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Refractive Intervention

Corneal Epithelial Remodeling Induced by Photorefractive Keratectomy Enhancement After Small-Incision Lenticule Extraction

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Purpose: To assess changes in corneal epithelial thickness (ET) within 9-mm diameter cornea after photorefractive keratectomy (PRK) retreatment after small-incision lenticule extraction (SMILE).

Methods: A total of 28 eyes of 19 patients with mean spherical equivalent of -1.30 ± 0.60 D who underwent retreatment after SMILE were included in this retrospective study. ET mapped across a 9-mm diameter area was obtained using wide-field optical coherence tomography (OCT) before and at one, three, and six months after surgery. The ET changes were compared between the different time points and analyzed zones.

Results: Before enhancement, the ET were 63.64 ± 6.01 µm and 61.25 ± 4.32 µm in central and paracentral zones, respectively. The ET of central and paracentral zones significantly decreased at one month and subsequently increased until six months. Six months after surgery, significant epithelial thickening occurred in 2- to 9-mm diameter cornea (all $P < 0.05$), whereas no significant change was observed in central 2-mm diameter cornea ($P = 0.460$). There was no significant difference in the ET between the central and paracentral zones ($P = 1.00$). The degree of myopic correction significantly correlated with the average ET in the central ($P = 0.046$) and paracentral ($P = 0.033$) zones at six months after PRK enhancement. No significant correlation was detected between the average ET of all zones and the postoperative spherical equivalent at six months after surgery (all $P > 0.05$).

Conclusions: PRK enhancement did not alter the overall trend of corneal epithelial remodeling induced by SMILE. An asymmetric and flatter lenticule-like pattern of epithelial remodeling was observed six months after surgery, which did not affect the refractive outcomes.

Translational Relevance: An asymmetric and centrally flattened lenticule-like pattern of epithelial remodeling was observed after PRK enhancement. Surgeons should consider expanding the intended optical zones for enhancement surgery after SMILE.

Introduction

Although small-incision lenticule extraction (SMILE) has been proven to be safe, effective, predictable, and stable for the treatment of myopia and myopic astigmatism over the past decade,[1–3] the incidence of enhancement after SMILE ranges from 2.2% to 7.1%, as reported in previous studies.[4–6] Several enhancement alternatives have been proposed and developed, including surface ablation, CIRCLE, and thin-flap laser in situ keratomileusis (LASIK).[7,8] Of these surgeries, surface ablation, which has less impact on the corneal biomechanical structure, remains the most widely used enhancement procedure.[9]

Previous studies have shown that epithelial hyperplasia in different areas of the cornea after surgery may be related to intended spherical equivalent (SE) correction, optical zone diameter, and other factors.[10–12] However, the relationship between corneal epithelial remodeling and postoperative refractive changes remains controversial among studies,[12–15] and the specific mechanism requires further study.

In recent years, wide-field OCT systems have been widely used to evaluate epithelial thickness (ET) changes in 9-mm area after corneal refractive surgeries. Previous studies have reported the pattern of corneal epithelial remodeling after various surgeries, such as PRK, LASIK, and SMILE.[11,13,16,17] Our previous studies have also reported an asymmetric lenticule-like pattern of epithelial remodeling occurring in a 9-mm corneal diameter after SMILE.[11,14] However, to our knowledge, no study has reported the corneal epithelial remodeling in patients who underwent surface ablation retreatment after SMILE. To better understand the characteristics of epithelial remodeling in eyes requiring retreatment and the influences of surface ablation enhancement on the corneal ET in different area, the current study observed corneal epithelial remodeling across a 9-mm corneal diameter before and after PRK enhancement following SMILE using wide-field OCT and further explored its potential effect on refractive outcomes.

Patients and Methods

Patients

This retrospective study included 28 eyes of 19 patients who underwent PRK retreatment after myopic SMILE surgery for residual myopia or myopic astigmatism. The retreatments were performed at the Zhongshan Ophthalmic Center (ZOC) between July 2018 and March 2022. The study was approved by the Medical Ethics Committee of the ZOC and was conducted following the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

The inclusion criteria were as follows: patients who had previously undergone SMILE and were unsatisfied with uncorrected distance visual acuity (UDVA) because of residual refractive error from undercorrection or regression. The residual refractive error also included residual or consecutive astigmatism $\geq$ 0.5D. The interval between the SMILE and PRK enhancement was at least six months with a stable refraction (within 0.25D) for at least three months. Patients with postoperative complications (e.g., ocular hypertension, corneal scars and ectasia) and with systemic diseases or other ocular pathologies were excluded.

