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Evaluation of OCT findings in Age-related Macular Degeneration: A Reproducibility Study of two independent Reading Centers

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33 **Abstract :**

34 **Background/aims :**

35 To determine the reproducibility among readers of two independent certified centers, the
36 Vienna Reading Center (VRC) and the University of Wisconsin-Madison Reading Center
37 (UW-FPRC) for OCT images in age-related macular degeneration (AMD).

38 **Methods :**

39 Fast macular thickness scans and 6 mm cross hair scans were obtained from 100 eyes with all
40 subtypes of AMD using Stratus OCT. Consensus readings were performed by two certified
41 OCT readers of each Reading Center using their grading protocol. Common variables of both
42 grading protocols, such as presence of cystoid spaces, subretinal fluid, vitreomacular traction
43 and retinal pigment epithelial detachment were compared using kappa statistics. In addition,
44 the intraclass correlation coefficient (ICC) was calculated for center point thickness (CPT) of
45 values remeasured manually in the presence of alignment errors.

46 **Results :**

47 The reproducibility was dependent on the variable measured with a kappa value of 0.81 for
48 the presence of cystoid spaces, 0.78 for the presence of subretinal fluid and 0.795 for the
49 presence of vitreomacular traction. The lowest reproducibility was found for the presence of
50 retinal pigment epithelial detachment with a kappa value of 0.51. The CPT was remeasured in
51 29 out of 100 scans at both sites with an ICC of the remeasured thicknesses of 0.92.

52 **Conclusion :**

53 OCT scan data are crucial in monitoring treatment efficacy in AMD clinical trials. For
54 comparison of results obtained by different Reading Centers, the inter-Reading Center
55 reproducibility is essential. Although the reproducibility is generally high, the reliability
56 depends on the selected morphological parameters.

57

58 **Introduction**

59

60 Optical coherence tomography (OCT) is a rapid, noninvasive imaging method capable
61 of generating high-resolution optical cross sections of the macula. A number of studies have
62 elucidated the usefulness of OCT in the evaluation and follow-up of retinal conditions such
63 as age-related macular degeneration (AMD) (1,2).

64 OCT has also become a critical tool for assessing the morphologic response of the
65 retina to therapeutic interventions. OCT-derived measurements of the central retinal thickness
66 are important outcome measures in clinical trials for treatment of macular edema (3,4,5) and
67 choroidal neovascularisation (6,7). In addition to quantitative metrics, OCT is widely used for
68 qualitative assessment to establish the presence of cystoid spaces, pigment epithelium
69 detachments (PED), subretinal fluid (SRF) or vitreomacular pathologies such as vitreomacular
70 traction (VMT). Recently, some of these variables have been used to determine the need for
71 initial therapy and subsequent retreatment in clinical trials evaluating novel treatment
72 modalities in the management of neovascular AMD (8). In current clinical trials of
73 neovascular AMD, the most commonly used OCT system is the Stratus OCT (Carl Zeiss
74 Meditec, Dublin, California, USA) with the the fast macular thickness map (FMTM) scan
75 mode. However, the automated algorithms frequently misidentify the inner and outer retinal
76 boundaries. This leads to an inaccurate thickness measurement, requiring a manual
77 remeasurement. For the evaluation of the various morphologic characteristics of exudative
78 AMD, typically the cross hair line scans have been obtained.

79 In multicenter AMD clinical trials, OCT scans are being sent to a central reading
80 center (RC) for evaluation of morphology and accuracy of automated thickness
81 measurements. Certified readers interpret retinal morphology according to standardized
82 protocols and the center point thickness (CPT) is remeasured manually when the automated
83 measurement is incorrect. Controlled RC procedures provide the most reliable method to

84 obtain realistic and solid OCT data and to conclude on the value and benefit of OCT imaging
85 in intravitreal therapy of AMD. Certified RCs, therefore, play an important role for defining
86 OCT strategies.

