BMJ Open

Visual and Refractive Outcomes of Small-Incision Lenticule Extraction for the Correction of Myopia: One-Year Follow-Up.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008268
Article Type:	Research
Date Submitted by the Author:	24-Mar-2015
Complete List of Authors:	Kamiya, Kazutaka; University of Kitasato School of Medicine, Department of Ophthalmology Shimizu, Kimiya; Kitasato University, Ophthalmology Igarashi, Akihito; Kitasato University, Ophthalmology Kobashi, Hidenaga; University of Kitasato School of Medicine, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology
Keywords:	OPHTHALMOLOGY, Cataract and refractive surgery < OPHTHALMOLOGY, Corneal and external diseases < OPHTHALMOLOGY

Title Page:

Title: Visual and Refractive Outcomes of Small-Incision Lenticule Extraction for the Correction of Myopia: One-Year Follow-Up.

Authors: Kazutaka Kamiya, MD, PhD; Kimiya Shimizu, MD, PhD; Akihito Igarashi, MD, PhD; Hidenaga Kobashi, MD.

Author Affiliations: Department of Ophthalmology, University of Kitasato School of Medicine, Kanagawa, Japan.

Short title: Clinical outcomes of small incision lenticule extraction

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Competing interest: *The authors have no commercial or propriety interest in the product or company described in the current article.*

The study was approved by the Institutional Review Board at Kitasato University

School of Medicine.

Key words: *femtosecond laser; small-incision lenticule extraction; safety; efficacy; predictability; stability; myopia.*

Correspondence: Kazutaka Kamiya, MD, PhD, Associate Professor, Department of Ophthalmology, University of Kitasato School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa, 252-0374, Japan; kamiyak-tky@umin.ac.jp

ABSTRACT

OBJECTIVE: To assess the 1-year clinical outcomes of small-incision lenticule extraction (SMILE) for the correction of myopia and myopic astigmatism using a 500-kHz femtosecond laser system.

METHODS: This prospective study evaluated fifty-two eyes of 39 consecutive patients with spherical equivalents of -4.11 ± 1.73 D [mean ± standard deviation] who underwent SMILE for myopia and myopic astigmatism. Preoperatively, and 1 week and 1, 3, 6 and 12 months postoperatively, we assessed the safety, efficacy, predictability, stability, corneal endothelial cell loss, and the adverse events of the surgery.

RESULTS: The logMAR uncorrected distance visual acuity (UDVA) and LogMAR corrected distance visual acuity (CDVA) were -0.16 ± 0.11 and -0.22 ± 0.07, respectively, 1 year postoperatively. At 1 year, all eyes were within ± 0.5 D of the targeted correction. Manifest refraction changes of -0.05 ± 0.32 D occurred from 1 week to 1 year postoperatively. The endothelial cell density was not significantly changed from 2804 ± 267 cells/mm^2 preoperatively to 2743 ± 308 cells/mm^2 1 year postoperatively (p=0.12, Wilcoxon signed-rank test). No vision-threatening complications occurred during the observation period.

CONCLUSIONS: SMILE performed well in the correction of myopia and myopic

astigmatism, and no significant change in endothelial cell density or any other serious complications occurred throughout the 1-year follow-up period, suggesting SMILE's viability as a surgical option for the treatment of such eyes.

Strengths and limitations of this study.

Early visual and refractive outcomes of small incision lenticule extraction (SMILE) are encouraging, but most of these postoperative follow-up are spanning 3 to 6 months.

Moreover, the endothelial cell loss after this surgical procedure, which is a major concern in the prognosis of the patient, has not so far been investigated.

Although we did not assess the other aspects of this surgical technique on corneal biomechanics and ocular surface in this study, this is one of the longest-term studies to assess the safety, efficacy, predictability, stability, and adverse events of SMILE, and the first study to assess the endothelial cell density after SMILE.

SMILE was beneficial in all measures of safety, efficacy, predictability, and stability for the correction of myopia and myopic astigmatism, and neither significant endothelial cell loss nor vision-threatening complications occurred throughout the 1-year follow-up period.

INTRODUCTION

The femtosecond laser allows very precise cuts with less thermal damage to the tissues than seen with other lasers, and it is therefore one of the most revolutionary technologies to be seen in medical care in recent years. In ophthalmology, it has been used mainly for the creation of corneal flaps for laser in situ keratomileusis (LASIK) with high precision, as an alternative to the mechanical microkeratome. A recent breakthrough of this technology has resulted in a novel refractive procedure called refractive lenticule extraction (ReLEx), which requires neither a microkeratome nor an excimer laser, but uses only the femtosecond laser system as an all-in-one device for flap and lenticule preparation. The first clinical results with laser-induced extraction of a refractive lenticule were reported in highly myopic eyes,[1] and in blind or amblyopic eyes.[2] Additionally, the ReLEx technique, which can be used for femtosecond lenticule extraction (FLEx) [3-6] by lifting the flap and by small-incision lenticule extraction (SMILE) [4,6-21] without lifting the flap, has been proposed as an alternative to conventional LASIK for the correction of refractive errors.

