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Brief report

Subfoveal choriocapillaris, Sattler's and Haller's layer thickness predict clinical response to stereotactic radiotherapy in neovascular age-related macular degeneration patients

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Abstract

Purpose: To evaluate the significance of choroidal substructure analysis in predicting the clinical response to adjuvant stereotactic radiotherapy (SRT) in neovascular age-related macular degeneration (nAMD) patients.
Methods: Patients with nAMD, who underwent SRT (baseline) in addition to common intravitreal injections (IVIs) and subsequently had at least 12 months of complete follow-up, were enrolled. In a post hoc analysis, optical coherence tomography (OCT) data were reviewed, and subfoveal choroidal thickness (CT) as well as the thickness of choroidal substructures, such as choriocapillaris (CC), Sattler's layer (SL), and Haller's layer (HL), was measured to determine if these influenced SRT efficacy.
Results: A total of 35 eyes of 35 patients were included. While each of the 4 choroidal metrics significantly forecasts the clinical response to SRT, combining them all together produced the most reliable prediction model.
Conclusion: In terms of clinical response to SRT in nAMD patients, choroidal substructure analysis does improve the quality of the prediction model when combined with subfoveal CT.
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Keywords: Neovascular age-related macular degeneration; Stereotactic radiotherapy; Choroid; Choriocapillaris; Sattler's layer; Haller's layer

Introduction

Neovascular age-related macular degeneration (nAMD) is one of the leading causes of blindness in the elderly.[1] Commonly, the treatment involves intravitreal injections (IVIs) of drugs, which primarily target the vascular endothelial growth factor A (VEGF A).[2,3] However, continual ophthalmic review and repeated IVIs are needed, which is often difficult to achieve due to various reasons.[4,5] For this matter, stereotactic radiotherapy (SRT) using the IRay® Radiotherapy System (Zeiss Meditec, Jena, Germany) has proven to be a useful addition to standard of care in nAMD patients.[6–8] The therapeutic effect is based on the anti-inflammatory, anti-fibrotic, and most notably anti-angiogenic properties of low voltage ionizing radiation.[9] Various parameters, like the size of the choroidal neovascularization (CNV) and the macular volume, have turned out to be important baseline characteristics for determining the clinical response to SRT. Recently, we reported the significance of subfoveal choroidal thickness (CT)

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in this context, as patients who had a thicker choroid at time of irradiation responded better to SRT in terms of lesser IVIs needed to control disease activity over 12 months.[10] Vessels contribute mostly to CT, and the choroidal vasculature is subdivided into small vessels in the choriocapillaris (CC), medium-sized vessels in Sattler's layer (SL), and large-sized vessels in Haller's layer (HL).[11] Therefore, we decided to review the data of the same SRT-treated nAMD patients in a post hoc analysis to determine the significance of each layer to predict the clinical outcome after SRT.

Methods

This study was conducted in accordance with the Declaration of Helsinki, and institutional review board approval was obtained. Informed consent was obtained from all individual participants included in the study. The methodology has been reported elsewhere.[10] Briefly, medical records were screened for patients with treatment-experienced nAMD, who, in addition to pro re nata IVIs, received SRT and had at least 12 months of complete follow-up afterwards. Patient charts were reviewed to collect demographic and clinical data at time of irradiation (baseline, BL) and 12 months afterwards (FU). Enhanced depth imaging (EDI) spectral domain (SD) optical coherence tomography (OCT) (Spectralis® SDOCT; Heidelberg Engineering, Heidelberg, Germany) data of the patients were reviewed, and subfoveal CT, CC thickness (CCT), SL thickness (SLT), as well as HL thickness (HLT) were measured at BL and at FU, using the built-in caliper tool (Heidelberg Eye Explorer, Version 1.9.10, Heidelberg Engineering) at a single point below the fovea (Fig. 1A). All measurements were made by two experienced graders (M.P. and M.K.), and values were averaged. The graders were blinded to clinical information about the eyes. Data were analyzed with continuous variables by linear regression using Prism GraphPad (Version 8.0, La Jolla, CA, USA) and IBM SPSS (version 24.0; Chicago, IL). Changes in CT, CCT, SLT, and HLT from baseline to final follow-up at 12 months were