Patients underwent thorough preoperative ophthalmic examinations, including UDVA and corrected distance visual acuity (CDVA) assessment, manifest and cycloplegic refraction assessment, noncontact tonometry, slit-lamp biomicroscopy, dilated fundus examination, tear film breakup time assessment, Scheimpflug tomography with Pentacam HR (Oculus Optikgerate, Wetzlar, Germany), Sirius system combining Placido disk topography with Scheimpflug tomography (CSO, Florence, Italy), and ultrasound pachymetry (AL-1000; TOMEY, Nagoya, Japan). ET (9 mm diameter) was measured using RTVue-XR OCT one week before the PRK enhancement (version 2017.1.0.155; Optovue, Inc., Fremont, CA, USA).

SMILE Procedure

All SMILE procedures were standardized and sequentially performed under surface anesthesia by the same experienced surgeon (K.Y.). Manual corneal marking was performed preoperatively to ensure accurate axis alignment, as described in our previous studies.[18,19] A VisuMax 500-kHz femtosecond laser (Carl Zeiss Meditec, Jena, Germany) was used to create a refractive lenticule and a 2-mm incision at 130° with an intended cap thickness of 110 to 120 µm. The lenticule diameter was set as 6.0 to 6.8 mm, and the transition zone was set at 0.1 mm during cylinder correction. The surgical procedures were centered on the coaxially sighted corneal light reflex. After scanning, the lenticule was dissected using a blunt dissector and extracted through a side cut. The interface was flushed with a balanced salt solution.

PRK Enhancement Procedure

All surgical procedures were performed under surface anesthesia by the same surgeon (K.Y.) using an AMARIS 750S excimer laser (Schwind Eye-Tech-Solutions, Kleinostheim, Germany). The central 9.00-mm cornea epithelium was delineated with a trephine and removed mechanically using a dull-edged spatula in a centripetal fashion. Then the excimer laser ablation was performed on the corneal stroma with a standard ablation algorithm afterward. All procedures were performed with at least a 6.80-mm ablation zone, with a transition zone between 0.33 and 1.1 mm. At the end of each procedure, a soft-bandage contact lens (Pure Vision Technology, Inc., Fort Lupton, CO, USA; Bausch & Lomb, Rochester, NY, USA) was placed on the treated eyes until re-epithelialization was complete. A drop of 0.5% moxifloxacin (Vigamox; Alcon Laboratories, Inc., Geneva, Switzerland) was administered to the treated eye. Patients were prescribed 0.5% moxifloxacin eye drops and a combination of 0.3% tobramycin and 0.1% dexamethasone eye drops (Maxidex; Alcon Laboratories, Inc.) four times per day for one week, 0.1% fluorometholone eye drops, and preservative-free lubricating drops were administered four times daily for the following three weeks. The eye drops were tapered over three months.

Patients were followed up at one day, one month, three months, and six months after PRK enhancement. The UDVA and slit-lamp examinations were performed during each follow-up visit. CDVA, manifest refraction, IOP measurement and OCT scanning were performed at one, three, and six months after surgery.

Corneal Epithelial Thickness Measurements

The RTVueXR OCT system (Optovue, Inc) with a corneal adaptor module was used to measure the corneal ET using the "Pachymetry-Wide" scan mode before and after surgery. The ET map of the 9 mm diameter zone was automatically generated and divided into 25 sectors by four circles and eight meridians, including the central (within 2 mm), paracentral (2–5 mm), mid-peripheral (5–7 mm), and peripheral (7–9 mm) zones. The mean ET was displayed for each sector.

The same experienced investigator (Y.Y.) performed all the OCT scans before and at one, three, six months after PRK enhancement. The accuracy and repeatability of this OCT device in ET measurement have been proved in various studies,[20–22] and the protocol was consistent with our published studies.[11,23,24] In brief, the use of eye drops was prohibited for two hours before each scan. While "Green" was displayed on the signal strength bar, both horizontal and vertical reflection stripes were simultaneously observed. Patients were told to blink quickly, and the scan was acquired. Three consecutive scans were conducted on each eye centered on the pupil with a difference of no more than 1 μm in ET among them, and the average value was selected for analysis. All measurements were conducted between 2:00 PM and 5:00 PM to reduce the impact of diurnal variations on ET.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 23.0; SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD). The normality of the variables was assessed using the Kolmogorov–Smirnov test.

