OPTICAL COHERENCE TOMOGRAPHY BIOMARKERS IN WET AGE-RELATED MACULAR DEGENERATION

PhD Thesis

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V. Katona M, **Kovacs A**, Degi R, Nyul LG. **Segmentation of Subretinal Hyperreflective Material and Pigment Epithelial Detachment Using Kernel Graph Cut.** In: Burduk R., Kurzynski M., Wozniak M. (eds) *Progress in Computer Recognition Systems. CORES 2019.* Advances in Intelligent Systems and Computing, vol 977. pp.: 98-106, Springer, Cham.

INTRODUCTION

The globally experienced growth of life expectancy has led to an increase in the number of age-related diseases, thus age-related macular degeneration (AMD) has become the leading cause of vision loss in the Western World, and a health problem worldwide. Because of the large prevalence of AMD, the proper management is crucial.

AMD can be divided into dry (nonexudative) form that accounts for approximately 90% of all cases and wet (exudative, neovascular) form that accounts for the remaining, but more severe and rapid cases of vision loss. Although the exact pathogenesis of AMD is not yet fully understood, vascular endothelial growth factor (VEGF) plays a central role in the development of the wet form. The first choice of treatment for wet AMD is anti-VEGF intravitreal injection, but as a chronic condition, the injection should be repeated. Early diagnosis and rigorous monitoring are the key for successful management of AMD. The question may arise: how to diagnose early and monitor rigorously? The answer was optical coherence tomography (OCT). OCT imaging can visualize the layers of the retina and the effects of the disease, the so-called OCT biomarkers, such as subretinal/intraretinal fluid accumulation (SRF/IRF), pigment epithelial detachment (PED), outer retinal tubulation (ORT), hyperreflective foci (HF) or subretinal hyperreflective material (SHRM). Biomarkers are providing information about the activity of the disease; therefore, their assessment is the key to make adequate decisions for treating, re-treating or observing a patient.

Despite the extensive knowledge about OCT biomarkers provided by literature, there are questions still to be answered. Our work concentrated on these biomarkers from a clinical point of view. At first our attention was turned to a then relatively novel biomarker, the ORT, investigating its characteristics and potential role in treatment prognosis. In addition, automated algorithms were developed, automatically identifying and quantifying OCT biomarkers. Utilization of an automated algorithm could result in a considerably faster and more precise measurement, thereby exploring further correlations between these biomarkers and their response/effect to therapy, leading us to better understand the disease.

PART I: OUTER RETINAL TUBULATION

BACKGROUND

ORT as per definition is a hyporeflective, branching tubular structure with hyperreflective borders within the outer nuclear layer of the retina. ORTs have been observed in many retinal diseases, including exudative age-related macular degeneration. They can be classified as either open (incomplete closure with curving external limiting membrane at the ends, horizontally elongated shape in cross-section) or closed (completely encircled, oval shape in cross-section) ORTs. ORT

can be mistaken for intraretinal cysts or subretinal fluid, thus leading to an unnecessary overtreatment in exudative AMD. The ORT prevalence in wet AMD is low at the time of first diagnosis but over time during anti-VEGF therapy its prevalence increases. The importance of ORT as an OCT biomarker for photoreceptor degeneration is due to its connection with reduced visual acuity. It has also been reported that ORTs develop above areas of SHRM or atrophy. SHRM usually represents either a type II choroidal neovascular complex or is the consequence of it.

The aim of our study was:

- to investigate the prevalence of ORTs in eyes with neovascular AMD undergoing treatment either with ranibizumab or aflibercept

- to examine the changes in the frequency of injections before and after ORT appearance

- to assess the presence of subretinal hyperreflective material and its relationship with ORT.