Early visual and refractive outcomes of SMILE are encouraging, but most of these postoperative follow-ups span 3 to 6 months,[6-14,16-19] except in a few studies.[15,20,21] In consideration of the prevalence of this new technique, more studies of long duration

using different groups are necessary for confirmation of these preliminary findings. Moreover, the endothelial cell loss after this surgical procedure, which is a major concern in the prognosis of the patient, since this technique requires photodisruption not only for thinner cap making but also for deeper lenticule manufacture, has not so far been investigated. The purpose of this study is to prospectively assess the 1-year clinical outcomes, including the endothelial cell loss, of SMILE for the correction of myopia and myopic astigmatism.

MATERIALS AND METHODS

Study Population

Fifty-two eyes of 39 consecutive patients (10 men and 29 women) who underwent SMILE for the correction of myopia and myopic astigmatism using the VisuMax femtosecond laser system (Carl Zeiss Meditec, Jena, Germany) with a 500 kHz repetition rate at the Kitasato University Hospital were included in this prospective study. The mean patient age at the time of surgery was 31.8 ± 6.9 years (range, 20 to 49 years). The sample size in this study offered 94% statistical power at the 5% level in order to detect a 0.10-difference in logarithm of the minimal angle of resolution (logMAR) of visual acuity, when the standard deviation (SD) of the mean difference

was 0.20, and offered 81% statistical power at the 5% level in order to detect a 80-cells/mm^2 difference in the endothelial cell density before and after surgery, when the SD of the mean difference was 200 cells/mm^2. The inclusion criteria for this surgical technique in our institution were as follows: unsatisfaction with spectacle or contact lens correction, manifest spherical equivalent of -1.25 to -9 diopters (D), manifest cylinder of 0 to 4 D, sufficient corneal thickness (estimated total postoperative corneal thickness > 400 μm and estimated residual thickness of the stromal bed > 250 μm), endothelial cell density ≥ 1800 cells/mm^2, no history of ocular surgery, severe dry eye, progressive corneal degeneration, cataract, or uveitis. Eyes with keratoconus were excluded from the study by using the keratoconus screening test of Placido disk videokeratography (TMS-2, Tomey, Nagoya, Japan). In all eyes, the preoperative manifest refraction was selected as the target correction. Routine postoperative examinations were performed at 1 day, 1 week, and 1, 3, 6, and 12 months after surgery. Preoperatively, and 1 week and 1, 3, 6 and 12 months postoperatively, we determined the following: logarithm of the minimal angle of resolution (logMAR) of uncorrected distance visual acuity (UDVA), logMAR of corrected distance visual acuity (CDVA), manifest spherical equivalent refraction, and endothelial cell density (preoperatively and 1-year postoperatively), in addition to the usual slit-lamp biomicroscopic and

funduscopic examinations. Before surgery, the mean keratometric readings and the central corneal thickness were measured using an autorefractometer (ARK-700A, Nidek, Gamagori, Japan) and an ultrasound pachymeter (DGH-500, DGH Technologies, Exton, US), respectively. The endothelial cell density was determined with a non-contact specular microscope (SP-8800, Konan, Nishinomiya, Japan). The manufacturer's software automatically produced an endothelial cell density measurement by visually comparing the cell size in the image with the predefined patterns on the screen. Each measurement was repeated at least 3 times, and the average value was used for analysis. The study was approved by the Institutional Review Board of Kitasato University and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients after explanation of the nature and possible consequences of the study.

Surgical Procedure

SMILE was performed using the VisuMax femtosecond laser system with a 500 kHz repetition rate. The laser was visually centered on the pupil. A small (S) curved interface cone was used in all cases. In order, the main refractive and nonrefractive femtosecond incisions were performed in the following automated sequence: the posterior surface of the lenticule (spiral in pattern), the anterior surface of the lenticule (spiral out pattern),

followed by a side cut of cap. The femtosecond laser parameters were as follows: 120 μm cap thickness, 7.5 mm cap diameter, 6.5 mm lenticule diameter, 140 nJ power for lenticule making, a 3-mm side cut for the access to the lenticule with angles of 90°. A spatula was inserted through the side cut over the top of the refractive lenticule dissecting this plane followed by the bottom of the lenticule. The lenticule was subsequently grasped with modified McPherson forceps (Geuder, GmbH, Heidelberg, Germany), and removed. After the removal of the lenticule the intrastromal space was flushed with balanced salt solution using a cannula. All surgeries were uneventful and no definite intraoperative complication was observed. No adjustments to the manufacturer's nomograms were done. After surgery, steroidal (0.1% betamethasone, Rinderon ™, Shionogi, Osaka, Japan) and antibiotic (0.3% levofloxacin, Cravit™, Santen, Osaka, Japan) medications were topically administered 4 times daily for 2 weeks, and then the frequency was steadily reduced.