Preoperative and postoperative comparisons of the average ET were performed for different zones and sections using the Friedman test or repeated measures ANOVA. Bonferroni correction was used for post hoc analysis. A paired *t*-test was used to detect differences in ET between different sections. Spearman's rank correlation test was used to determine the association between the average ET of different zones and treatment parameters and the relationship between ET remodeling and refractive error at six months. Statistical significance was set at $P < 0.05$.

Results

Demographics

This study included 28 eyes of 19 patients out of 39476 consecutive eyes (0.07%) with post-SMILE residual refractive error for refractive enhancement. PRK treatment was bilateral in nine (47.37%) and unilateral in 10 (52.63%) patients (seven patients in the right eye and three patients in the left eye). The mean time interval between SMILE and PRK enhancement was 15.25 ± 7.95 months (range 6 to 28 months). Demographic data and surgical parameters of the SMILE and PRK groups are presented in Table 1. No postoperative complications such as epithelial defects, diffuse lamellar keratitis, or intraocular pressure spikes caused by steroid use were observed in the participants, except for that in one patient with grade 1 corneal haze in the left eye.

Visual and Refractive Outcomes After PRK Enhancement

The visual and refractive outcomes at all follow-up points after PRK enhancement are summarized in Table 2. UDVA (logMAR) and SE improved significantly compared to the preoperative values at each follow-up point (all $P < 0.05$), with a final mean UDVA of 0.00 ± 0.06 and a final SE of 0.06 ± 0.29 D at six months after surgery. All eyes had a UDVA of 0.1 logMAR (Snellen: 20/25) or better, and 23 eyes (82.14%) had a UDVA of 0.0 logMAR (Snellen: 20/20) or better (Fig. 1). Twenty-seven (96.43%) eyes were within ± 0.50 D, and all eyes were within ± 1.0 D of the attempted SE correction. The efficacy and safety index were 0.99 ± 0.19 and 1.05 ± 0.18, respectively.

Table 1. Demographic Characteristics and Surgical Parameters Before SMILE and PRK Enhancement

Parameters	SMILE	PRK Enhancement
No. of eyes (n)	28	28
Patients (n)	19 (9 male, 10 female)	19 (9 male, 10 female)
Age at SMILE (years)	28.11 ± 6.53 (19–39)	28.11 ± 6.53 (19–39)
Time between SMILE and PRK (mo)	15.25 ± 7.95 (6–28)	15.25 ± 7.95 (6–28)
Sphere (D)	−7.24 ± 1.62 (−3.75 to −9.50)	−1.06 ± 0.73 (−3.25 to 1.00)
Cylinder (D)	−0.80 ± 0.92 (0 to −3.75)	−0.47 ± 0.53 (0 to −2.50)
SE (D)	−7.64 ± 1.51 (−4.62 to −10.50)	−1.30 ± 0.60 (−0.25 to −3.25)
UDVA (logMAR)	1.36 ± 0.20 (0.92–2.00)	0.33 ± 0.17 (0.10 to 0.92)
CDVA (logMAR)	−0.02 ± 0.05 (−0.08 to 0.15)	−0.01 ± 0.07 (−0.18 to 0.15)
Central corneal thickness (µm)	551.46 ± 26.01 (510–591)	450.71 ± 25.43 (410–500)
Keratometry (D)	43.94 ± 1.44 (41.45–46.40)	39.17 ± 1.67 (39.54–41.85)
TBUT (s)	8.58 ± 1.9 (5–12)	7.67 ± 2.1 (4–10)
Surgical Parameter		
Optical zone (mm)	6.44 ± 0.25 (6.00–6.80)	6.67 ± 0.19 (6.20–7.00)
Ablation zone (mm)	6.54 ± 0.25 (6.10–6.90)	7.44 ± 0.21 (6.83–7.89)
Planed ablation max (µm)	136.64 ± 19.94 (87–165)	27.13 ± 9.84 (13–52)
Planed ablation center (µm)	NA	24.69 ± 8.21 (12.37–44.22)

Central corneal thickness was measured by ultrasound pachymetry. Values are presented as mean ± standard deviation (range).