METHODS

This retrospective study was performed at the Medical Retina Unit of the Ophthalmology Department, University of Szeged, Hungary. The study was approved by the Institutional Review Board of University of Szeged and was in accordance with the ethical standards of the Declaration of Helsinki. Treatment-naïve exudative AMD patients were enrolled in the study. For the ranibizumab group, enrollment took place between October 2014 and April 2016, while patients in the aflibercept group were enrolled between April 2015 and April 2016. The mean follow-up period was 16.3 months and 9.2 months (ranged from 6-24 months and 6-12 months) in the ranibizumab and aflibercept groups, respectively. During each visit a comprehensive ophthalmic examination was carried out including best-corrected visual acuity (BCVA, Early Treatment Diabetic Retinopathy Study (ETDRS) score) assessment, slit-lamp biomicroscopy, dilated funduscopy and SD-OCT examination (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany). Treatment regimen for both ranibizumab (0.5 mg) and aflibercept (2 mg) started with 3 monthly injections. After initiation phase the ranibizumab group was treated by a pro re nata (PRN) regimen with follow-up visits scheduled monthly. The retreatment criteria in the PRN period consisted of any SRF or IRF on OCT, or new haemorrhage on funduscopy. In the aflibercept group follow-up after the loading phase was scheduled every two months, treatment was given at each follow-up. The above regimens were in accordance with the available treatment guidelines in Hungary at the time of the study.

For OCT imaging, a pattern size of 5.8 x 5.8 mm was applied with 25 B-scans, using the „follow-up" mode. By manual review of the scan volumes the first appearance of the ORT was determined. Presence of ORT was assessed at fixed time points at baseline, month 6 and 12 in both groups and at months 18 and 24 in the ranibizumab group. Two independent retina specialists evaluated the images. In case of incongruity, a third retina specialist was involved. During the evaluation of OCT

scans, both open and closed forms of ORT were considered an ORT positive case. The readers also identified the presence or absence of SHRM on SD-OCT images at treatment initiation.

Statistical methods

The BCVA was compared across the two groups using the Mann-Whitney U-test. The survival analysis for ORT development was analyzed by a Cox proportional hazard model. We analyzed the correlation between the presence of SHRM at treatment initiation with the development of ORT by Chi-square test and calculated relative risks. The injection rate was calculated only in the PRN treated ranibizumab group due to the fixed 2-month therapeutic regimen of aflibercept. We assessed the injection rate before versus after the appearance of ORT and compared using the Mann-Whitney U-test. In order to correct bias rising from the unequal follow-up time (some patients had a higher number of injections due to longer follow-up), monthly injections were calculated so that follow-up time was divided with the number of injections. A p-value of $p<0.05$ was taken as statistically significant.

RESULTS

In the ranibizumab group 184 eyes of 179 patients were evaluated, with a median age of 74 years (range 51 to 88), while in the aflibercept group there were 52 eyes of 51 patients with a median age of 75 years (range 58 to 87). The mean baseline best corrected visual acuities in the two groups were (mean±SD) 59.16±13.9 (median 61) and 53.96±13.54 (median 55.5) ETDRS letters in the ranibizumab and aflibercept group, respectively (Mann-Whitney U-test $p=0.083$). The BCVA at the end of the follow-up was 57.19±20.19 (median 63) and 59.46±15.54 (median 64) ETDRS letters in the ranibizumab and aflibercept group, respectively (Mann-Whitney U-test $p=0.69$).

In the ranibizumab group ORT was observed in 17.4% of cases at baseline, in 33.7% of cases at month 6, in 45.3% of cases at month 12, and in 55.3% and in 60.8% of cases at months 18 and 24, respectively. The ORT prevalence in the aflibercept group was 23.1% at baseline, 40.4% at month 6, and 50% at month 12.

The survival analysis showed no significant difference between the ranibizumab and aflibercept treated groups in terms of ORT development ($p=0.79$, hazard ratio 0.92).

As per the injection rate, mean injection number per month before ORT appearance was 0.37±0.17, while after ORT development decreased to 0.21±0.17 (Mann-Whitney U-test $p=0.004$).

In the ranibizumab treated group ORT developed in 85 eyes of 139 eyes with SHRM (61.15%), while without SHRM (45 eyes) ORTs were found merely in 10 eyes (22.2%) corresponding to a relative risk of 2.75. ($p<0.01$). In the aflibercept treated group 55.81% of eyes with SHRM developed ORT (24 eyes of 43). No ORT developed in the eyes without SHRM (out of 9 eyes), consistent with a relative risk of 11.14 ($p<0.01$).