Statistical Analysis

All statistical analyses were performed using a commercially available statistical software (Ekuseru-Toukei 2010, Social Survey Research Information Co, Ltd., Tokyo, Japan). The normality of all data samples was first checked by the Kolmogorov-Smirnov test. Since the data did not fulfill the criteria for normal

distribution, the Wilcoxon signed-rank test was used for statistical analysis to compare the pre- and post-surgical data. Unless otherwise indicated, the results are expressed as mean ± SD, and a value of $p<0.05$ was considered statistically significant.

RESULTS

Patient Population

Preoperative patient demographics of the study population are summarized in Table 1. No eyes were lost during the 1-year follow-up in this series.

Safety Outcomes

LogMAR CDVA was -0.15 ± 0.07, -0.19 ± 0.07, -0.20 ± 0.08, -0.20 ± 0.07, and -0.22 ± 0.07, 1 week, and 1, 3, 6 and 12 months after surgery, respectively. We found no significant difference between preoperative CDVA and 1-year postoperative CDVA ($p=0.48$, Wilcoxon signed-rank test). Thirty-three eyes (63.5%) showed no change in CDVA, 8 eyes (15.4%) gained 1 line, while 9 eyes (17.3 %) lost 1 line, and 2 eyes (3.8%) lost 2 lines 1year postoperatively (Figure 1). Although two eyes lost 2 lines, possibly because of a very mild interface haze formation and/or irregular astigmatism, the eyes had a CDVA of 20/20 or more.

Effectiveness Outcomes

LogMAR UDVA was -0.08 ± 0.13, -0.12 ± 0.11, -0.13 ± 0.13, -0.14 ± 0.12, and -0.16 ± 0.11, 1 week and 1, 3, 6 and 12 months after surgery, respectively. We found a significant difference between preoperative UDVA and 1-year postoperative UDVA ($p<0.001$, Wilcoxon signed-rank test). The cumulative percentages of eyes attaining specified cumulative levels of UDVA 1 year postoperatively are shown in Figure 2. One week and 1, 3, 6 and 12 months after surgery, 100%, 100%, 100%, 100%, and 100% of eyes, and 81%, 85%, 90%, 92%, and 94% of eyes had a UDVA of 20/40, and of 20/20 or better, respectively.

Predictability

A scatter plot of the attempted versus the archived manifest spherical equivalent correction at 1 year postoperatively is shown in Figure 3. The percentages of eyes within different diopter ranges of the attempted spherical equivalent correction are shown in Figure 4. One week, and 1, 3, 6 and 12 months after surgery, 94%, 98%, 96%, 96%, and 100% of eyes, and 98%, 100%, 100%, 100%, and 100% of eyes were within ± 0.5, and ± 1.0 D of the attempted spherical equivalent correction, respectively.

Stability

The change in the manifest spherical equivalent is shown in Figure 5. One week and 1, 3, 6 and 12 months after surgery, the mean manifest spherical equivalent was 0.00 ±

0.32, -0.06 ± 0.21, -0.05 ± 0.28, -0.09 ± 0.25, and -0.05 ± 0.16 D, respectively. Manifest spherical equivalent was significantly decreased, from -4.11 ± 1.73 D preoperatively, to -0.05 ± 0.16 D 1 year postoperatively ($p<0.001$, Wilcoxon signed-rank test). Changes in manifest spherical equivalent from 1 week to 1 year were -0.05 ± 0.32 D.

Endothelial Cell Density

The endothelial cell density was decreased, but not significantly, from 2804 ± 267 cells/mm^2 preoperatively to 2743 ± 308 cells/mm^2 1 year postoperatively ($p=0.12$, Wilcoxon signed-rank test). The mean percentage of endothelial cell loss was 2.0 % 1 year after surgery. We found no significant correlation between the endothelial cell loss and the amount of spherical equivalent correction (Pearson correlation coefficient $r=0.16$, $p=0.25$).

