• Clinical Research •

One year results of presbyLASIK using hybrid bi-aspheric micro-monovision ablation profile in correction of presbyopia and myopic astigmatism

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Abstract

● **AIM:** To analyze one year clinical outcomes and subjective rating of hybrid bi-aspheric multifocal central presbyLASIK with micro-monovision for correction of presbyopia and myopic astigmatism.

● **METHODS:** Seventy-four eyes of 37 patients consecutively treated with presbyLASIK were assessed. The mean age of the patients was 43.8±3.0y with a mean spherical equivalent refraction of -5.21±1.87 diopters (D) and mean astigmatism of -0.82±0.64 D. Visual acuity, manifest refraction, contrast sensitivity, aberrometry and patients' subjective rating were evaluated pre- and postoperatively.

● **RESULTS:** At 1y postoperatively (68 eyes of 34 patients), the mean spherical equivalent (SE) refraction in distance eyes was 0.06±0.05 D, whereas the achieved SE in near eyes was -0.83±0.05 D. Ninety-nine percent of eyes were within ±0.50 D of target correction of SE. The binocular mean uncorrected distance visual acuity (UDVA) was 0.00±0.18 logMAR (20/20). Sixty-four percent of patients achieved 0.0 logMAR (20/20) or better of UDVA and 0.1 logRAD or better of UNVA as well. There was a binocularly loss of one line CDVA after surgery for only one patient (3%, 1/34) and no patient lost 2 lines. The changes in binocular contrast sensitivity (CS) in all test conditions were not significant at any frequency after surgery. The changes of entire eye total higher order aberrations (tHOA) and spherical aberrations (SA) significantly higher in near eyes than in distance eyes. The overall satisfaction score for surgery was 93±8.

● **CONCLUSION:** The hybrid bi-aspheric multifocal central presbyLASIK with micro-monovision appears to be an efficacious option for myopic presbyopes. One year postoperative outcomes in a relatively young presbyopia population indicate improvements in both far and near vision with high satisfaction.

● **KEYWORDS:** presbyLASIK; presbyopia; monovison; myopia

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INTRODUCTION

With the development of refractive surgery technology, cornea laser refractive surgery is becoming more prevalent today in patients with myopic astigmatism. Among these patients, many of them with presbyopia or presbyopia-like syndrome in relatively young patients which manifests as decrease in accommodative amplitude and poor near vision. Presbyopia is an inevitable refractive disorder due to people aging, which commonly commence in people around 40y[1]. Nowadays, it's still a challenge to restore the decreased accommodation amplitude consequence of aging[2-3]. How to effectively treat refractive errors and simultaneously improve near vision in these patients has been an elusive goal for laser refractive surgeons.

Cornea has been found can partly compensate the loss of accommodation due to the crystalline lens stiffen with aging by special cornea surface ablation, such as creation of a multifocal optical profile. For this purpose, different laser platforms and surgical techniques have emerged in recent years for transferring controllable amounts of multifocality at the cornea surface and effectively alleviating presbyopia syndrome[4-7]. Vargas-Fragoso and Alió[3] performed presbyLASIK to create a multifocal corneal surface based on traditional LASIK. Due to add multifocal profile, presbyLASIK is able to correct distance visual defect while improve near vision performance as well in myopic or hyperopic presbyopia patients[4]. This presbyopia approach can be combined with distant emmetropia as well as myopia and hyperopia with or without astigmatism[8].

Table 1 Questionnaire of patients' satisfaction

1. Evaluate your near vision (*e.g.* reading book or cellphone) before/after treatment, the satisfaction score is:
Score (0-100): 0 indicated not at all satisfied and 100 indicated completely satisfied.
2. Evaluate your distance vision before/after treatment, the satisfaction score is:
Score (0-100): 0 indicated not at all satisfied and 100 indicated completely satisfied.
3. Do you depend on glasses before/after treatment?
Score (0-100): 0 indicated completely depend on glasses and 100 indicated have no need glasses.
4. Considering all the items related to the treatment , the overall satisfaction score is:
Score (0-100): 0 indicated not at all satisfied and 100 indicated completely satisfied.

