Student Name: Sanjay Bansal **Date:** Aug. 8, 2014

Project Title: Customizing epithelial ablation depth via optical coherence tomography in trans-epithelial phototherapeutic keratectomy (t-PTK) prior to CXL in patients with keratoconus

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SUMMARY: (no more than 250 words single spaced)

Objective: To compare epithelial thickness measurements provided by optical coherence tomography with intra-operative epithelial breakthrough point, determined by the surgeon, to provide customized ablation depth upon transepithelial-phototherapeutic keratectomy (t-PTK) prior to corneal collagen crosslinking (CXL).
Methods: Charts of 24 eyes (15 patients) were reviewed retrospectively. All patients were clinically diagnosed with keratoconus, and had undergone t-PTK followed by CXL. Epithelial thickness map was generated by Fourier-domain optical coherence tomography [RTVue, Optovue Inc., Fremont, CA, USA] pre-operatively, and the surgeon (GR) determined epithelial breakthrough point intra-operatively.
Results: Average planned epithelial ablation depth was 53.1 ± 4.4um, 52.8 ± 5.9um, and 54.6 ± 4.6um for all eyes, eyes with central cones, and eyes with eccentric cones respectively. Average depth of epithelial breakthrough was 38.7 ± 8.5um, 43.8 ± 6.3um, and 34.5 ± 8.3um for all eyes, central cones, and eccentric cones respectively. The average minimum epithelial thickness measured by the OCT generated epithelial thickness map was 42.8 ± 6.8um, 44.9 ± 6.3um, and 41.2 ± 7.3um for all eyes, central cones, and eccentric cones respectively. There was NO statistically significant difference between average minimum epithelial thickness (44.9 ± 6.3 microns) and average epithelial breakthrough depth (43.8 ± 6.3 microns) in eyes with eccentric cones.
Conclusions: results suggest that minimum epithelial thickness may be an effective marker in determining optimum epithelial ablation depth in eyes with eccentric cones. The results also indicate using epithelial thickness in the central zone of the OCT-generated map is an ineffective marker in planning epithelial ablation depth regardless of the location of the cone.

Student Signature **Supervisor Signature**

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Introduction

Keratoconus is the most common primary ectatic corneal disorder.[1] It is a non-inflammatory degenerative disease characterized by progressive corneal thinning, which forces the cornea to assume a conical shape due to the resultant biomechanical instability.[2] The cornea is responsible for 2/3 of total optical power, and thus alteration in shape induces variable degrees of irregular astigmatism, and myopia.[2] Onset of disease is typically during puberty, after which it typically progresses for about 10 to 20 years.[2] Keratoconus is generally bilateral, but asymmetric. It is estimated that about 1 in 2000 individuals in the general population are afflicted with this disease.[2] Although the exact etiology of keratoconus remains unknown, it is thought that the process is complex and involves genetic, physical, and biochemical factors. Disease has been shown to be related to repetitive ocular surface trauma including but not limited to hard contact lens wear, eye rubbing, and allergic eye disease. 10% of those with disease have a positive family history.[2] Furthermore, elevated protease activity in addition to decrease protease inhibitor activity has been identified in keratoconic corneas.[3] In the majority of cases keratoconus presents in isolation, however it has been associated with various systemic disorders such as atopy, Down's syndrome, Tuner syndrome, Marfans syndrome, Ehlers-Danlos syndrome, and others.[2]

Management of keratoconus varies depending on severity of disease. Mild disease can be corrected simply with soft toric contact lenses or spectacles. As disease progresses, and visual impairment worsens, rigid gas permeable lenses are required.[4] In 15-20% of keratoconic patients excessive corneal scarring and thinning, or development of contact lens intolerance, necessitate keratoplasty.[5] Though these therapies effectively improve visual acuity none of them aid in slowing progression of disease. In this regard corneal collagen cross-linking (CXL) has shown great efficacy.[6]