Table 2. Postoperative Refractive Outcomes of PRK Enhancement

	1 Month After Surgery	3 Months After Surgery	6 Months After Surgery
UDVA (logMAR)	0.03 ± 0.09 (−0.08 to 0.30)	0.00 ± 0.05 (−0.08 to 0.10)	0.00 ± 0.06 (−0.08 to 0.15)
CDVA (logMAR)	−0.02 ± 0.05 (−0.08 to 0.10)	−0.03 ± 0.04 (−0.08 to 0.05)	−0.03 ± 0.05 (−0.08 to 0.10)
SE (D)	0.22 ± 0.38 (−0.25 to 1.00)	0.04 ± 0.29 (−0.37 to 0.75)	0.06 ± 0.29 (−0.50 to 0.75)
Sphere (D)	0.36 ± 0.40 (−0.25 to 1.00)	0.18 ± 0.29 (−0.25 to 0.75)	0.10 ± 0.28 (−0.50 to 0.75)
Cylinder (D)	−0.28 ± 0.35 (−1.25 to 0)	−0.26 ± 0.40 (−1.50 to 0)	−0.08 ± 0.18 (−0.50 to 0)

Values are presented as mean ± standard deviation (range)

Corneal Thickness and ET Changes Before and After PRK Enhancement

Figure 2 shows the longitudinal changes in the average ET in 25 sections. Before PRK enhancement, the average ET of the central 2 mm diameter cornea was 63.64 ± 6.01 µm (range 53.33 to 74.00 µm), and the average ET decreased eccentrically to the peripheral zone. Moreover, there was an extra epithelial thickening of 2.39 ± 2.48 µm centrally than paracentrally ($P < 0.001$). The average ET of the temporal section was significantly greater than the nasal section in the paracentral zone (63.04 ± 5.09 vs. 60.39 ± 4.19 µm, $P < 0.001$) rather than the mid-peripheral zone (54.68 ± 3.92 vs. 54.07 ± 4.00 µm, $P = 0.400$).

The longitudinal ET changes in all analyzed zones are shown in Figure 3 and Table 3. In the first postoperative month, a significant decrease in the average ET was observed in the central and paracentral zones (all $P < 0.05$), whereas the average ET of the mid-peripheral and peripheral zones were unaltered compared to the preoperative values (all $P > 0.05$). The average ET in all zones continued to increase until the sixth month (all $P < 0.05$). Six months after surgery, the average ET in the central zone reached baseline values ($P = 0.460$), whereas the mean ET in the paracentral, mid-peripheral, and peripheral regions remained higher than the baseline values (the paracentral, mid-peripheral and peripheral mean epithelium is 2.82, 2.77, and 1.50 µm thicker than baseline values, respectively; all $P < 0.05$). Although, no significant difference was found in the mean ET between the central and paracentral zones ($P \geq 0.99$). A maximum ET increase of 4.02 ± 4.47 µm was observed in the temporal section of the paracentral zone. The average ET of the temporal section (67.64 ± 6.05 µm) was significantly greater than the nasal section (61.79 ± 5.96 µm) in the paracentral zone ($P < 0.001$). The