DISCUSSION

In the present study, treatment-naïve exudative AMD patients treated with ranibizumab and aflibercept were evaluated regarding the presence of outer retinal tubulation. Altogether 236 eyes were followed in both groups with no statistical difference between the baseline characteristics of the two groups considering age and BCVA.

The prevalence of ORT continuously increased during the follow-up period, in both groups. In the ranibizumab group its prevalence almost quadrupled at the 24-month follow-up, while there was a doubling in the aflibercept group in 12 months.

To our knowledge, our study was the first to report results in treatment naïve patients treated with aflibercept and its connection with ORT development. The Cox proportional hazard model analysis suggested that there was no difference between the two in-label therapies, ranibizumab and aflibercept regarding the prevalence of outer retinal tubulation.

A statistically significant difference was found in the monthly injection rate before and after the appearance of ORT in the ranibizumab treated group. These results suggest that a decrease in the retreatment rate can be expected at patients developing ORT, which may be a critical clinical marker.

There was a statistically significant connection between ORT development and the presence of SHRM at treatment initiation. In case SHRM was present, the chance of developing ORT was 2.75 and 11.14 higher in the ranibizumab and aflibercept groups, respectively.

PART II: AUTOMATIC IDENTIFICATION OF OCT BIOMARKERS

BACKGROUND

Retina specialists decide whether to treat or to observe a wet AMD patient relying on the information provided mainly by the OCT machines. Main criterion of the retreatment process is based on the recurrence of fluid (SRF, IRF) detected on OCT scans. However, consideration of other biomarkers could be expedient. Reports revealed that any growth in size of PED indicates urgent anti-VEGF therapy and therefore should be monitored precisely. The importance of SHRM lies in its connection with visual acuity, as increased thickness of SHRM and subsequent scar development is associated with decreased visual acuity and/or long-term visual loss. A decrease in retreatments can be expected upon the appearance of ORTs on OCT scans. In 2009, a new OCT biomarker was reported in exudative AMD, the hyperreflective dots, also known as hyperreflective foci (HF). Reports (based on manual HF counting often in a single B scan) demonstrated that HF response rapidly to anti-VEGF therapy, and were also found to be the first detectable change for

each clinical recurrence, even before fluid accumulation, meaning that the determination of the number of HF can be a potentially more sensitive biomarker than the fluid reappearance.

Still, evaluation of all the biomarkers supplied by OCT and integration of this data from each scan of the retina for every patient treated is no longer feasible for an ophthalmologist, and can only be realized with the help of classical image processing and artificial intelligence.

Hence our aim was to create algorithms to automatically identify biomarkers, namely:

SRF/IRF; PED; SHRM; ORT and HF.

METHODS

Our work was based on a cooperation with a group of image processing computer scientists from the Department of Image Processing and Computer Graphics, University of Szeged.

The first step of the process was to gather clinical data for the project. Our studies were carried out in accordance with the principles of the Declaration of Helsinki, and it was performed with the ethical approval of the Institutional Review Board of University of Szeged. During the 4 years course of the study, data of 28 eyes of 28 patients diagnosed with wet AMD were retrospectively selected at the Department of Ophthalmology, University of Szeged. These patients were either treatment-naïve or treated with anti-VEGF injections. SD-OCT volume scans with a quality score above 16 were acquired using a Heidelberg Spectralis OCT. 36 recordings from 28 patients were obtained, with parameter sets from everyday clinical practice: 14 SD-OCT sequences contained 49 B-scans, and 22 sequences contained 25 B-scans, giving 1236 B-scans altogether. The dimensions of each OCT image were 6 by 6 mm, a resolution of 512 by 496 pixels (pixel size 11.45 and 3.87 μm).