87 Although data have been published regarding reproducibility within OCT reading
88 centers (9), little information is available regarding reproducibility between RCs. However,
89 FDA approved trials are usually performed as two independent trials in US and non-US sites
90 with individual RCs responsible for each trial. Also, a comparison of strategies and results
91 from different centers allows a solid evaluation of reliability and reproducibility.

92 However, the comparability and reproducibility of OCT gradings of readers from
93 independent RCs using different grading protocols have not been evaluated to our knowledge.
94 Herein, we determine the inter-reading center reproducibility for OCT image evaluation
95 between an established European and an established U.S. Reading center, the Vienna
96 Reading Center (VRC) and the Reading Center of the University of Wisconsin-Madison
97 (UW-FPRC), respectively.

98

99 **Methods**

100

101 **Data collection :**

102 In this retrospective study, cases were collected sequentially from a list of patients
103 with the clinical diagnosis of AMD who underwent Stratus-OCT imaging of the macula at the
104 retina unit of the Department of Ophthalmology of the Medical University of Vienna.
105 Approval for the analysis of OCT images was obtained from the Institutional Review Board
106 of the Medical University of Vienna and of the University of Wisconsin-Madison. The
107 research adhered to the tenets set forth in the Declaration of Helsinki.

108 All scans were acquired by certified OCT operators following pupil dilatation using
109 the FMTM scan mode for quantitative measures of the CPT and the 6 millimeter cross hair
110 scan mode for qualitative assessment of retinal morphology.
111 The FMTM protocol acquires six 6-mm radial lines consisting of 128 A-scans per line in 1.92
112 seconds of scanning, whereas the cross hair protocol includes two 6 mm lines (6-12 to 9-3
113 o'clock) at 512 scan resolution.

114 Scans were analyzed with the version 4.0 software (Carl Zeiss Meditec), all patient
115 identifying data were removed and a consecutive patient number was given. Data for each
116 case were sent as print outs to the UW-FPRC and as digital data files to the VRC. After
117 completion of the grading procedure, the data files with the results were independently sent by
118 the two RCs to the Department of Medical Statistics of the Medical University of Vienna for
119 data analysis, keeping each of the RCs blinded from the results of the other RC.

120

121 **Grading Procedure :**

122 The OCT image sets were examined as print outs at the UW-FPRC. Standard grid
123 templates for identification of the center point and the central millimeter, printed on a
124 transparent stock were overlaid, on the scans and used for grading of location and extent of
125 the variables.

126 A validated computer assisted grading software was used at the VRC. This software
127 imports OCT scan data exported from the Stratus-OCT and allows the grader to electronically
128 measure various parameters in the 6 mm cross hair and FMTM scans. The distances are
129 calculated in pixels and using the dimensions of the B scan image, the pixels are converted
130 into micrometers. A superimposed grid indicating the center point and the central millimeter
131 was used for grading of location and extent of parameters.

132 A consensus reading was performed by two certified readers at each RC. The readers
133 were trained according to the individual protocol of the related RC and certification was

134 awarded on the successful completion of all requirements. All readers are actively
135 participating in the grading of Stratus OCT scans of clinical trials evaluating treatments for
136 AMD.

137 6 mm cross hair scans were graded for presence and location of cysts, subretinal fluid
138 (SRF),pigment epithelial detachment (PED),vitreomacular traction (VMT). FMTM scans
139 were graded for presence of alignment errors at the center point. Scans with with alignment
140 errors of more than 25% of the retinal thickness at the CP in at least one of the six FMTM
141 scans and with a standard deviation of CPT at >10% were manually remeasured using a
142 calibrated ruler at the UW-FPRC and digitally at the VRC.

143

144 **Definition of morphologic parameters :**

145 Before the start of the study, staff from the two RCs discussed the grading parameters
146 but did not thereafter interact. Cysts were defined as round, minimally reflective spaces within
147 the neurosensory retina. SRF was identified as a non-reflective space between the posterior
148 boundary of the neurosensory retina and the retinal pigment epithelium/choriocapillaris
149 reflection. Localisation of cysts and SRF was categorized as : 1. being outside the central
150 millimeter, 2. involving the central millimeter. In addition, central cysts were categorized as
151 small (<200 μm), medium (<400 μm) or large (>400 μm).