The purpose of this study was to identify whether presbyLASIK with the aspheric ablation algorithm using a hybrid bi-aspheric multifocal central protocol with micro-monovision is a safe and effective method to treat myopic astigmatism with presbyopia.

SUBJECTS AND METHODS

Ethical Approval This study followed the tenets of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Zhongshan Ophthalmic Center; Sun Yat-Sen University (No.2016-012). All patients had been fully informed of the purpose and methods of the present study and provided written informed consent from themselves or their guardians.

Patient Population and Examinations This study was a prospective, non-comparative case series. Seventy-four eyes of 37 patients were enrolled from Zhongshan Ophthalmic Center in Guangzhou, China. Inclusion criteria include suitable for LASIK, presbyopic with a corrected distance visual acuity (CDVA) of 20/25 or better in both eyes, tolerance of at least -0.75 D anisometropia, photopic pupil diameter smaller than 3.5 mm and mesopic pupil diameter lager than 4.5 mm [the photopic pupil data from topografic (offset) information but mesopic/scotopic from pupillometry], had stable refraction for at least 1y before the study [<0.5 D change in mean spherical equivalent (SE)], and discontinued contact lenses for at least 2wk before the preoperative evaluation[9]. Exclusion criteria were systemic illness, previous ocular surgery, abnormal corneal topography and clinically relevant lens opacity, any signs of binocular vision anomalies at distance and near and a pupil offset of 0.7 mm or more.

A complete slit-lamp examination of the anterior segment was performed pre- and post- operation. Baseline examinations included measurement of manifest refraction, corrected and uncorrected distance visual acuity (CDVA and UDVA) and uncorrected near visual acuity (UNVA), corrected near visual acuity (CNVA), distance corrected near visual acuity (DCNVA), aberrometry, contrast sensitivity and presbyopic addition. Postoperative follow-up visits were scheduled at 1d, 1wk, 1, 3, 6mo, and 1y after surgery. Near acuity was measured using the Sloan Letter Near Vision Card-729000 (GOOD-LITE®, IL, USA). Contrast sensitivity measured with iTrace (Tracey Technologies Corp. Houston, USA).

Patient satisfaction was evaluated pre- and at 1, 3, 6mo, and 1y after surgery using satisfaction questionnaire[10-11]. Questionnaire of patients' satisfaction was shown in Table 1.

The Sirius tomograph and corneal topographer (Schwind eye-tech-solutions, software version 2.6.3, Kleinostheim, Germany) was used to capture corneal data for surgery design and to obtain pupil data at mesopic and scotopic conditions. For perfect corneal data and alignment of patients, only high quality acquisitions of cornea tomography [with static cyclotorsion component (SCC) check passed and 14th placido circle (approx. 7 mm coverage) completed as minimum] were used for surgery design.

Treatment Plan Patients were tested to determine their dominant eye by the "hole test"[12]. No multifocal contact lens trials were performed. However, postoperative micro-monovison was simulated using trial frames. After applying full manifest correction in both eyes using trial frame, a positive sphere (from +1.50 D) was added to the non-dominant eye while the examiner explain to the patient about the different impression between two eyes for distance and near using and ask the patient about the general impression of the visual discomfort and any possible visual disturbances. Patients were counseled to expect an adaptation period to the new vision impressions of up to 3mo after surgery. The PresbyMAX treatment planning module in hybrid mode (Schwind eye-tech-solutions, Kleinostheim, Germany) was used to generate the ablation profiles. The sphere and cylinder values entered into the laser were based on the manifest refraction without nomogram adjustment. The patient's addition value was proposed by the planning software according to the age of the patient, and was changed manually according to the patient's SE refraction to ensure inducement of multifocality (2.15±0.32 D; range, 1.75 to 2.50 D; median, 2.00 D). In our study an addition value was overplanned by 0.50 to 0.75 D when patient's SE greater than -4 D. All eyes underwent the refractive treatment using 6.0 to 7.0 mm diameter optical zones (OZs). Selection based on the preoperative scotopic pupil diameter. The size of the optimal transition zone was calculated depending on the preoperative refraction and OZ. The total ablation zone ranged from 6.5 to 8.3 mm.