The biomarkers were annotated by two independent graders (ophthalmology trainees), previously educated by retina specialists using particular definitions for each OCT biomarker examined. The software used for annotation was the Medical Imaging Interaction Toolkit. After grader annotation, images were transformed using various image processing techniques. The methods presented are based on both classical image processing operations and deep learning approaches, involving new ideas and combining them with generally known techniques.

First we had to delineate the boundary layers of the retina, namely the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE), then search for an approach for measuring a newly introduced non-biomarker abnormality, the layer distortion, which is caused by either accumulation of SRF or the elevation of PED or SHRM, or all of these together.

Delineation of boundary layers: ILM/RPE

Here we introduce two methods to delineate the boundary layers of the retina.

1. *Algorithm based on vertically projected data*

Noise filtering and contrast enhancement was applied by using a fuzzy operator. To avoid false detections caused by retinal vessel shadows, the image was divided into columns with fixed width size of 10 pixels (based on our observations that the maximal width of detected blood vessel shadows was 10 pixels). The next major step of our proposed method was calculation and analysis of the vertical profiles of these columns, because large intensity steps in pixel density are assumed to correspond to change of tissue. To further smoothen the signal, we applied the Savitzky-Golay filter. The algorithm chose the most important local minimum in the top and bottom of that given image column (in our case the ILM and RPE) from the projected data to identify the possible inner and outer boundaries. In the last step, with the bars of image columns next to each other we filtered out the outliers and fitted a curve to the remaining points, drawing the possible ILM and RPE.

2. *Graph-cut based approach*

The vertically projected data approach showed some inappropriate results in layer detection, especially when distortion due to PED or SHRM was present, thus we upgraded it, with keeping some steps of the previous idea, resulting in better outcomes. Graph cut is a semi-automated method that requires seed points. It works as a connection network and with the help of clustering technique, the seed points were automatically determined. The clusters of pixels are based mainly upon their intensity and proximity from each other. In higher quality images, 5 clusters were isolated empirically, while in other cases this number was increased. With the help of graph cut, partitioning was optimized resulting in a better classification. The ILM can be determined using a simple Otsu thresholding because the foreground and background (the vitreous and retina) can be clearly distinguished in the clustered image. For the designation of RPE the previous method based on vertical projection was applied. Outlier points were extracted again, and a shape-preserving piecewise cubic spline interpolation was used to determine the RPE layer.

Evaluation and results

The algorithm was evaluated and validated during comparison of its results against the manual delineations of the graders (7 annotated sequences, 343 B-scans altogether), calculating the mean, maximum and standard deviation of boundary errors for each surface and producing an average result of 1,98, 16,57 and 0,94 pixel respectively. In most cases, the mean errors were under 2 pixels and deviations were insignificant between layers delineated by the annotators and the boundaries determined automatically. The greatest advantage of our proposed method is its simplicity, using plain image processing operations that can be highly parallelized, without relying on many parameters difficult to tune.

Measurement of retina layer distortion

The detection and determination of start and end points of distorted regions is a useful prior information for biomarker identification. From previously defined ILM layer points we select the highest point. Using this point, the image is split into two parts, left and right retinal segment.

Lowest ILM points were also determined in the right and left retinal segment and with lines fitted to these side points and the previously defined outer boundary layer (RPE), the starting and end point of the distortion were defined.

SRF/IRF

A method was developed that could simultaneously segment and differentiate fluid compartments. An edge-preserving **anisotropic diffusion filter** was utilized to eliminate various effects of artifacts and image noise. With **quantization** the grayscale image was classified into five intensity levels. During the **binarization** step, the brightest image points were kept, which corresponded to fluid regions. In the next phase an edge-based smoothening with **active contour** process was utilized. Possible important objects like SRF and IRF were identified, but false segments likewise, which needed to be separated from each other. The classification of these objects was based on three criteria at the given target level: the location of the object within the retina [next to the hyperreflective outer boundary (RPE or SHRM)] → SRF, *OR* further from the RPE in the neuroretina → IRF; whether the layer is distorted → SRF, or not → IRF; the extent and the shape of the object (smaller oval shape →IRF). False segments also appeared in the image, commonly caused by retinal vessel shadowing, but considering the fact that these are usually small objects, they can be removed with an area-based filtering.

