by this new technique, a new diagnostic approach in daily medical activity and comparative statistical studies with data from the literature.

Three main research directions have emerged:

1. Setting OCT examination protocols, algorithms to interpret the data from the scans and personal analyzing sheets for daily practice.

Using data published till, we built a synthesis used as a reference for all subsequent work. For each structure of interest in the posterior pole, which has to be seen in daily practice, we have carefully established criteria for classification in normal or defined margin of deviation for different pathologies. Such were systematized both language analysis and ranges of values for each parameter measured in the optic nerve, the retinal nerve fiber layer (RNFL), optic disc (ONH) and macula. Finally, many syntheses have come, several worksheets that have proven useful over time as the number of patients investigated rose more than expected, and collected data would otherwise be difficult to be managed.

2. Qualitative studies of OCT scans:

OCT scans proved an invaluable help in situations where the patient would have been difficult to be classified as normal or pathological. Thus:

• I had a chance to make a diagnosis almost impossible to be certain without this "histological" analysis : cone dystrophy;

• I describe new semiological OCT elements useful in the diagnosis of pigmentary retinopathy

• I have described a new type of complication in a patient treated with tamoxifen

• optic disc drusen - a clinical issue that involves multiple laboratory investigations for differential diagnosis - has become more recognizable with OCT

• many of the pathologies in children - otherwise hard to classify due to the difficulties of collaboration became more easily diagnosed by rapid and noninvasive OCT scans

• OCT data brought novelties in medical knowledge in a chiasmatic syndrome; they have been very useful in the case diagnosis and follow-up

• Important structural data provided by OCT, with functional information from fluorescein angiography, have allowed the diagnoses of scientific accuracy and a better understanding of the physiological and morphological pathology of ocular diseases, this time studied "in vivo" ! (not as learned in college laboratory)

All the data collected were completed in papers, communicated at conferences and congresses of ophthalmology conducted nationally or internationally during this period; some of which are published or in press.

3. Quantitative studies and statistical analysis of data collected

We practice an "evidence-based medicine" ; data should be collected, systematized and analyzed. We therefore studied the extensive database accumulated with technical support for high accuracy, and we were able to outline new elements useful for the diagnostic in daily medical practice:

• new features of OCT data collected from patients myopic

• correlation between OCT data and information provided by other diagnostic tools (corneal endothelial specular microscopy, Pentaclam, Ocular Response Analyzer (ORA)

• quantifying loss of the optical fibers in parallel with altered visual function measured with computerized perimeter

• I imagine a new automated scale for glaucoma risk classification in patients, according to the data from OCT and ORA

• using OCT parameters we calculated the value of routine parameters picked from ophthalmologic examinations (eg. Intraocular pressure, corneal characteristics, age) as risk factors for glaucoma (disabling disease if not diagnosed early)

The most important results of the work I select:

- Summaries and worksheets for daily practice with OCT scans
- New features that complete the clinical pictures of the pathologies mentioned in qualitative studies conducted
- There RNFL thickness variations depending on ocular refractive status, namely a linear relationship between RNFL and spherical equivalent (SE)
- Is this a circumpapilary redistribution in myopic optical fibers: temporal fewer, more upper and lower
- Correlations between ocular structures described are useful to know what are the morbid predisposition in patients and recommend minimum investigations required for diagnosis

- Concordances between visual field (VF) and RNFL sectors are higher circumpapilary, nasal and temporal, minimum in the lower quadrant; Global defects of VF or OCT findings are less important than the sectorial
- O.C.T. change the approach of patients in practice: for glaucoma suspects: confirme disease or ensure that they are healthy; glaucomatous patients: can be monitored with high accuracy, reduces uncertainty in the diagnosis and follow-up, increases patient trust in physician
- Calculation of corneal dumping coefficient (ω) and ESS scale proposed method improves the ability to automatically classify patients examined as normal (borderline) or pathological (in the glaucomatous disease)
- Age is the main predictors for optical fiber thickness; It is statistically correlated well with the average thickness of the RNFL and also with the one-quadrant: S, I, N, T
- The lowest yet statistically significant correlations are of CRF with age and RNFL thickness
- Correlations between IOPcc, CH and ω with the RNFL are generally stronger than the correlations with IOPg
- The best predictors for glaucoma, with negative correlation are associations: IOPc age + age + CH + ω years, but they still are only responsible for 11% of the variability in RNFL
- association Age + corneal dumping coefficient (ω) and the association age + IOPcc have the highest predictive value, similar in subgroups of patients studied and found to be responsible for 22-23% of the variation in thickness of fibers in IOPg over 24-25 mmHg
- Age can predict> 30% of RNFL change in patients over 40 years with values above 30 mmHg IOPg (R square 0.32)
- Association of age - ω increase the possibility of predicting the variation RNFL (R square 0.39) in the same group of patients, and is the best predictor found in the study

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List of publications :

ISI Journals:

ISI paper accepted for publication:

1. **Demea Horea**, Demea Sorina, Holonec Rodica, Anca Demea - *The biophysical properties of cornea in analyzing glaucoma risk* - in Romanian Reports in Physiscs; impact factor 2013/2014 =1.137

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