Excimer Laser All surgeries were performed by one experienced surgeon (Liu Q). All eyes underwent presbyLASIK using an AMARIS 750S excimer laser (SCHWIND eye-tech-solutions, Kleinostheim,Germany). LASIK flaps were all cut using VisuMax femtosecond laser platform (Carl Zeiss Meditec, Jena, Germany) with superior hinge, 100-μm intended flap thickness, and a 8.4 or 8.5 mm intended flap diameter.

Alignment and Eye Movement Track After patient lie on the operative bed of the excimer laser machine, the surgeon adjusted patient's head position to check for possible cyclotorsion. After lifting the flap, the surgeon chose the SCC check button to begin the SCC check procedure. If the SCC measurement was successful and the absolute value of SCC was ≤2 degrees, then the SCC value was taken immediately for treatment. If the absolute value of first SCC measurement was >2 degrees, it was repeated to a maximum of 3 tries to check consistency before taken for treatment. If no successful measurement was obtained, new SCC measurement tries were carried out (to a maximum of 3). After 3 tries, either the SCC value was reproducible and taken or no SCC value was used for treatment. Dynamic cyclotorsion was corrected automatically by the laser integrated 6D eye tracking system during the whole ablation process in all cases. Patients were informed to concentrate on the fixation light and the dynamic cyclotorsion component (DCC) was recorded during whole excimer laser. The ablation profile was centered on the corneal vertex - with use of Schwind's symmetric centring strategy-determined by the Sirius diagnostic device topographer (taking 70% of the pupil offset value), which closely approximates the visual axis[9,13].

Data Analysis Outcome measures were assessed for normality according to the standardized guidelines set out by Waring[14]. Distance visual acuity was evaluated in logMAR but converted to equivalent Snellen fractions for reporting comparability. Statistical analysis used the SPSS statistical package (version 16.0; SPSS, Inc., Chicago, IL, USA). For normally distributed data, student paired *t*-tests were used. For non-normally distributed data, Friedman tests were performed. A *P* value less than 0.05 was considered statistically significant. Paired Student's *t*-tests were performed for UDVA, UNVA, CDVA, DCNVA and contrast sensitivity.

RESULTS

The average age of the 37 patients (11 males and 26 females) was 43.8±3.0y (range 40 to 51y). The mean preoperative SE was -5.21±1.87 D (-2.25 to -9.50), the mean preoperative astigmatism was -0.82±0.64 D (0 to -3.25) and the mean spectacle near addition of these 37 patients was +1.75±0.23 D (+0.75 to +2.00 D). Preablation iris recognition (SCC) was performed successfully in all eyes (74 out of 74; Table 2). In all these cases, the procedure was linked to the diagnostic image of the Sirius device. The mean amount of preablation SCC, *i.e.* the cyclotorsion of the eye while changing from upright to supine position, was -0.16±0.18 degrees, ranging from -3.4 to 2.7 degrees. The mean absolute SCC was 2.02±1.08 degrees. A total of 95% of SCC measurements were within 3 degrees, and no eyes showed SCC values >5 degrees.

Table 2 Summary of the preoperative data

Preoperative	Monocular eyes	Binocular patients
No.	74	37
Age (y)	-	43.8±3.0 (40 to 51)
Gender ratio (M:F)	-	0.42 (11:26)
UDVA (logMAR)	1.01±0.67 (1 to 2)	1.03±0.76 (1 to 2)
CDVA (logMAR)	-0.10±0.06 (-0.18 to 0.10)	-0.18±0.04 (-0.20 to 0.10)
UNVA (logRAD)	0.65±0.32 (0.4 to 1.0)	0.62±0.43 (0.3 to 1.0)
CNVA (logRAD)	0.00±0.08 (-0.1 to 0.2)	0.00±0.05 (-0.1 to 0.1)
SE (D)	-5.21±1.87 (-2.25 to -9.50)	-
Astigmatism (D)	-0.82±0.64 (0 to -3.25)	-
Add (D)	+1.75±0.23 (+0.75 to +2.00)	-
Pupil diameter (mm)		
Photopic pupil	2.76±0.12 (2.00 to 3.50)	-
Mesopic pupil	5.31±0.24 (4.50 to 6.70)	-
Scotopic pupil	6.12±0.45 (5.50 to 7.30)	-
Planned add (D)	-	2.15±0.32 (1.75 to 2.50)
Optical zone (mm)	6.51±0.32 (6.00 to 7.00)	-
Total ablation zone (mm)	6.89±0.24 (6.50 to 8.30)	-
Preablation SCC	-0.16±0.18 (-3.4 to 2.7)	-

UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; UNVA: Uncorrected near visual acuity; CNVA: Corrected near visual acuity; SE: Spherical equivalent; logMAR: Log minimum angle resolution; logRAD: Log reading acuity determination, the reading equivalent of logMAR; SCC: Static cyclotorsion component.