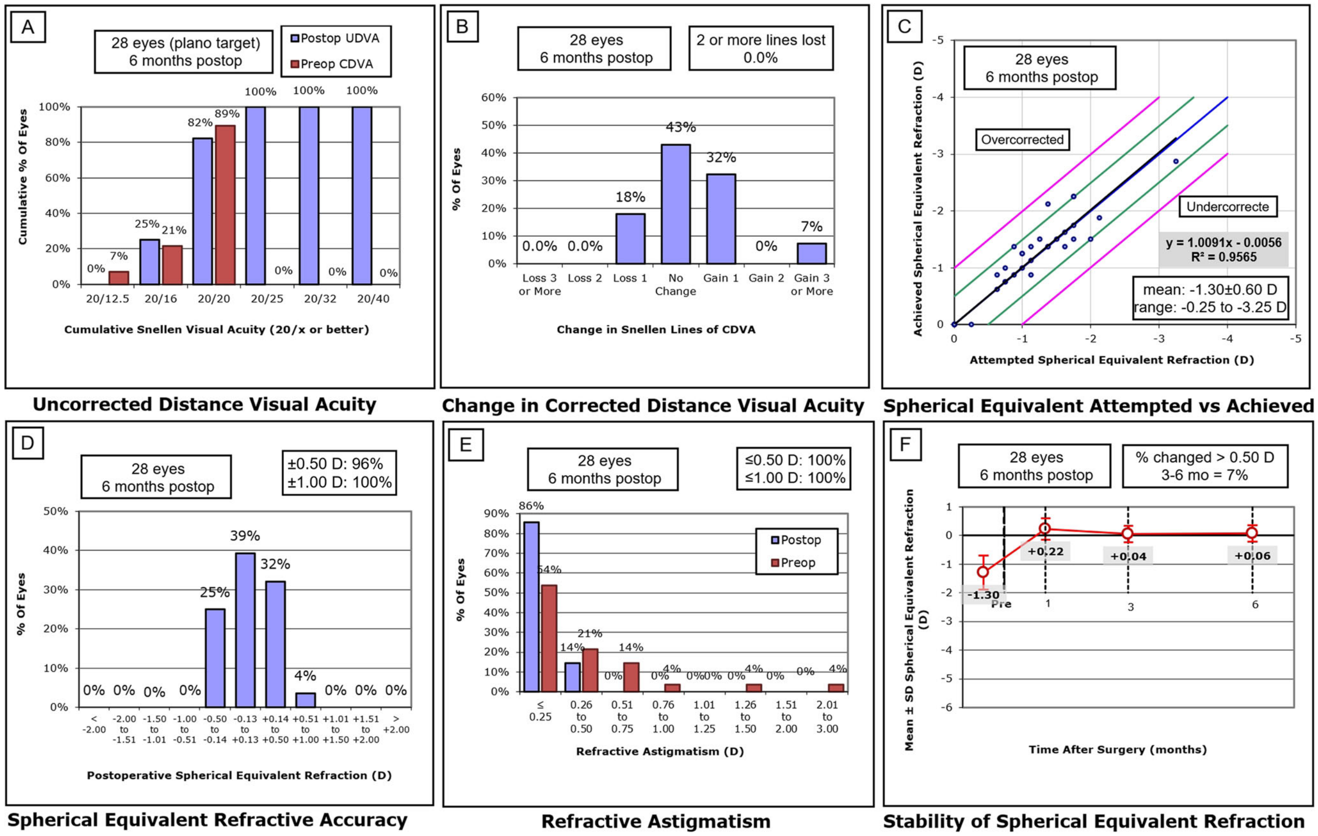

Figure 1. Visual and refractive outcomes at six months after PRK enhancement. (A) Cumulative UDVA six months after surgery and CDVA before surgery. (B) Changes in Snellen lines of CDVA after surgery. (C) Attempted versus achieved spherical equivalent refraction at six months after surgery. (D) Spherical equivalent refraction accuracy. (E) Comparative amplitude of preoperative and six-month postoperative astigmatism. (F) Spherical Equivalent Refraction Stability.

central corneal thickness significantly decreased after PRK enhancement at all follow-up time points (all $P < 0.001$), and average central corneal thickness at six months was significantly greater than that at 1 month after surgery ($P < 0.05$).

Correlation Analysis

The pre-SMILE spherical diopters were significantly related to the average ET in central and paracentral zones before and six months after PRK enhancement (before PRK: central: $r = -0.410$, $P = 0.030$; paracentral: $r = -0.413$, $P = 0.029$; after PRK: central: $r = -0.416$, $P = 0.028$; paracentral: $r = -0.479$, $P = 0.010$). Moreover, the pre-PRK SE was also negatively correlated with the average ET in the central ($r = -0.424$, $P = 0.024$) and paracentral ($r = -0.379$, $P = 0.047$) zones before and six months after PRK enhancement (before PRK: central: $r = -0.424$, $P = 0.024$; paracentral: $r = -0.379$, $P = 0.047$; after PRK: central: $r = -0.381$, $P = 0.046$; paracentral: $r = -0.404$, $P = 0.033$). However, there was no significant correlation between the postoperative SE and ET six months after PRK enhancement in all analyzed zones (all $P > 0.05$). Additionally, the intended diameter of optical zone in PRK enhancement was positively correlated with the difference of ET between paracentral and central zones ($r = -0.381$, $P = 0.045$), and with the difference of ET between mid-peripheral and central zones ($r = -0.379$, $P = 0.047$) at six months after surgery.

Discussion

In this study, we mapped a 9-mm diameter area of corneal ET in patients who required PRK enhancement after SMILE. The post-SMILE corneal epithelial remodeling presented an asymmetric lenticule-like pattern in which the ET was thickest in the central 2-mm zone and progressively thinning from center to periphery, the mean ET of temporal zone was thicker than the nasal zone in 2-5 mm annular area. These phenomena were consistent with the results of our previous study[11] and with the results of Fan et al.[25]