CXL is a normal physiologic process that occurs via enzymatic pathways involving transglutaminase and lysyl oxidase. This natural process can be articifically mimicked by administration of Riboflavin droplets (Vitamin B2) with simultaneous exposure to Ultraviolet A (UVA) light, as developed by Spoerl and Seiler at the University of Desden.[7] Though the exact mechanism has not been fully elucidated it is known that the interaction between riboflavin and UVA produces oxygen free radicals, which trigger cross-link formation through various mechanisms, thereby strengthening the cornea.[8] Riboflavin also absorbs UVA as to prevent damage of deeper ocular structures.[9] According to a review article by O'Brart multiple prospective studies have shown support for the efficacy of CXL.[6] A randomized, prospective study carried out by O'Brart et al. reported stabilization in all treated eyes with statistically significant improvement in best corrected visual acuity (BCVA), corneal power and higher order aberrations, compared to progression in 14% of untreated eyes over an 18 month follow up period.[10] Spoerl has shown that complete debridement of central epithelium ("epithelium-off" technique) is necessary to ensure adequate stromal uptake of riboflavin, as there was no change in biomechanical properties of corneal tissue when CXL was performed while leaving epithelium intact.[7] This is because riboflavin is a hydrophilic molecule, which cannot permeate the tight junctions of the epithelial barrier. Adequate stromal absorption of riboflavin is essential as it acts as a photosensitizer responsible for triggering collagen cross-linking and as a shield to protect deep ocular structures from UVA irradiation induced damage. Recently novel riboflavin formulations have been developed to eliminate the need for epithelium removal. Results have

been encouraging, although somewhat ambiguous as some studies have shown similar efficacy to standard 'epithelium-off' techniques,[11-12] while others have shown less pronounced effects.[13-15] In light of this, and the fact that the majority of long term data published regarding CXL has been with 'epithelium-off' techniques, the standard 'epithelium-off' CXL remains the gold standard.[6]

Traditionally, epithelial debridement is done mechanically using an Amoils brush or other similar device. Another emerging option is to use excimer laser transepithelial phototherapeutic keratectomy (t-PTK). Studies by both Kapasi et al. and Kymionis et al. have reported that patients who underwent t-PTK prior to CXL had statistically significant better visual and refractive outcomes compared with patients who underwent mechanical epithelial debridement.[16-17] This is likely because, in addition to removing epithelium, t-PTK can smoothen out the anterior corneal stroma to decrease keratoconus induced irregular astigmatism. It is well documented that there is epithelial thinning over the cone in keratoconic corneas, as demonstrated using optical coherence tomography.[18-19] Furthermore Reinstein et al used 3-dimensional epithelial thickness mapping to demonstrate an epithelial doughnut pattern characterized by centralized thinning surrounding by a ring of thickened epithelium.[20] To this effect, both Kymionis et al. and Kapasi et al. have used an ablation depth of 50 microns in order to use patients' epithelium as a masking agent while removing corneal stromal tissue at the apex of the cone to regularize the corneal surface.

Optical coherence tomography (OCT) is a non-invasive imaging technique that can produce cross-section images of the eye. Fourier-domain OCT has been shown to have better reliability than time-domain OCT.[21] Additionally, Fourier-domain OCT has a lower image acquisition time and higher image resolution when compared to time-domain OCT. Multiple studies have demonstrated the reliability and repeatability of central corneal epithelium thickness measurements.[22-24] A more recent study confirmed this, and went on to show that Fourier-domain OCT also has excellent reliability and repeatability in para-central zones up to a 6-mm diameter.[25]

As mentioned previously both Kymionis et al. and Kapasi et al. used a standardized ablation depth of 50 microns based on findings of epithelial thickness mapping studies done in the past.[18-20] Both studies have shown good outcomes. However, we believe that this can be further improved upon. Localized regions of epithelial thickening or thinning cannot be predicted by corneal curvature or by total corneal thickness.[26] Clinically epithelial distribution is unpredictable, necessitating direct measurement of epithelial thickness in situations, such as t-PTK, where variations from expected patterns may be of clinical significance.[26] 50 microns is an adequate target for the general population, as keratoconic eyes typically have thinner epithelium over the cone, but at an individual level epithelial thickness is patients can be quite variable. Some patients, even with keratoconus, may have almost normal epithelial thickness, while others still may have dramatically reduced epithelial thickness. Epithelial thickness maps generated by Fourier-domain OCT can be used to provide individualized ablation depths for each patient. In this study we compare ablation depths suggested by epithelial thickness maps to the epithelial thickness at which breakthrough can be visualized by the surgeon during t-PTK procedure to determine whether epithelial thickness mapping can be used to predict customized optimal ablation depth.