Efficacy The mean UDVA for distance eyes, near eyes, and binocularly was 0.00±0.09 logMAR (20/20), 0.27±0.15 logMAR (20/40), and 0.00±0.18 logMAR (20/20), respectively. The mean UNVA for distance eyes, near eyes, and binocularly was 0.25±0.18 logRAD, 0.01±0.14 logRAD, and 0.00±0.16 logRAD, respectively (Table 3). The distribution of binocular UDVA and UNVA are presented in Figure 1. The 79% (27 out of 34) of patients achieved 0.0 logMAR (20/20) or better binocular UDVA; 79% (27 out of 34) of patients achieved 0.1 logRAD or better UNVA; 64% of patients achieved at least 0.0 logMAR (20/20) of binocular UDVA and 0.1 logRAD of UNVA at the same time.

Safety All eyes achieved CDVA of 0.1 logMAR (20/25) or better postoperatively. The 6% (2/34) of distance eyes and 12% (4/34) of near eyes lost one line of CDVA. For near eyes, there is still 9% (3/34) lost 2 lines. There was a binocularly loss of one line CDVA after surgery for only one patient (3%, 1/34) and no patient lost 2 lines (Figure 2). No intraoperative complications occurred. At 1-year follow-up, monocular DCNVA ranged from +0.1 to +0.5 logRAD and from -0.1 to +0.4 logRAD binocularly. The improvement in binocular DCNVA was statistically significant (P<0.0001).

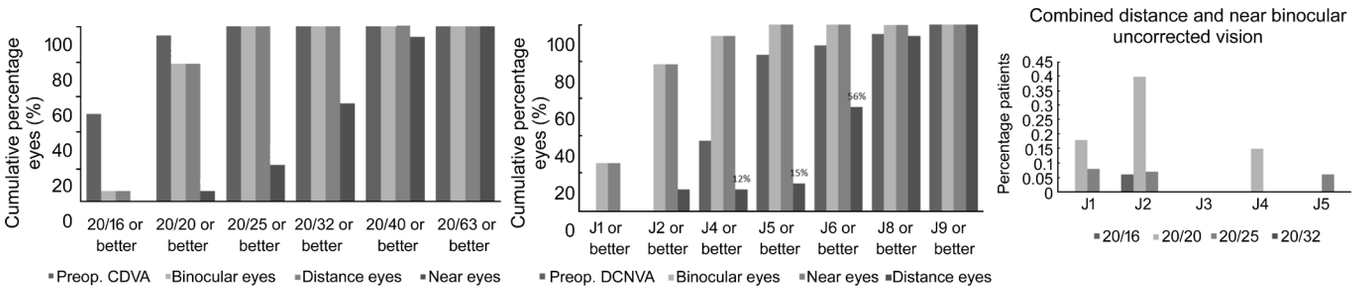

Figure 1 Changes in binocular uncorrected visual acuity at 1-year follow-up after treating with hybrid biaspheric multifocal central presbyLASIK.

Table 3 Summary of the postoperative data

1-year postoperative	Monocular eyes	Binocular patients
No.	68	34
UDVA (logMAR)	0.01±0.15 (-0.18 to 0.1)	0.00±0.18 (-0.18 to 0.1)
CDVA (logMAR)	0.00±0.04 (-0.18 to 0.0)	-0.05±0.05 (-0.18 to 0.0)
UNVA (logRAD)	0.10±0.13 (0.0 to 0.4)	0.00±0.16 (0.0 to 0.4)
CNVA (logRAD)	0.07±0.09 (0.0 to 0.1)	-0.03±0.05 (0.0 to 0.1)
SE (D)	-0.56±0.13 (-1.25 to 0.75)	-
Dominant eyes	-	0.06±0.05 (-0.25 to 0.75)
Non-dominant eyes	-	-0.83±0.05 (-0.50 to -1.25)
Astigmatism (D)	-0.23±0.24 (-1.00 to 0.25)	-
Dominant eyes	-	-0.18±0.15 (-0.75 to 0.00)
Non-dominant eyes	-	-0.27±0.12 (-1.00 to 0.25)

UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; UNVA: Uncorrected near visual acuity; CNVA: Corrected near visual acuity; SE: Spherical equivalent; logMAR: Log minimum angle resolution; logRAD: Log reading acuity determination, the reading equivalent of logMAR.

Aberration Outcomes The preoperative and postoperative entire eye (ocular) aberrations, cornea aberrations and internal aberrations were demonstrated in Table 4. Only values that obtained from a 5 mm scan diameter were used for compare. There were no statistically significant differences between the distance eyes (DE) and near eyes (NE) in all aberrations preoperatively. However, postoperative entire eye tHOA and SA in NE higher than DE significantly. tHOA and SA in NE also higher than DE significantly. There is no significant change in internal aberrations before and after surgery in both DE and NE. There were no statistically significant differences between DE and NE in coma, second astigmatism and trefoil aberrations before and after surgery.

Accuracy After 1y, the mean SE refraction of the distance eye was 0.06±0.05 D (range: -0.25 to 0.75), the attempted target SE for the near eye was -0.89 D, and the postoperative achieved SE was -0.83±0.05 (range: -0.50 to -1.25; Table 2). At one year postoperative, 99% of eyes were within ±0.50 D and 100% were within ±1.00 D of the attempted SE. 97% (33 out of 34) of distance eyes were within ±0.5 D of emmetropia while 91% (31 out of 34) of near eyes were within ±0.5 D of the intended micro-monovision target (-0.89 D); 97% (33 out of 34) of distance eyes and 94% (32 out of 34) of near eyes were within 0.5 D of refractive astigmatism. There were no eyes in which the SE refraction changed by over 0.75 D between 1d and 1y. At one year after surgery, the surgically induced astigmatism was within ±0.50 D of the target induced astigmatism in 90% (61 out of 68) of the eyes (Figure 3).

Contrast Sensitivity Compared in logarithmic scale, the changes in binocular contrast sensitivity from the preoperative values in all test conditions were not significantly different at any frequency (P>0.05). A more severe drop of contrast sensitivity threshold was observed at all spatial frequencies under mesopic lighting condition, but there were no significant differences before and after surgery (Figure 4).

Patient Satisfaction Questionnaire Table 5 presents patients' satisfaction scores after treating with hybrid biaspheric multifocal central presbyLASIK. One year after treatments, subjective satisfaction scores increased significantly (P<0.05 in all scales, paired Student's t-tests) and the satisfaction with correction was 93±8. Table 1 shown the questionnaire of patients' satisfaction.

DISCUSSION

This consecutive case series investigated the efficacy and safety in 37 presbyopic myopia patients or 74 myopic eyes, respectively, over a 1-year period. After 1y, most of our patients significantly improved in both far and near distances uncorrected binocular vision. The mean preoperative spectacle