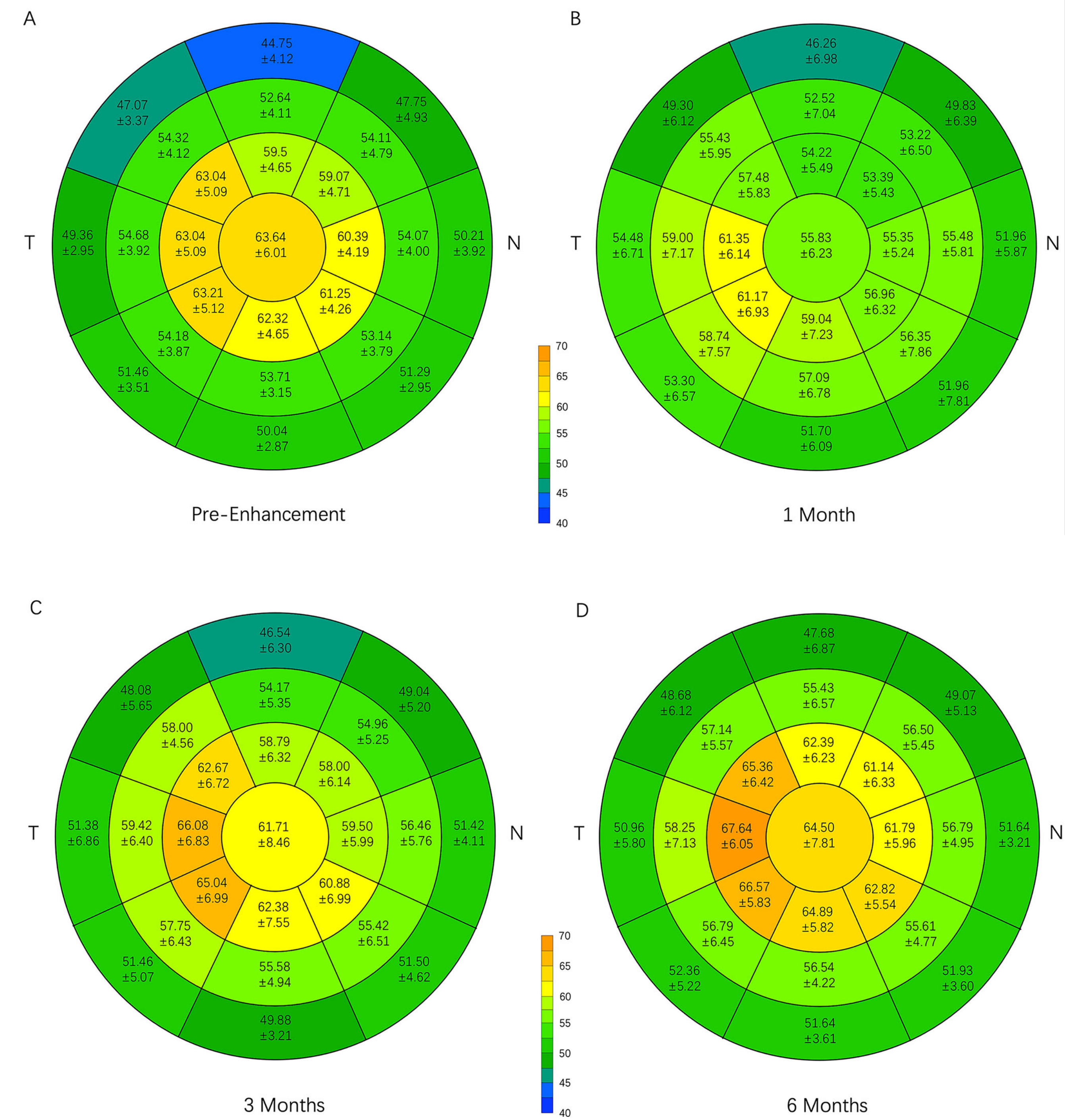

Figure 2. The 9-mm diameter epithelial thickness map from pre-enhancement to six months postoperatively. The corneal epithelial thickness of all 25 sections was presented by the mean and standard deviation (n = 28 eyes). N = nasal; T = temporal

on myopic eyes after femtosecond-assisted LASIK. However, the distribution of ET in this study differed from that of healthy patients after SMILE in other studies,[10,16] in which epithelial hyperplasia was more pronounced in the paracentral 2-5mm zone than that in the central 2-mm zone. The present results further identified the relationship between the postoperative refraction and ET difference in the central and paracentral zones in our previous study,[11] indicating that a more protrusive "epithelium lenticule" within the central 5-mm areas might play an important role in postoperative refractive regression. In addition, horizontal asymmetry of epithelial thickening in the temporal and nasal zones could be explained by the