Methods

The charts of 15 patients (24 eyes) whose cases dated from November 2012 to May 2013 were retrospectively reviewed. Patients were recruited from the GRMC Vision Centre (Brandon, Manitoba, Canada). Data was collected pre-operatively and intra-operatively. Pre-operative data included demographic information (age, gender, eye in question), cone location as determined by Scheimpflug imaging [Pentacam, Oculus, Wetzlar, Germany], and epithelial thickness map generated by Fourier-domain optical coherence tomography [RTVue, Optovue Inc., Fremont, CA, USA]. Intra-operative data was the point at which the excimer laser broke through epithelium as determined by the surgeon (GR). The Research Ethics Board (REB) of the University of Manitoba (Winnipeg, Manitoba, Canada) approved the study protocol.

All patients were clinically diagnosed with Keratoconus by the surgeon (GR), and were candidates for CXL therapy as per guidelines in keratoconus management.

The eyes were examined via Fourier Domain-OCT (RTVue, Optovue, Fremont, CA, USA) with a low-magnification cornea lens adaptor. The image scan rate of the device is 26 000 A-scans per second, and the vertical resolution is 5 microns. A cross pattern of horizontal and vertical lines was used, with each line scan consisting of 1024 A-scans over a 6-mm diameter. Scans were centered over the pupil. Epithelial thickness maps were generated by automated software developed by Optovue.

All patients received Vigamox (moxifloxacin 0.5%) (Alcon Laboratories, Fort Worth, TX) for 2 days prior to treatment. All procedures were performed by GR. One drop of each of the following was given pre-operatively: Vigamox (moxifloxacin 0.5%) (Alcon); isoptocarpine (pilocarpine hydrochloride 2%) (Alcon); and topical anesthetic (Minims; tetracaine hydrochloride 0.5%) (Bausch & Lomb, Rochester, NY).

Transepithelial PTK was performed at a variable depth based on the pre-operative plan determined using the Fourier Domain-OCT generated epithelial thickness map, in a 6 mm central zone, and at 8 Hz, using autocentration for all patients using the excimer laser (Visx Star S4 IR, Visx, Abbott Medical Optics, Santa Ana, CA). Following the epithelial ablation a stromal refractive ablation was provided, individualized for each eye, targeting mainly the cylindrical correction. Mitomycin C 0.02% (MMC) was then applied for 30 seconds.

If pachymetry was >400 microns, 0.1% riboflavin (0.1% solution of 10 mg riboflavin-5-phosphate) in 0.5% Isopto Tears (Alcon) was used. If pachymetry was found to be <400 microns at any time during the procedure, hypotonic 0.1% riboflavin in a balanced salt solution (BSS) was used until pachymetry of >400 microns was re-established. Riboflavin was applied every 2 minutes for 30 minutes to ensure complete stromal penetration. Calibration to 9.0 mW/cm2 was completed using a meter (YK-34UV, Lutron Electronic Enterprise, Taipei, Taiwan) supplied with the UV-X system (Koehler Optics, version 1000, IROC, Zurich, Switzerland). UV-A was then applied for 10 minutes. Riboflavin drops and UV-A light exposure was administered simultaneously. Drops were given at a constant rate of 1 drop every 2 minutes, while UV-A light exposure occurred continuously. Throughout the procedure, tetracaine and BSS were used as needed. The procedure was completed with a bandage contact lens placement.

Postoperatively, a bandage contact lens was applied for 1 week with Vigamox (moxifloxacin 0.5%; Alcon) 4 times per day. FML (fluorometholone 0.1% [Allergan, Irvine, CA]) was given 4 times per day, tapered down over a month.

For statistical analysis the paired Wilcoxon signed-rank test was used. This test is the non-parametric equivalent to the student's t-test, meaning that it is appropriate for comparing matched samples when the population is not normally distributed. The test involves a series of calculations that yield a 'test statistic'. The test statistic is compared to the critical value, which is obtained from a standardized table. When the critical value is > than the test statistic the null hypothesis cannot be rejected, suggesting that there is no significant difference between the two samples. We chose critical values based on an alpha = 0.05, which means that there is a 5% chance of type 1 error occurring.

Results

The study consisted of 24 eyes (15 patients). 19 eyes were male (12 patients) and 5 eyes were female (3 patients). The average age was 28.0 ± 8.4 years (range, 17-50). 14 eyes had central cones and 10 eyes had eccentric cones. There were 11 right eyes, and 13 left eyes.