Evaluation and results

The annotations were not yet available at this stage of the research, so a visual comparison was made of our results with the outcome of two different methods (both segmenting IRF) from the literature, re-implemented by our research group according to the original papers. Both literature algorithms and our approach applied various **simple** classical image processing solutions but starting the biomarker segmentation with defining the boundary layers was the only similarity between them. The segmentation results of the method developed by Wilkins were almost the same as ours, but in many cases, it kept false objects. The other method from literature by Wieclawek detected fewer possible IRF regions. In contrast, our method used dynamic requirements based on prior information, thereby these mistakes could be eliminated. In addition, our algorithm could distinguish IRF and SRF from each other marked with a different color.

PED

PED is a separation of the RPE from the underlying Bruch membrane. With the help of our graph cut based approach the boundary layers were determined (the elevated RPE was found) and using the layer distortion measurement method the start and end point of distortion (in this case the RPE elevation) was located. In order to identify a PED, the original position of the RPE was needed to be defined in the distorted region. The points of the RPE layer were taken until the previously detected starting point of the distortion was reached in both sides and a quadratic curve was fitted to these data. The height of the PED can be defined as the distance between the maximum point of the distorted zone (maximum point of PED) and the pertaining minimum point of the potential normal layer. The extent of the PED can be calculated from the enclosured area.

SHRM

In early stages of the disease the border (RPE) of the PED is clearly distinguishable from the SHRM and can be separated from each other. Nevertheless, due to fibrosis of the neovascular tissue, the SHRM and the vascularised PED become isoreflective and the location and presence of RPE will be unclear. In these cases, the abnormalities are so inseparable that they are managed as one structure (PED+SHRM).

Classification of PED vs. SHRM

To localize these biomarkers, we used our graph cut technique with clustering. These biomarkers are located around the RPE layer, along or near the distortion (determined utilizing the previous approach), so clusters are sampled from these areas. To reduce the clusters to the sought segments only, our prior technique was applied of the possible fluid areas to exclude them. We investigated in a specific range around the RPE layer, since SHRM is located above the RPE in the subretinal space. For this, a threshold was determined using the thickness of the retina. The clusters above the RPE are separated as SHRM, and underneath it as PED.

Evaluation and results

594 B-scans in 18 recordings were available for evaluation. The results of our method were compared with the annotations produced by the graders, using the Dice coefficient and Recall metrics. Most of the errors committed by our algorithm were detected in the parts, which where annotated as PED+SHRM by the graders. Even so, the average Dice coefficients were above 0.75 in both cases and the Recall was 0.93 for PED and 0.77 for SHRM. This means that to segment PED and SHRM a complex system with a large image database is not definitely necessary.

ORT

To our knowledge, our study was the first to report methods of automatic identification for ORT segmentation. Two sorts of approaches were tried: a classical image processing technique and a machine learning method.

Detection using classical image processing operators

The ORT has hyperreflective border with a hyporeflective content, thus our procedure is based on finding the hyperreflective points of its border. Using Wiener filter the image noise was reduced, then applying a Hessian detector the reflective points were localized. Since ORT is in the outer nuclear layer, within the distorted retina region or its neighborhood, we used our prior method for distortion location and also calculated the retina thickness (knowing the boundaries of the retina with our graph cut method) keeping those points only located in the outer third of the retina. Previously identified SRF/IRF were excluded using their detection methods. After this step, points that were part of an object were retained, and their distance map was computed. The map was thresholded and finally the convex hull of the objects was computed.