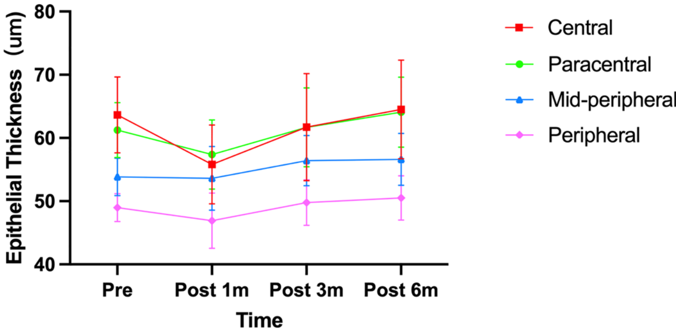

Figure 3. Line chart of mean epithelial thickness before and after photorefractive keratectomy enhancement separately in the central (2 mm), paracentral (2 to 5 mm), midperipheral (5 to 7 mm), and peripheral (7-9 mm) zones (n = 28 eyes).

mechanical force exerted by blinking and correction of astigmatism of the SMILE surgery[25].

Corneal epithelial changes after PRK surgery have been reported in various studies.[16,26–28] Unlike these studies, the mean preoperative ET of the central 5-mm diameter cornea in the present study was significantly thicker than the normal cornea, which was caused by the compensatory thickening of corneal epithelium after SMILE. At one month after surgery, the average ET of the central and paracentral zones was still lower than the preoperative values, whereas the average ET of the mid-peripheral and peripheral zones recovered to the preoperative values. The ET of all zones continued to increase from one month to six months after PRK enhancement. This trend of epithelial remodeling was similar to the findings of Sedaghat et al.[16] and Latifi et al.,[28] although they reported a significant decrease of ET in mid-peripheral and peripheral zones in 1 month after PRK. This discrepancy may be due to the different diameter of ablation zone and the different surgical procedure, in which Sedaghat et al.[16] applied mitomycin C to minimize the incidence of postoperative haze. In contrast, Chen et al.[26] reported that the average ET of the central and paracentral zones was thicker at postoperative one month compared to preoperative measurements, and the highest increase in ET was observed between postoperative one and three months, with no significant change from three to six months. These difference could be explained by the lower amounts of refractive correction and ablation depth in our study.

At six months after surgery, our results showed no significant difference of ET in the central 2-mm zone compared with the preoperative value, whereas the mean ET of the paracentral, midperipheral, and peripheral zones were higher than the preoperative values. Moreover, no significant difference in the mean ET was found between the central and paracentral zones, the ET across 9-mm diameter cornea exhibited an asymmetric lenticular pattern with a flatter central 5-mm zone compared with the pre-PRK epithelial pattern. Although previous studies [16,26] in normal patients have shown a thicker ET in the paracentral zone than in the central zone, this variation may be attributed to the discrepancy of preoperative ET differences between the central and paracentral zones. The optical zone diameter (6.2 to 7.0 mm) of PRK enhancement was significantly larger than that of primary SMILE surgery in this study, which may also account for the flatter "epithelium lenticule" in the central 5-mm diameter cornea after surgery. The positive correlation between the intended diameter of OZ and the differences between the central and paracentral mid-peripheral zones at six months after

Table 3. Central Corneal Thickness and Corneal Epithelial Thickness (µm) Before and After PRK Enhancement

Parameters	Preop (1)	1 Month Postop (2)	3 Months Postop (3)	6 Months Postop (4)	*P* Value
Central corneal thickness (µm)	449.50 ± 26.76 (411 to 495.33)	412.74 ± 29.22 (375 to 468)	419.42 ± 27.59 (376.33 to 467)	424.61 ± 28.41 (380 to 477.66)	*P* < 0.001 [2, 3: 0.460; 3,4:0.134; Other pairs: < 0.05]
Central ET (µm) (a)	63.64 ± 6.01 (53.33 to 74.00)	55.83 ± 6.23 (47.66 to 68.00)	61.71 ± 8.46 (52.00 to 82.33)	64.50 ± 7.81 (54.00 to 81.33)	*P* < 0.001 [1, 3: 0.826; 1, 4: 0.460; Other pairs: < 0.05]
Paracentral ET (µm) (b)	61.25 ± 4.32 (53.88 to 68.00)	57.37 ± 5.48 (49.63 to 70.13)	61.67 ± 6.23 (53.38 ± 76.00)	64.08 ± 5.55 (56.25 to 72.50)	*P* < 0.001 [1, 3: 1.00; 3 ,4: 0.099; Other pairs: < 0.05]
Mid-peripheral ET (µm) (c)	53.86 ± 2.97 (47.75 ± 58.88)	53.60 ± 5.06 (47.00 to 68.50)	56.41 ± 3.98 (49.75 to 64.13)	56.63 ± 4.11 (49.38 to 65.13)	*P* = 0.001 [1, 2: 1.00; 1, 3: 0.460; 2, 3: 0.084; 3, 4: 1.00; Other pairs: < 0.05]
Peripheral ET (µm) (d)	48.99 ± 2.20 (44.88 to 54.00)	46.93 ± 4.39 (41.45 to 59.45)	49.79 ± 3.61 (44.50 to 56.13)	50.50 ± 3.51 (43.88 to 57.75)	*P* = 0.002 [1, 2: 0.115; 1, 3: 1.00; 2, 3: 0.072; 3, 4: 1.00; 1, 4: 0.826; Other pairs: < 0.05]
P value	*P* < 0.001 [all pairs: < 0.001]	*P* < 0.001 [a, c: ≥0.99; a, b: 0.520; b, c: 0.061; Other pairs: < 0.05]	*P* < 0.001 [a, c: ≥0.99; a, b: 0.974; b, c: 0.071; Other pairs: < 0.05]	*P* < 0.001 [a, b: ≥0.99; Other pairs: < 0.05]	