152 PED was described as a focal elevation of the reflective RPE band over an optically
153 clear or moderately reflective space. A PED was graded if the elevation was greater than 400
154 microns at the base and/or greater than 200 microns from the surface of the RPE band to the
155 surface of the choriocapillaris. Location of PED was described as : 1. being outside the
156 central millimeter, 2. involving the central millimeter .

157 VMT was identified if a thickened posterior hyaloid was observed to insert in the
158 foveal/perifoveal area. No grading regarding extend of VMT was performed.

159 Both RCs followed their own grading protocols for the selected parameters. To
160 compare gradings between the two RCs, a comparison key was developed.

161

162 **Statistical Methods :**

163 Analyses were conducted using the software package SPSS version 17.0 (SPSS Inc, Chicago,
164 Ill). To quantify the reproducibility of manual remeasurements of the CPT in cases of
165 alignment errors, the intraclass correlation coefficient (ICC) was calculated. In addition, the
166 mean, standard deviation, standard error, Pearson ρ and Bias correction factor C_b was
167 determined. For CPT remeasurements, absence/presence, location and extend of cysts, SRF,
168 PED and VMT, the percentage of agreement and the kappa statistic were calculated. Kappa
169 statistics were interpreted using the ranges suggested by Landis and Koch: (10) 0 to 0.20,
170 slight agreement; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and more
171 than 0.80, almost perfect agreement.

172

173 **Results**

174 The study included 100 eyes of 89 patients with an average age (\pm standard deviation) of $67 \pm$
175 8 years (59 female, 41 male). The OCT scans showed a wide range of morphologic changes
176 associated with AMD including drusenoid changes, serous, haemorrhagic and fibrovascular
177 PED, SRF, intraretinal cysts, VMT or macular edema.

178

179 **Manually remeasured CPT :**

180 The CPT was remeasured in 29 out of 100 FMTM scans at both sites (in 35 scans at the VRC
181 and in 37 scans at the UW-FPRC). **Table 1a shows the reproducibility as to whether or**
182 **not a remeasurement was necessary.** Table 1b shows the mean, minimum and maximum

183 CPT, standard deviation, standard error, ICC, Pearson p and Bias correction factor Cb for the
 184 remeasured CPTs at both sites.

185

Table 1a. No of remeasured FMTM scans

UW-FPRC	VRC		Total no.
	no	yes	
no	57	6	63
yes	8	29	37
Total no.	65	35	100
Kappa	0,70		
<i>Standard Error</i>	0,07		
<i>95% CI</i>	0,55 to 0,84		

186

Table 1b. Manually remeasured Center Point Tickness

<i>No. of remeasured scans at both sites</i>	29
<i>Intraclass correlation coefficient</i>	0,92
<i>95% Confidence interval</i>	0,845 to 0,96
<i>Pearson p (precision)</i>	0,94
<i>Bias correction factor Cb (accuracy)</i>	0,9824

	VRC	UW-FPRC
<i>Mean (μm)</i>	298	276
<i>Standard Error</i>	21,3	22,5
<i>Standard Deviation</i>	114,9	121,2
<i>Minimum</i>	139	115
<i>Maximum</i>	501	544

187

188 Figure 1a shows the Bland-Altman plot of the differences in the remeasured CPTs (x axis: the
 189 average of the CPT values of the two RCs; y axis: the differences of the CPT measurements
 190 between the two RCs). Figure 1b shows the scatter plot of the same measurements.

191

192 **Presence of cysts, SRF, PED and VMT**

193 Results of gradings for presence of cysts, PED, SRF and vitreomacular traction are
 194 summarized in Table 2. The shaded cells represent consistent gradings. The highest
 195 reproducibility was found for presence of cysts with a k value of 0,81 (almost perfect) the
 196 lowest for PED with a k value of 0,51 (moderate).