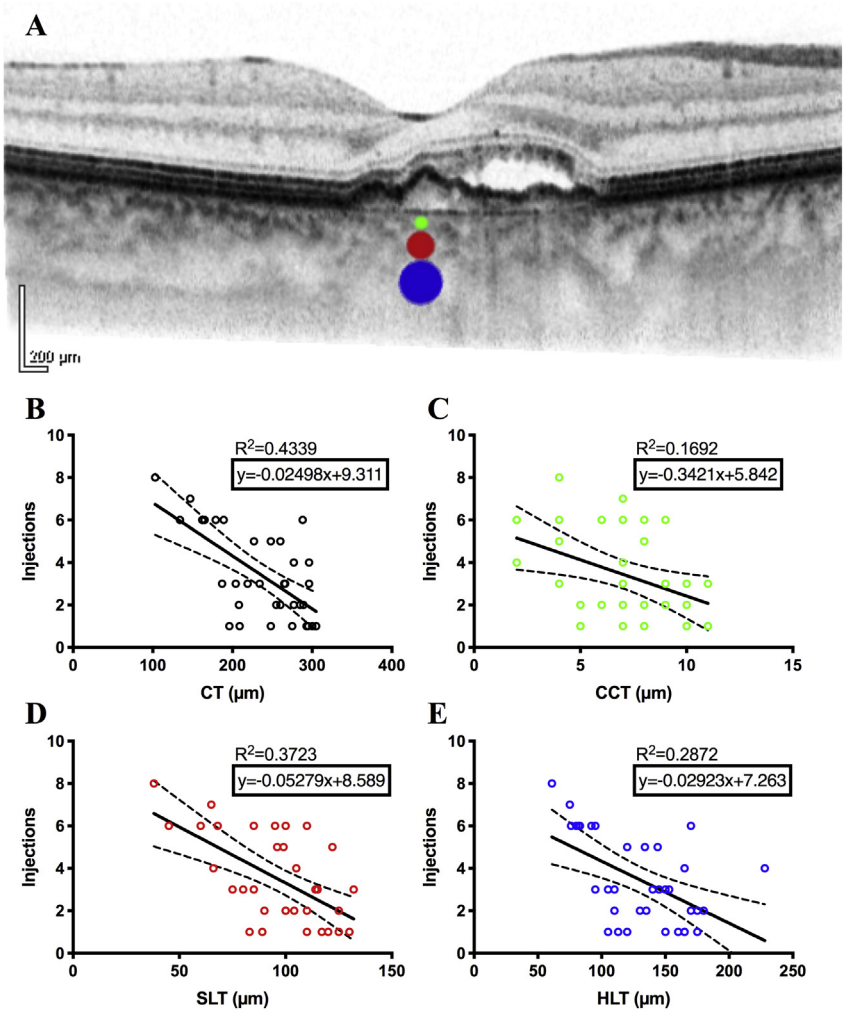

Fig. 1. **Choroidal substructure analysis and linear regression**. (A) Subfoveal choroidal thickness (CT) was measured manually using enhanced depth imaging (EDI) spectral domain (SD) optical coherence tomography (OCT). Besides subfoveal CT, choriocapillaris thickness (CCT, green), Sattler's layer thickness (SLT, red) as well as Haller's layer thickness (HLT, blue) were measured. (B–E) Data were analyzed with continuous variables by linear regression, and results are illustrated as graphs with the corresponding regression equation. All sublayers significantly predict the number of intravitreal injections (IVIs) (clinical response) after stereotactic radiotherapy (SRT).

evaluated by non-parametric univariate analyses using the Wilcoxon signed rank test. Results with $P < 0.05$ were considered statistically significant.

Results

A total of 35 eyes from 35 patients (18 women and 17 men) diagnosed with treatment-experienced nAMD were included in this study. The age at time of irradiation was 76.23 ± 7.05 years, and patients had received a total of 15.83 ± 6.29 IVIs over 34.57 ± 16.96 months.

The annual IVI rate decreased considerably from 6.86 ± 1.57 before to 3.46 ± 2.09 after SRT, which represents a highly significant 50% reduction ($P < 0.001$). Visual acuity improved significantly from 0.49 ± 0.28 logMAR at BL to 0.37 ± 0.29 logMAR at FU.

Subfoveal CT ($R^2 = 0.434$; $P < 0.001$), CCT ($R^2 = 0.169$; $P = 0.014$), SLT ($R^2 = 0.372$; $P < 0.001$), and HLT ($R^2 = 0.287$; $P = 0.001$) were found to be significant predictors for the number of IVIs needed after SRT (Fig. 1B−E). Including all 4 metrics into the same regression model improved the coefficient of determination ($R^2 = 0.498$; $P < 0.001$).

CT decreased significantly from BL (234 ± 55 μm) to FU (197 ± 47 μm; $P < 0.001$) after 12 months. Substructure analysis revealed similar trends for CCT (from 7 ± 3 μm to 5 ± 2 μm; $P < 0.001$), SLT (from 97 ± 24 μm to 78 ± 19 μm; $P < 0.001$), and HLT (from 130 ± 38 μm to 113 ± 31 μm; $P = 0.004$).

Discussion

In this post hoc analysis, we investigated the predictive value of choroidal substructure analysis for treatment response to SRT in nAMD patients. While we previously demonstrated that subfoveal CT can be a good baseline indicator to predict SRT outcome, this study is the first to report the impact of each of the three choroidal vascular layers as well as the combination of all these choroidal metrics in this context.[10]

The choroid plays a vital role in maintaining the outer retinal layers as well as the retinal pigment epithelium (RPE), and pathological changes of its circulation may lead to the development of AMD.[12] It has been speculated that in nAMD eyes, anti-VEGF treatment favorably influences not only retinal, but also the underlying choroidal exudation, which is based on choroidal vascular hyperpermeability induced by elevated levels of VEGF A.[13] Therefore, choroidal dimensions may to some extend reflect nAMD disease activity, which explains that a thicker CT at time of irradiation resulted in lesser need for IVIs afterwards.

Since the RPE is the major source of VEGF A in nAMD, it might be plausible that VEGF A levels vary across the choroid. Consequently, vascular hyperpermeability may also be different in the different choroidal layers. Furthermore, it has been shown that the composition of the vascular layers in the choroid changes in nAMD.[11] Hence, we expected substructure analysis of the CC, SL, and HL to add further information as well as to enhance our prediction model of clinical response to SRT. Separately, each of the three vascular sublayers was not able to improve the performance of the prediction model set by subfoveal CT. However, combining all 4 choroidal metrics produced a more reliable model and may potentially refine our knowledge of whom best to treat with SRT. The hypotheses, generated from this post hoc analysis, need to be tested in a prospective trial.

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