ORT localization with neural network – i.e., machine learning method

The previously presented method based on classical image processing operators was overly meticulous against more diverse images, thus a more general approach was developed, the convolutional network (CNN). 8 sequences containing 320 B-scans were annotated by each grader, but for the network training only the ORT positive images were used, ergo 132 scans altogether. Since the available amount of training data was small, real time augmentation techniques were administered to raise the data, thus reducing overfitting. The techniques for augmentation were rotation, horizontal mirroring, shearing, and vertical and horizontal shifting. To save computation time, the images were resized (220×256 pixels), and the intensities were normalized and then standardized. Nested cross-validation was applied for hyperparameter tuning and for measuring the test error. The original version of the U-Net architecture, a type of CNN, was used, but slightly modified: reducing the number of layers - to accelerate training time; doubling the number of filters in each layer - to supply larger capacity to the model; administering Dropout between all convolutional layers but the last two - to prevent overfitting. Stochastic gradient descent was used for optimizing the loss function.

Evaluation and results

To create a union of annotations (a basis for statistical analysis) for the images, the masks of the graders' annotated image sets were combined using a logical operator. The object level Dice coefficient was better than the global one, suggesting that if ORTs were present the model could segment them properly. The object level Recall reached the performance of graders with 0.847, meaning that our model can assist ophthalmologists to identify ORT in OCT images. The reason for mistakes were usually elongated open-type ORTs.

HYPERREFLECTIVE FOCI

For the automatic identification of HF, 8 different machine learning techniques (neural networks) were developed, consisted of 4 basic types: Artificial Neural Networks (ANN), Deep Rectifier Neural Networks (DRNs), Convolutional Neural Networks (CNN), and Fully Convolutional Neural Networks (FCN), and 4 modified types: Pixel ANN and Pixel DRN (just using raw pixel data to validate the quality of the extracted features), Split DRN (containing a split first hidden layer; half of the neurons being connected to the pixel input and the other half being connected to the feature vectors), Dice DRN (trained with the same error measure that was used in the final evaluation). When constructing our automatic segmentation framework, data processing was divided into data preparation, feature extraction, training, and evaluation. The 8 different methods required different pre- and post-processing steps.

Data preparation

Two sets of OCT data were used for our study. The **first data set** was collected from 16 eyes of 16 patients (23 sequences, 911 B-scans altogether), and was annotated by the two graders. The first dataset was divided into two parts. Here, 19 out of 23 sequences were used for the preparation of the methods, i.e., designing the features and training the networks. 4 sequences (which we called

the test dataset), each containing 49 slices, were kept for evaluation purposes. The **second dataset** – which we called secondary test dataset consisted of 8 sequences of 7 patients (200 B-scans) and was used entirely for further validation of the best performing network.

The input of the Convolutional and Fully Convolutional networks were the images themselves, while the input of other neural networks was created on a pixel-by-pixel basis. A feature vector was generated for each pixel that served as a basis for classification. These features characterize the indicators of HF and were extracted by applying image processing techniques.

Image preprocessing and feature generation

The HF are small bright spots with a reflectivity higher than the RPE band and have a diameter between 20 and 40 μm. First, feature vectors contained raw pixel information. For each pixel, the first feature was its intensity, and the 23 × 23 vicinity and local information was provided concerning the intensity of the pixels for the neural networks.

Eleven feature values were obtained by convolving the images with different Laplacian of Gaussian (LoG) filters, providing a basis for bright spot detection. The spatial properties of the HF were also exploited, i.e., commonly located in the outer retinal layers, and/or around pockets of fluid accumulation. For this reason, ILM and RPE layers were determined. Subretinal fluid was also detected using our methods described earlier. Distance maps were generated from the specified regions, and for each pixel, three distance values were included (the distance between the processed pixel and the ILM, RPE and SRF) in the feature vector. Next, difference between HF, pigment particles and blood vessels was quantified. Pigment fragments and blood vessels cast shadows on OCT images, which appear as a 20–40 pixel long vertical dark area under the bright spot, whereas HF do not generate such shadow. Differentiating between HF, pigments and blood vessels was achievable by calculating the average of the pixel values below the pixel coordinate.

Training the nets

Using the training dataset and the extracted features, several networks were trained for the task to classify the pixels as either HF pixels or as part of the background. As only a small percentage of the training data pixels belonged to the HF (less than 1 thousandths of the pixels were HFs), we chose to re-sample the data during training using **probabilistic sampling** to optimize the networks.