197 The number of detected VMT was low with only 2 cases identified at both sites and one
 198 additional at the UW-FPRC.
 199

Table 2. Presence of Cystoid spaces, SRF, PED and Vitreomacular traction

VRC						
UW-FPRC	Cystoid spaces			SRF		
	no	yes	Total no.	no	yes	Total no.
no	65	8	73	52	8	60
yes	0	27	27	3	37	40
Total no.	65	35	100	55	45	100
Kappa	0,81			0,78		
<i>Standard Error</i>	0,06			0,06		
<i>95% CI</i>	0,69 to 0,94			0,65 to 0,90		

200
201

VRC						
UW-FPRC	PED			Vitreomacular traction		
	no	yes	Total no.	no	yes	Total no.
no	32	26	58	97	0	97
yes	0	42	42	1	2	3
Total no.	32	68	100	98	2	100
Kappa	0,51			0,795		
<i>Standard Error</i>	0,07			0,20		
<i>95% CI</i>	0,37 to 0,65			0,40 to 1,0		

202

203

204 **Location and extend of cysts, PED and SRF**

205 Results of gradings for location and extent of cysts, PED and SRF are summarized in Table
 206 3a, 4a and 4b. Table 3b shows the reproducibility of thickness gradings of cysts at the center
 207 point. The shaded cells represent consistent gradings.

Table 3a. Cystoid spaces - Location and Extent

VRC				
UW-FPRC	0	1	2	Total no.
0	65	0	0	73%
1	2	3	0	5%
2	6	2	22	30%
Total no.	73%	5%	12%	100%

0 - Absent
 1 - Definite, outside central 1mm
 2 - Definite, central 1mm involved

Kappa 0,78
Standard Error 0,07
95% CI 0,53 to 0,82

208

221 **Discussion**

222 The introduction of a novel diagnostic method such as OCT of the retina into clinical
223 practice and the acceptance/approval of used parameters by the responsible institution,
224 requires solid proof of the value and relevance of the acquired data. In order to assess
225 treatment efficacy and to evaluate treatment indications, it is important to gather robust data
226 sets in a controlled manner. Few prospective clinical trials have included OCT measurements
227 in a rigorous fashion using a standardized protocol. Due to the limited availability of solid
228 data, the technique, although widely used in clinical routine, has not yet obtained general
229 acceptance as a gold standard method for monitoring patients with AMD, by institutions and
230 the community. The data available from trials such as PRONTO (Prospective Optical
231 Coherence Tomography Imaging of Patients with Neovascular Age-Related Macular
232 Degeneration Treated with intraocular Ranibizumab) (11), EXCITE (Efficacy and Safety of
233 Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-
234 Related Macular Degeneration) (12) and SUSTAIN (Study of Ranibizumab in Patients With
235 Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration)
236 (13) are uniformly based on conventional time domain (TD) OCT using the Stratus-OCT.

237 Standardized assessment of morphologic changes in OCT scans by one central RC,
238 is becoming a widely used method of determining outcomes in large clinical trials. Benefits of
239 using a central RC include : Standardized data acquisition procedures at the clinical sites,
240 standardized grading procedures by the use of certified readers and masking of readers to
241 patient data regarding treatment assignment. An additional advantage is that the
242 reproducibility of the readings can be easily assessed (9). Measurement of retinal thickness
243 and grading for presence, location and extent of intraretinal cysts, SRF and PED are currently
244 defined as the primary morphologic outcomes in recent clinical trials evaluating novel
245 treatments for neovascular AMD (11). Although these morphologic parameters have been
246 similarly applied by several RCs, there are no studies comparing OCT gradings between

247 them, despite the fact that RCs often cooperate in clinical trials. RCs developed individual
248 grading protocols, software tools and measuring devices. There is only one study comparing
249 results from two fundus photograph reading centers in grading cytomegalovirus retinitis
250 progression (14). Gradings were performed on light boxes using standard grid templates and
251 measuring circles by an ophthalmologist grader at one RC and by a group of four certified
252 graders at the other RC. Another study investigated agreement between clinician and RC
253 gradings of fundus photographs of diabetic retinopathy (15). The agreement between diabetic
254 retinopathy severity classification as determined by ophthalmoscopy performed by retina
255 specialists and gradings of stereoscopic fundus photographs at a RC was determined.
256 However, to our knowledge no study has been published on the inter-reading center
257 reproducibility of OCT gradings.