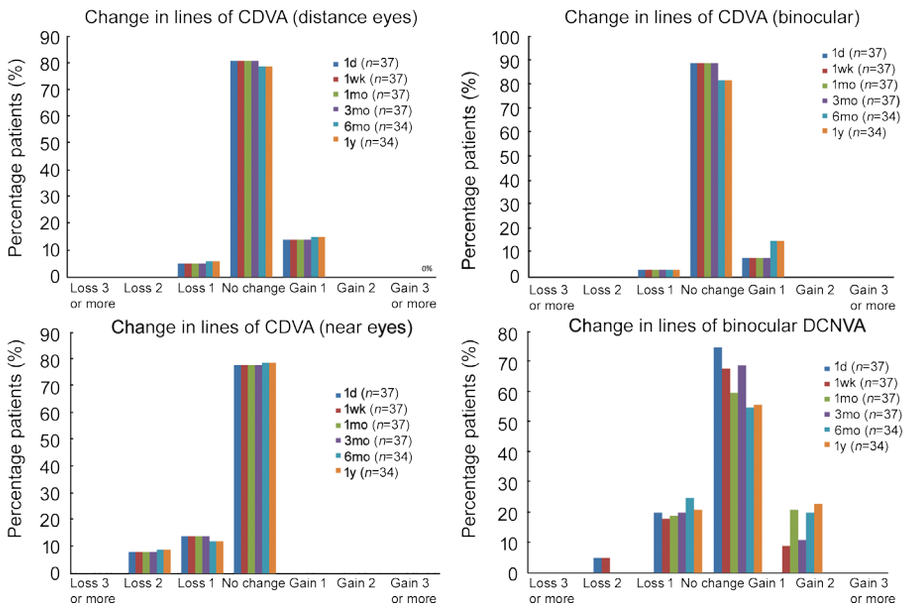

Figure 2 Changes in CDVA and DCNVA at 1y follow-up after treating with hybrid bi-aspheric multifocal central PresbyLASIK.

Table 4 Zernike coefficients of preoperative and postoperative aberrations in iTrace (analyzed diameter=5 mm)

Parameters	Pre-operation			Post-operation		
	DE	NE	*P*	DE	NE	*P*
Ocular						
tHOA	0.179±0.125	0.181±0.115	0.87	0.211±0.117	0.301±0.115	0.037
SA	0.023±0.035	0.021±0.075	0.94	-0.048±0.033	-0.121±0.047	0.000
Coma	0.091±0.047	0.090±0.061	0.76	0.161±0.037	0.184±0.028	0.37
Second astig	0.035±0.014	0.034±0.028	0.86	0.039±0.022	0.041±0.014	0.82
Trefoil	0.082±0.051	0.079±0.047	0.91	0.173±0.051	0.175±0.038	0.36
Conea						
tHOA	0.140±0.026	0.138±0.036	0.75	0.201±0.135	0.276±0.115	0.046
SA	0.044±0.009	0.046±0.011	0.85	-0.002±0.015	-0.061±0.019	0.000
Coma	0.084±0.035	0.081±0.018	0.74	0.086±0.041	0.091±0.054	0.76
Second astig	0.035±0.029	0.033±0.021	0.65	0.038±0.018	0.041±0.031	0.74
Trefoil	0.083±0.048	0.081±0.037	0.81	0.079±0.052	0.079±0.041	0.85
Internal						
tHOA	0.139±0.060	0.142±0.050	0.79	0.137±0.014	0.1356±0.031	0.73
SA	-0.027±0.047	-0.021±0.053	0.81	-0.024±0.047	-0.028±0.038	0.91
Coma	0.081±0.042	0.079±0.042	0.68	0.084±0.047	0.083±0.042	0.78
Second astig	0.041±0.038	0.043±0.038	0.76	0.052±0.018	0.054±0.027	0.93
Trefoil	0.074±0.035	0.072±0.015	0.46	0.068±0.015	0.066±0.005	0.95

DE: Distance eye; NE: Near eye; tHOA: Total higher order aberrations; SA: Spherical aberrations; Second astig: Second astigmatism.

near addition in our cohort was +1.75±0.23 D (+0.75 to +2.00 D).However, most of patients achieved significant enhancement in monocular and binocular postoperative UNVA. The myopic target in the non-dominant eye (target refraction -0.89 D) alone would not be enough for "spectacle-free" functional near vision. The post-surgery bi-aspheric multifocal cornea shape increases the depth of field, which as a result, provides functional near vision by non-accommodative factors (pseudo-accommodation)[6,9-10] .The DCNVA outcome of this study supports the efficacy.