All thickness were measured by OCT; Values are presented as mean ± standard deviation (range).

surgery also supported this hypothesis from another perspective.

In agreement with previous studies, the greatest thickening annular analysis area herein was observed in the paracentral zone (2.82 μm) at six months after enhancement surgery. However, the value of ET thickening was lower than that of these studies.[16,28] Moreover, the degree of epithelial thickening in the midperipheral zone, rather than the central zone, was found to be second only to the paracentral zone, which was in contrary to the results of Sedaghat et al.[16] and Latifi et al.[28] The possible explanations were the relatively lower SE of correction and larger intended diameter of OZ in our study, which allows the transition zone to fall in the peripheral zone.

The correlation analysis in our study showed that the pre-SMILE spherical errors not only correlated with the ET in central and paracentral zones before the PRK retreatment, but also after the retreatment. Although the corneal stromal tissue ablation depth in our enhancement was relatively small, the ET of central and paracentral zones before and after enhancement were still negatively correlated with the pre-PRK refractive error. These results indicated that the enhancement procedure has not changed the overall trend of epithelial thickening in moderate to high myopic eyes after SMILE surgery, which could be explained by the "rate of change of curvature" hypothesis[29] and the mechanical pressure of the eyelids. In contrast, no significant correlation was found between the postoperative SE at six months and the average ET of different zones after PRK retreatment in the current study, which corresponds with previous findings.[15,26,30] This phenomenon may be attributed to our study's relatively small sample size, good refractive results, less epithelial thickening, and smaller differences between central and paracentral ET.

The incidence of enhancement after SMILE in our study was 0.07%, which was far lower than that reported in other literature.[5–7] There are several possible explanations for this. First, the patients in the present study were enrolled from July 2018; the use of coaxially sighted corneal light reflex centering method and cyclotorsion compensation may have reduced the incidence of enhancement because of decentration and irregular astigmatism. Second, the nomogram of SMILE (10% correction increment over the SE value) used in our clinic may have minimized the incidence of undercorrection. Third, plenty of patients with mild refractive regression have acceptable UDVA and were unwilling to undergo retreatment.

Our study had some limitations. First, this retrospective study lacked data of ET and stromal thickness before SMILE surgery; thus their changes could not be comprehensively analyzed after SMILE. The corneal stroma or the epithelium, which plays a more important roles in refractive regression, still needs to be further studied. Second, we did not analyze the influence of postoperative dry eye on ET changes. Previous studies reported that dry eyes could affect ET.[31,32] However, the patients with preoperative moderate-to-severe dry eyes were excluded before SMILE, and no patient has severe complaints and symptoms of dry eye before and after PRK enhancement. Hence, the present results should not be significantly influenced by the dry eye. Third, the relatively small sample size limited multiple linear regression analysis. Further multicenter studies are warranted to include more patients and determine the specific mechanism.

In conclusion, this is the first study to report a wide-field epithelial remodeling profile across a 9-mm diameter cornea after PRK enhancement. The retreatment procedure did not alter the overall trend of corneal epithelial thickening, and an asymmetric and flatter lenticule-like pattern of epithelial remodeling was observed six months postoperatively. The present results suggest that a larger diameter of optical zone may contribute to a flatter corneal epithelial lenticule in central 5-mm cornea, which could minimize postoperative epithelial hyperplasia and obtain a stable refractive outcome in surface ablation retreatment after SMILE. A comprehensive evaluation of wide-field ET maps may help clinicians better understand the influence of ET on refractive regression and enhancement surgery.

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* YY and XH contributed equally as co-first authors.

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