258 As more competing trials are being performed world-wide with increasing numbers of
259 study participants, more RCs are being involved to satisfy the need for certified data analysis.

260 The comparison of consensus readings of different OCT parameters in AMD showed a
261 high level of agreement between the VRC and the UW-FPRC. The reproducibility was,
262 however, dependent on the specific morphologic parameters measured with a kappa value of
263 0.81 for the presence of cystoid spaces, 0.78 for the presence of SRF and 0.795 for the
264 presence of VMT. The lowest reproducibility was found for the presence of PED with a kappa
265 value of 0.51. Reproducibility of gradings for localisation and extend of the selected
266 parametes was lower, but still “moderate” with k values of 0.54 for SRF and 0,51 for PED
267 and “substantial” for intraretinal cysts with a kappa value of 0,78. These findings, based on
268 the capability of trained analysts in a standardized setting also highlight the difficulties in
269 identifying specific morphologic pathologies in general, e.g. lesions of the RPE clearly
270 represent a challenge for diagnosis and grading, while the identification of intraretinal cysts

271 appears to be more reliable. These observations from a certified center condition allow an
272 estimation of the value of such data from studies not using certified procedures.

273 These data appear even more relevant as that a digital grading method at the VRC
274 was compared with a paper print grading method at the UW-FPRC. In general, all reading
275 parameters were discussed by members of the two RCs and defined prior to the study but
276 there was no interaction between the two RCs thereafter offering completely independent
277 analysis. Limitations of this analysis include the restricted range of morphologic parameters
278 included and the relatively small number of study cases. In addition, this study is based solely
279 on Stratus OCT data, which is still the most commonly used OCT in research protocols to
280 date, however, it will be probably replaced soon by Fourier domain OCT (FD-OCT) devices.
281 Stratus OCT imaging is based on 6 radial, cross-sectional scans, and the information therefore
282 is limited to a few randomly selected locations and an overall low resolution of structural
283 details. The FD-OCT uses a fast spectral-domain technique and performs scans in a raster
284 pattern throughout the entire macular area, at a superior resolution of 5 μm in axial and 20 μm
285 in transverse directions. As a result, the retinal morphologic features such as RPE or
286 vitreomacular interface abnormalities can be imaged at all locations and in more details.

287 In AMD, there may be up to a 92% rate of inner or outer retinal boundary errors with
288 subsequent incorrect segmentation for retinal thickness (16). Recently, studies have shown the
289 superiority of the central subfield for analysis of the central retinal thickness when compared
290 to the center point thickness because of reduced variability. (17). Although the majority of the
291 FD-OCT platforms will allow recalculation of central subfield thickness measurements, only
292 the center point thickness can be remeasured manually on Stratus OCT when the automated
293 algorithm fails. The CPT measurements in case of alignment errors were highly reproducible
294 between the two RCs with a kappa value of 0,70 and an ICC of 0,92. However the mean CPT
295 remeasured by readers of the VRC was 22 μm higher than the mean of the reameasured CPT

296 at the UW-FPRC. The agreement on thickness gradings of central cysts was “substantial”
297 with a kappa value of 0,75. This high degree of measurement agreement is relevant for
298 clinical trials in which lesion thickness is a primary or secondary study end point.

299 A constant high level of agreement between RCs probably requires the development
300 of a quality control program and RCs may need to consider establishing and maintaining
301 cooperative programs to harmonize their measuring and grading procedures and settings.
302 Otherwise, a comparison of results from trials analyzed by different RCs cannot be certain of
303 the impact of possible differences between RCs. Optimal standardisation and reliability is,
304 however, essential to identify the value of new surrogate parameters in the development of
305 novel treatment strategies which also introduce appropriate strategies for patient management
306 and follow-up.