The average planned epithelial ablation depth was 53.5 ± 5.4 microns (range, 44-64), 52.8 ± 5.9 microns (range, 44-64), and 54.6 ± 4.6 microns (range, 47-60) for all eyes, eyes with central cones, and eyes with eccentric cones respectively. The average depth at which epithelial breakthrough was observed was 38.4 ± 8.7 microns (range, 24-55), 34.5 ± 8.3 microns (range, 24-48), and 43.8 ± 6.3 microns (range, 35-55) for all eyes, eyes with central cones, and eyes with eccentric cones respectively. The average minimum epithelial thickness measured by the OCT generated epithelial thickness map was 42.8 ± 7.0 microns (range, 23-54), 41.2 ± 7.3 microns (range, 23-52), and 44.9 ± 6.3 microns (range, 31-54) for all eyes, eyes with central cones, and eyes with eccentric cones respectively. Results have been visualized in Table 1 and Figure 1.

When looking at results for all eyes (n=24) there was a statistically significant difference between average planned ablation depth (53.5 ± 5.4 microns) and average epithelial breakthrough depth (38.4 ± 8.7 microns) (critical value = 81; test statistic = 0), average planned ablation depth (53.5 ± 5.4 microns) and average minimum epithelial thickness (42.8 ± 7.0 microns) (critical value = 81; test statistic = 1), and average minimum epithelial thickness (42.8 ± 7.0 microns) and average epithelial breakthrough depth (38.4 ± 8.7 microns) (critical value = 73; test statistic = 38). Comparison of test statistics and critical values for all eyes are shown in figure 2. The average difference between planned ablation depth and average epithelial breakthrough depth was 15.2 ± 9.3 microns (range, 0-34).

For eyes with central cones (n=14) there was a statistically significant difference between average planned ablation depth (52.8 ± 5.9 microns) and average epithelial breakthrough depth (34.5 ± 8.3 microns) (critical value = 17; test statistic = 0), average planned ablation depth (52.8 ± 5.9 microns) and average minimum epithelial thickness (41.2 ± 7.3 microns) (critical value = 21; test statistic = 0), and average minimum epithelial thickness (41.2 ± 7.3 microns) and average epithelial breakthrough depth (34.5 ± 8.3 microns) (critical value = 21; test statistic = 2.5). Comparison of test statistics and critical values for eyes with central cones are shown in figure 3.

The average difference between planned ablation depth and minimum ablation depth was 6.7 ± 4.8 microns (range, (-2)-13).

For eyes with eccentric cones (n=10) there was a statistically significant difference between average planned ablation depth (54.6 ± 4.6 microns) and average epithelial breakthrough depth (43.8 ± 6.3 microns) (critical value = 5; test statistic = 0), average planned ablation depth (54.6 ± 4.6 microns) and average minimum epithelial thickness (44.9 ± 6.3 microns) (critical value = 8; test statistic = 1).

For eyes with eccentric cones there was NO statistically significant difference between average minimum epithelial thickness (44.9 ± 6.3 microns) and average epithelial breakthrough depth (43.8 ± 6.3 microns) (critical value = 5; test statistic = 18). Comparison of test statistics and critical values for eyes with central cones are shown in figure 4. The average difference between planned ablation depth and minimum ablation depth was 1.1 ± 5.6 microns (range, (-9)-9).

When critical value > test statistic the samples are NOT statistically significant; i.e. there is no difference between the two groups.

Discussion

The efficacy of t-PTK over mechanical has been documented.[16-17] Prior studies used a standard ablation depth of 50 microns for all patients. This value was based on the fact that on average normal epithelial thickness is 50 microns. In the keratoconic eye epithelium tends to be thinner than this, especially over the cone.[27] Using an ablation depth of 50 microns would permit the excimer to not only remove epithelium, but also smooth out the irregular anterior stromal layer beneath it.[28-29] Though this is true as a general rule, this may not hold true for all patients at an individual level. Clinically in keratoconus epithelial distribution is unpredictable, and therefore it cannot be assumed that all patients will display the expected pattern.[26] It is especially important to keep this in mind when epithelial distribution is of clinical significance, as in t-PTK. It is inevitable that some patients with keratoconus will have epithelium thicker than 50 microns, while others may have an epithelium that is substantially thinner. An ablation depth of 50 microns in a patient with epithelial thickness >50 microns would result in inadequate removal of epithelium. The same ablation depth in a patient with epithelial thickness <<50 microns may result in excess removal of corneal stroma, putting the patient at risk for damage from UV-A irradiation in subsequent stages of treatment. Our results showed that planned epithelial depth differed with statistical significance from observed epithelial breakthrough point in all eyes, eyes with central cones, and eyes with eccentric cones. Planned epithelial ablation depth was based on the epithelial thickness value given in the central zone of the OCT-generated map (Figure 5). In all cases, except one, there was a difference of >0 microns between planned ablation depth compared to the point at which epithelial breakthrough was observed (Figure 6). In the exception breakthrough occurred at the same point as the planned depth. This suggests that planned ablation depth based on the central zone will overestimate the amount of corneal epithelium that should be removed, potentially risking excess removal of stromal tissue. When comparing epithelial breakthrough to minimum epithelial thickness the values differed with statistical significance in eyes with central cones, and in all eyes overall. The results showed that there was no statistical significance in observed epithelial breakthrough and minimum epithelial thickness