Clinical outcomes of multifocal corneal ablation designs seems less predictable and at higher risk than those for other corneal modalities such as monovision or "laser blended vision (LBV)" in previous studies[3,15]. But our results look better than those of other researches in presbyLASIK treatment field[4,8] and seem to compared favorably with the results of other micro-monovision treatments[11-12]. The satisfaction questionnaire scores improved significantly after treatment. The high precision and small standard deviation in our refractive results should be one reason. In addition, the average age of patients in our study was 43y with the need of a spectacle near addition of 1.75 D in average which is considered a low to moderate

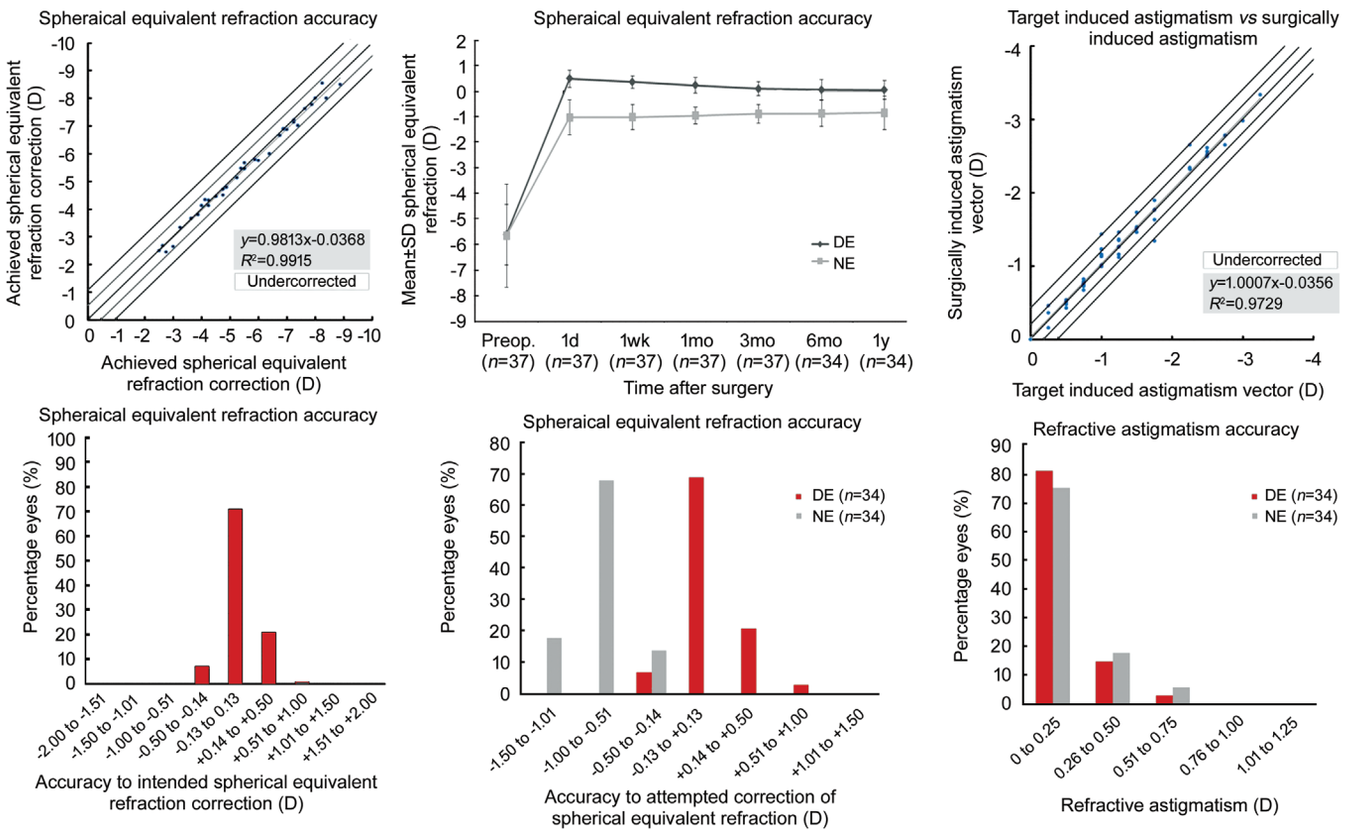

Figure 3 Refractive outcomes of the patients.