Evaluation

After the training phase, segmentation of the test data was performed with the trained nets. Numerical measurements were performed using the Dice coefficient and compared with the annotations of the two graders. To get a baseline for the desired accuracy, annotations of the graders were compared with each other.

Results and discussion

The values were nearly as accurate (they had a Dice coefficient higher than 95%) as the overlap between the two annotating doctors. The best results were produced by the FCN. In most cases its

score was close to – or even higher than – the baseline between the annotators. Apart from the FCN, other networks performed quite well, especially the DRN using all the features, and the Dice DRN. The good performance of the Dice DRN can be accounted for by its loss function. The DRN with the full feature set, however, had additional information extracted from the image, and helped to find a better model. Based on the results, it can be concluded that FCN, Dice DRN and Full DRN could provide accurate segmentations of HF on OCT images. As a further validation of the best performing net, the FCN, the secondary test dataset was used. We found that the results for first and second datasets were comparable, and in both cases, the FCN produced results close to the baseline in the Dice, Precision, Recall and AUC values. Our study focused on the automatic segmentation of HF in whole OCT sequences. The novelty of our study lies in testing various neural networks for the automatic segmentation of HF. Unlike previous studies, our neural networks were trained not only by relying on raw pixel information, but also on features extracted by image preprocessing steps. We compared the annotations of two different graders with each other to determine a baseline accuracy for HF segmentation as a reference for our methods. Lastly, we demonstrated that in contrast to current trends, small networks can also provide reasonably good results, and enormous amounts of training are not needed.

SUMMARY AND CONCLUSIONS

Technological and scientific progress experienced in the field of retina is unlike any other subfields of ophthalmology lately. Optical coherence tomography (OCT) reinterpreted the definition of imaging by providing an unprecedented resolution of ophthalmic structures. However, recognition, quantification, and processing of all these details does not appear viable in the routine work of a physician. This antilogy could only be resolved in an interdisciplinary approach, combining the expertise of clinicians and modern computational tools used in the fields of classic image processing and artificial intelligence (AI). Because of the large prevalence of AMD its proper management is crucial. Fine changes of OCT biomarkers determine whether to treat or not, thus there is a need for a diversified and profound knowledge with an increasingly precise decision making in order to maximize the effects of the therapy, but also to reduce unnecessary costs.

The PhD thesis summarized the work of improving our comprehension of OCT biomarkers in wet AMD. First, ORTs were investigated in a retrospective real-life study.

1.) Our study found no significant difference between the ranibizumab and aflibercept treated groups according to ORT development, meaning ORT is independent of the chosen anti-VEGF drug or the dosing regimen of intravitreal anti-VEGF treatment. To our best knowledge this was the first publication, which presented results in treatment naïve patients treated with aflibercept and its connection with ORT development.

2.) There was a statistically significant reduction in the frequency of injections in the pro re nata ranibizumab treated group before and after ORT appearance, meaning that the clinician can expect a decrease in the number of injections after ORT development. Our fixed bimonthly treatment with aflibercept did not allow us to analyze the injection rate before and after ORT development in this group. Our study was the first to report results according to injection rate.

3.) The presence of SHRM at treatment initiation as a biomarker had a statistically significant correlation with the development of ORT in both groups. When SHRM was present the chance of developing ORT was 2.75 and 11.14 higher in the ranibizumab and aflibercept groups, respectively. No previous reports were found, which presented results in treatment naïve patients treated with aflibercept in this topic.

In the second part of the thesis our collaboration with computer scientists was presented that resulted in novel algorithms, which can automatically identify and quantify OCT biomarkers (such as SRF, IRF, PED, SHRM, ORT, HF) using classical image processing and artificial intelligence. The developed toolset is essential for further investigations of medically relevant questions in relation with OCT.

4.) I acted as the key medical expert in the development of an OCT image analysis toolset. My contributions were: raising the problem; selecting the adequate OCT images; performing and supervising biomarker annotations required for training and validation; explaining the properties and thus the characteristic features of biomarkers; evaluation of the results from a medical point of view.

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