in eyes with eccentric cones. From this we may potentially take away the fact that in eyes with eccentric cones optimum epithelial ablation depth may be predicted based on the minimum epithelial thickness as measured by OCT.

We also noticed that in eyes with central cones, in all cases except one, the difference between minimum epithelial thickness and depth at epithelial breakthrough occurred was >0 microns (figure 7). On the contrary, in eyes with eccentric cones there were some cases where the difference was <0 microns and other cases where the difference was >0 microns (figure 8). We are not exactly sure of what significance this is but it may suggest that the accuracy of the RTvue's measurements may vary between eyes with central cones and eyes with eccentric cones.

The purpose of this study was to use OCT-generated epithelial thickness maps to provide customized t-PTK to patients undergoing CXL for keratoconus. Due to the retrospective nature of our study there are some limitations. We had an unequal amount of eyes with central and eccentric eyes, and they were not matched for pre-operative parameters such as keratometry, and pachymetry. Observed epithelial breakthrough is a subjective parameter, determined intra-operatively by the surgeon, and is therefore potentially subject to human error.

In conclusion our results suggest that minimum epithelial thickness may be an effective marker in helping to determine optimum epithelial ablation depth in eyes with eccentric cones. The results also suggest that using epithelial thickness in the central zone of the OCT-generated map is an ineffective marker in planning epithelial ablation depth regardless of the location of the cone.

Future prospective studies would be better in comparing eyes with eccentric and central cones by recruiting a larger number of patients, and matching these patients with respect to pre-operative parameters. Furthermore, future studies should aim to collect data on post-operative visual indices in order to assess whether or not patients receiving customized t-PTK ablation depth have better outcomes than patients with a uniform ablation depth of 50 microns.

This study lays the groundwork in suggesting that the RTvue may be quite effective in helping to plan optimum ablation depth, a marker we hope could be used to generate customized treatment that would yield improved visual outcomes.

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Figures

Table 1: Average epithelial thickness for planned epithelial ablation depth, observed epithelial breakthrough, and minimum epithelial thickness for all eyes and segmented based on cone location

	Number of Eyes (n)	Planned epithelial ablation depth (microns)	Observed epithelial breakthrough (microns)	Minimum epithelial thickness (microns)
Average (All eyes)	24	53.5 ± 5.3	38.4 ± 8.7	42.8 ± 7.0
Average (Central cone)	14	52.8 ± 5.9	34.5 ± 8.3	41.2 ± 7.3
Average (Eccentric cone)	10	54.6 ± 4.6	43.8 ± 6.3	44.9 ± 6.3

Figure 1: Average epithelial thickness for planned epithelial ablation depth, observed epithelial breakthrough, and minimum epithelial thickness for all eyes and segmented based on cone location.