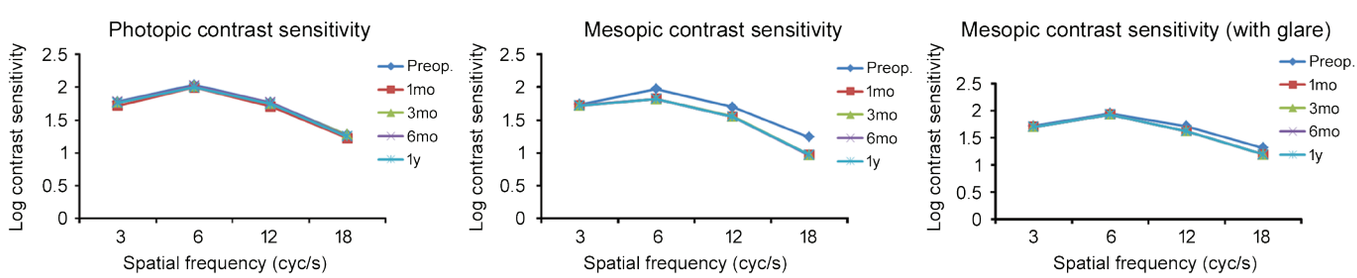

Figure 4 The preoperative and postoperative contrast sensitivity visual acuity.

Table 5 Postoperative patient satisfaction scores

Scale	Preoperative	Postoperative	*P*
Near vision	30±11	94±6	<0.05
Distance vision	37±12	92±7	<0.05
Dependence on correction	30±15	95±2	<0.05
Satisfaction with correction	56±14	93±8	<0.05

presbyopia. The micro-monovision portion with a myopic target of around 1.00 D is of additional help for sufficient UNVA. Like in other corneal refractive corrections[3,16], centering on the corneal vertex-in reference to the photopic pupil diameter for eye tracking purposes-is essential in central presbyLASIK also. Therefore, careful patient selection and proper alignment are crucial for good postoperative vision performance. In our present study, preablation iris recognition was performed successfully in all eyes (74 out of 74)[13,17-19]. The 6D eye tracker dimensions used, including both SCC and DCC cyclotorsion control, provided well centralization in central presbyLASIK and resulted in better refractive outcomes in (myopic) presbyopia correction.

For presbyopia treatment, there is still no perfect strategy to restore the decreased accommodation amplitude consequence of aging[2-3,11]. For aging patients, different multifocal or monovision designs for presbyopia correction also apply to intraocular lenses. Thus, other options exist with the potential to dramatically improve a patient's spectacle independence. However, for patients in young presbyopic ages (40 to 50y) and have non-clinical relevant lens opacity, especially for patients who are considering cornea refractive surgery, cornea ablation may be an alternative. It is certain that any preoperative residual accommodation is an advantage for near performance to the cornea excimer laser multifocal ablation protocols. The hybrid surgical technique treats the dominant eye toward distance vision (target refraction -0.13 D) and the nondominant eye toward near vision (target refraction -0.89 D) for achieving micro-monovision, and the myopia target for

nondominant eye is even smaller than LBV that is -1.5 D for most patients. However, due to the decrease of anisometropia, the efficacy of near vision should be concerned. In our experience based on 1-year outcomes, presbyLASIK seems to be particularly superior and advantageous in young presbyopic ages (40 to 50y) and non-clinical relevant lens opacity. Since this approach combines a micro-monovision strategy with and a different magnitude of mulitfocality in distant and near eyes, a concern still existed regarding the impairment and the imbalance between the two eyes treated.

No retreatment was requested and no patient asked to reverse the intended multifocal design for better distance vision during the 1y of following-up. The 100% of patients achieved both 20/25 or better UDVA and J5 or better UNVA at the 1y follow-up visit. In our cohort, only one patient binocularly loss of one line CDVA after surgery and no patient lost 2 lines, most of them have no change or gain one line of CDVA from pre to post operation.

The limitation of our study was that most patients in this study with moderate myopia with low astigmatism and this relatively young presbyopic group partly results in good performance for near vision acuity. However, people over the age of 45 years old aren't the most common population who are considering corneal refractive surgery in China, there are no enough aged presbyopic patients with refractive errors were enrolled during our study period.

In conclusion, the hybrid bi-aspheric multifocal central presbyLASIK with micro-monovision appears to be an efficacious option for myopia patients with presbyopia who are considering cornea excimer laser refractive surgery. One year postoperative outcomes in a relatively young population indicate improvements in both far and near distances uncorrected binocular vision with high satisfaction.

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Conflicts of Interest: Liu F, None; **Zhang T,** None; **Liu Q,** None.

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