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355

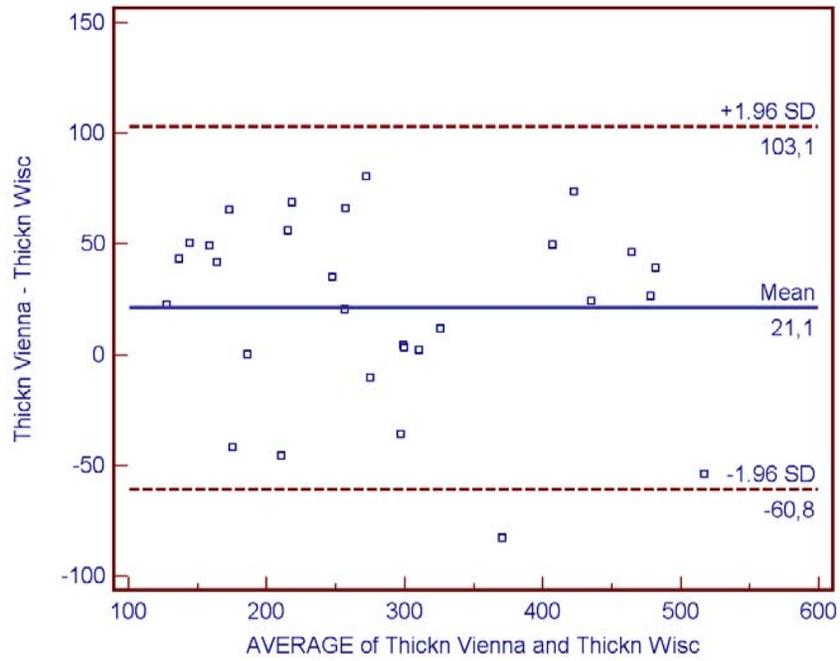


Figure 1a

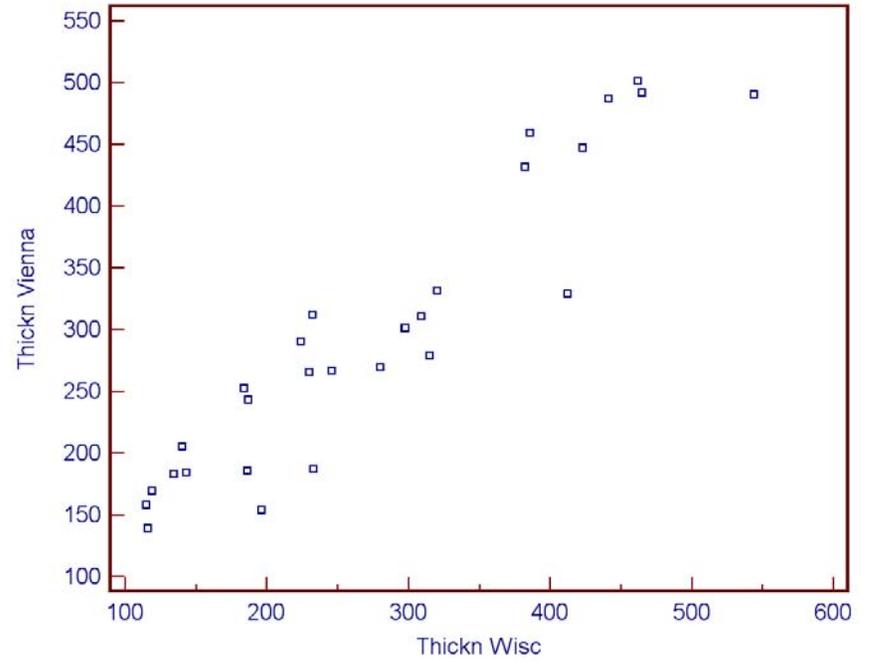


Figure 1b