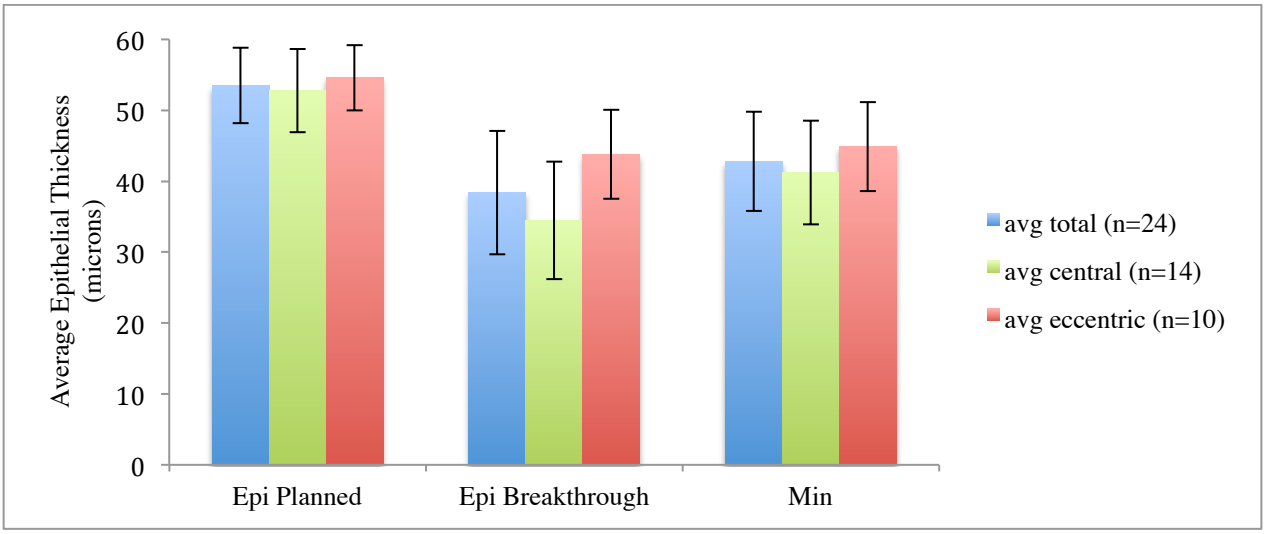

Figure 2: Difference between test statistic and critical value of Paired Wilcoxon signed-rank test for all eyes (n=24) when comparing: epithelial breakthrough depth (BK) vs. minimum epithelial thickness (min), planned epithelial ablation depth (plan) vs. minimum epithelial thickness (min), and planned epithelial ablation depth (plan) vs. epithelial breakthrough depth (BK)

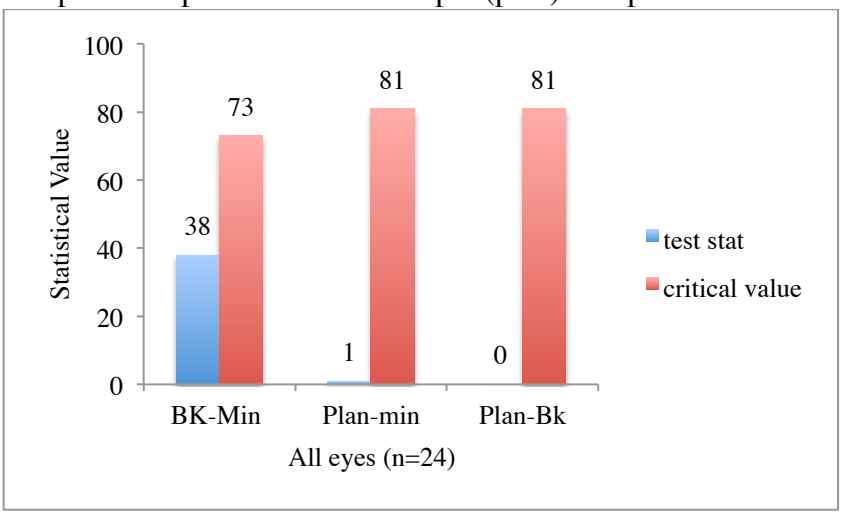

Figure 3: Difference between test statistic and critical value of Paired Wilcoxon signed-rank test for eyes with eccentric cones (n=14) when comparing: epithelial breakthrough depth (BK) vs. minimum epithelial thickness (min), planned epithelial ablation depth (plan) vs. minimum epithelial thickness (min), and planned epithelial ablation depth (plan) vs. epithelial breakthrough depth (BK)

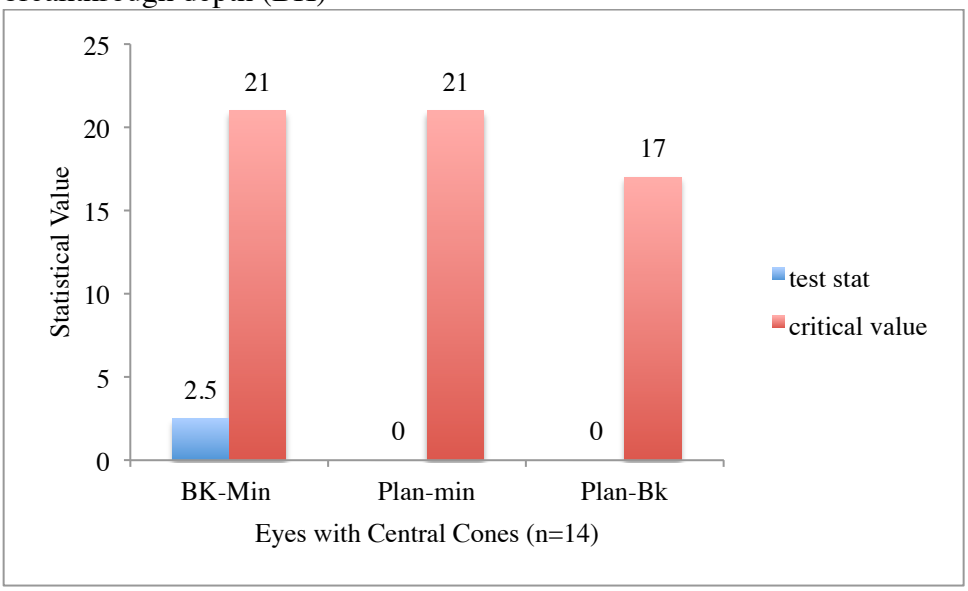

Figure 4: Difference between test statistic and critical value of Paired Wilcoxon signed-rank test for eyes with eccentric cones (n=10) when comparing: epithelial breakthrough depth (BK) vs. minimum epithelial thickness (min), planned epithelial ablation depth (plan) vs. minimum epithelial thickness (min), and planned epithelial ablation depth (plan) vs. epithelial breakthrough depth (BK)

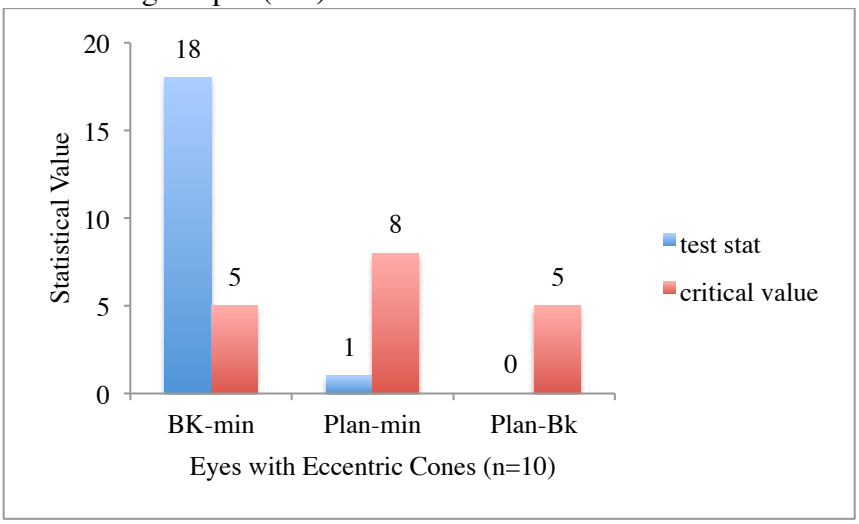

Figure 5: RTvue Optical Coherence Tomography (OCT) generated corneal epithelial thickness map. Central zone (circled in red) was used as planned epithelial ablation depth.

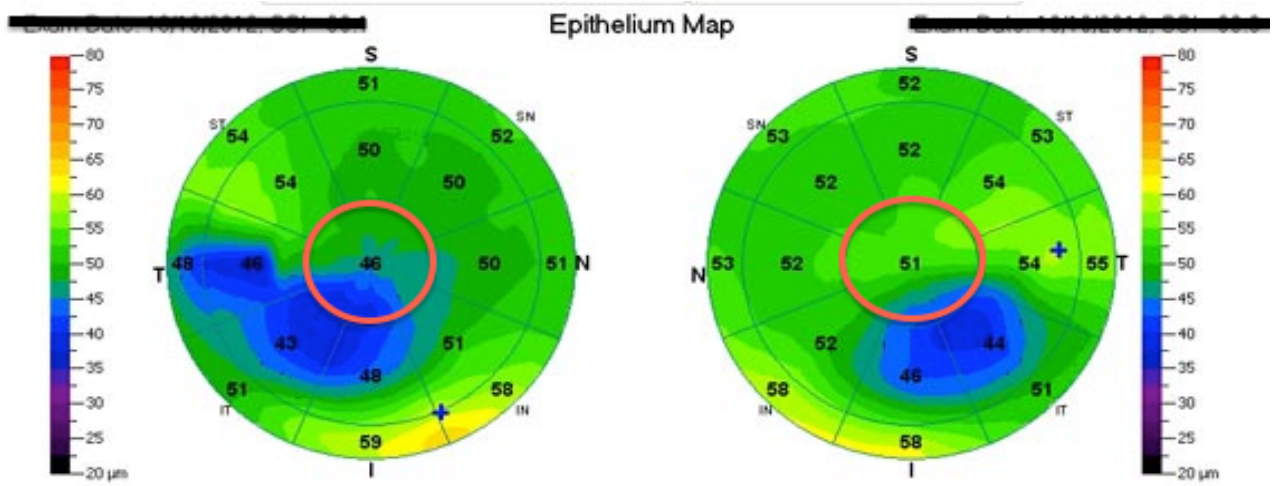

Figure 6: Comparing planned epithelial ablation depth with observed epithelial breakthrough point in all eyes (n=24).

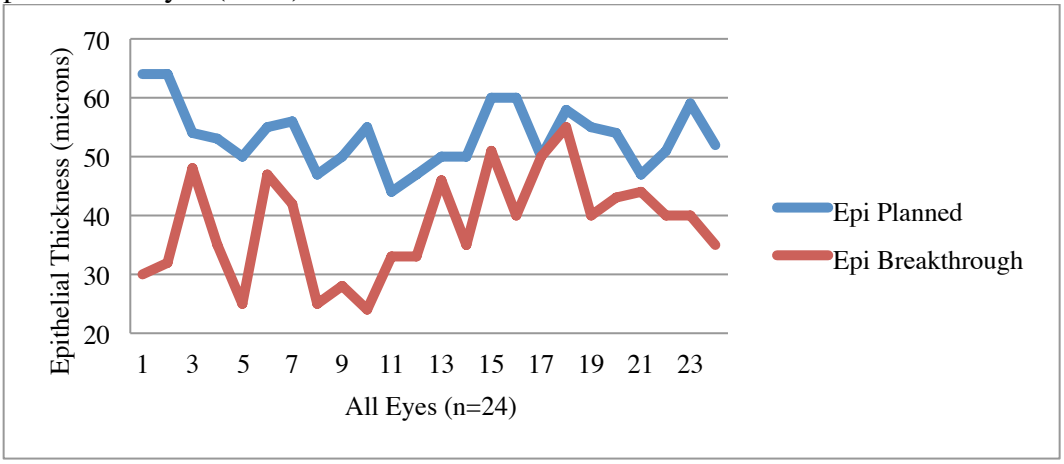

Figure 7: Comparing observed epithelial breakthrough with minimum epithelial thickness in eyes with central cones (n=14).

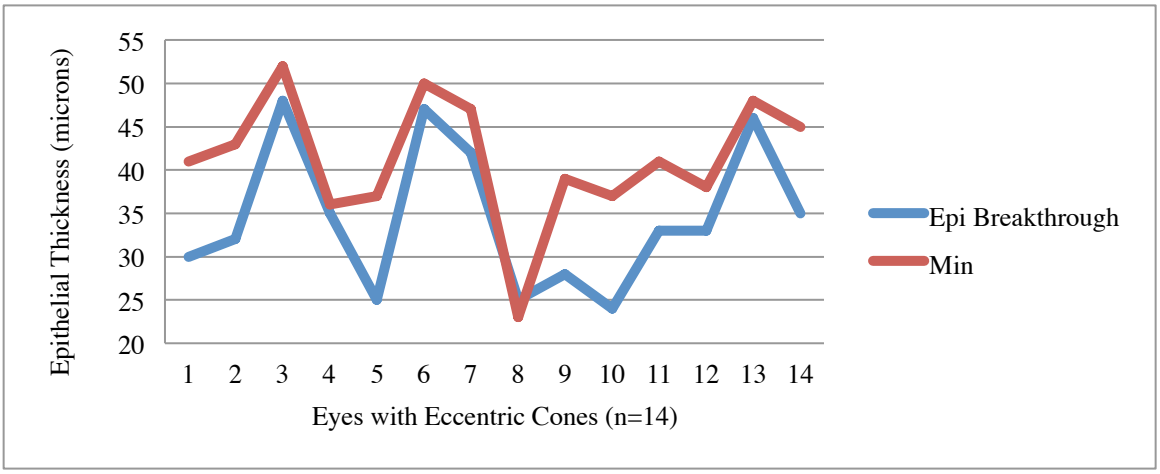

Figure 8: Comparing observed epithelial breakthrough with minimum epithelial thickness in eyes with eccentric cones (n=10).