Secondary Surgeries / Adverse Events

A suction loss occurred in 1 eye (2%), but we successfully completed the procedure after the contact glass was immediately reattached. Otherwise, all surgeries were uneventful and no significant intraoperative complication was observed. Transient interface haze and optically insignificant peripheral microstriae developed in 6 eyes (12 %) and 2 eyes (4 %), respectively, during the first postoperative month. All these eyes were followed without additional surgical intervention, and gradually resolved

thereafter. No epithelial ingrowth, diffuse lamellar keratitis, keratectasia, or any other vision-threatening complications were seen at any time during the 1-year observation period.

DISCUSSION

In the present study, our results showed that SMILE was beneficial in all measures of safety, efficacy, predictability, and stability for the correction of myopia throughout the 1-year follow-up period. To the best of our knowledge, this is one of the longest-term studies to assess the safety, efficacy, predictability, stability, and adverse events of SMILE.[15,20,21] Previous studies on the visual and refractive outcomes of SMILE are summarized in Table 2.

With regard to the safety and efficacy of the procedure, Shah et al[7] demonstrated that 70%, 25%, and 6% of eyes had an unchanged CDVA, gained 1 line or more, and lost 1 line or more, respectively, and the 79% of all eyes in which the full refractive correction was attempted had a UDVA of 20/25 or better. Sekundo et al[8] reported that 53% of eyes remained unchanged, 32.3% gained one line, 3.3% gained two lines, 8.8% lost one line and 1.1% lost 2 lines of CDVA, and that 97.6% and 83.5% of treated eyes had a UCVA of 20/40, and of 20/20 or better 6 months postoperatively. In a different study, they

stated that the safety and efficacy indices were 1.08 and 0.99, respectively.[15] Vestergaard et al[10] reported that logMAR CDVA was -0.03 ± 0.07, and that 95% of eyes had a UDVA of 10/20 or more 3 months postoperatively. Hijordal et al[11] also demonstrated that the safety and efficacy indices were 1.07 ± 0.22 and 0.90 ± 0.25 3 months postoperatively, respectively. In another study, we reported that logMAR CDVA and UDVA were -0.19 ± 0.22 and -0.15 ± 0.20 six months postoperatively, respectively.[6] Reinstein et al[20] and Xu et al[21] reported that 91% and 99% of eyes had an unchanged CDVA or gained lines, and that 96% and 83% of eyes had a UDVA of 20/20 1 year postoperatively, respectively. Our current findings were comparable with the results of these previous studies in terms of safety, but the efficacy achieved in the current study was slightly better than that of previous studies, presumably because of the slightly lower myopic correction and/or the use, in this study, of the newer generation femtosecond laser with its higher repetition rate. There was a tendency for a slight delay in UDVA recovery in the early postoperative period (especially 1 week postoperatively) after SMILE, which were in line with that after FLEX.[5,6] Kunert et al[22] showed that the surface regularity index decreased as pulse energy increased, and that cases of interface haze were uncommon, since they had begun to apply lower energies. Further refinement of the energy settings of the femtosecond laser is necessary to improve visual outcomes

not only after FLEx[5,6] but also after SMILE.

With regard to predictability, 77 to 100% and 94.2 to 100% of eyes have been reported to be within ± 0.5 and 1.0 D of the targeted correction, respectively.[6-8,10,11,15-21] Hijordal et al[11] stated that the average difference between achieved correction and attempted correction was 0.25 D of undercorrection, which may be added when planning SMILE. The predictability achieved in this study was comparable to, or slightly higher than, that in other previous studies.[6-8,10,11,15-21] The discrepancy may be also attributed to the slightly lower myopic correction and/or to the use of the newer generation femtosecond laser with its higher repetition rate in the current study.

With regard to the stability, Shah et al[7] showed that the mean change in refraction from 1 month postoperatively was -0.02 ± 0.18 and -0.06 ± 0.27 D at 3 and 6 months postoperatively, respectively. Sekundo et al[8] demonstrated that the mean refraction was 0.05 D, 0.14 D, and 0.10 D, 1 week, 1 and 6 months after surgery, respectively. They also stated that the mean spherical equivalent gradually regressed by 0.08 D, from -0.11 D at 1 month postoperatively to -0.19 D at 1 year postoperatively.[15] Vestergaard et al[10] found a slight, but significant, regression from 1 week to 1 month, but no significant regression from 1 month to 3 months after SMILE. In another study, we showed that changes of 0.00 ± 0.30 D occurred in manifest refraction from 1 week to 6 months after

SMILE.[6] Reinstein et al[20] reported that the mean refraction was 0.10 D, -0.05 D, and -0.05 D, 1, 3, and 12 months after surgery, respectively. Xu et al[21] showed that the change in manifest refraction from 1 day to 1 year was -0.06 ± 0.37 D. We found no significant refractive regression from 1 week to 1 year after SMILE in the current study. A careful long-term follow-up is still necessary for confirming whether refractive regression occurs in the late postoperative period.

To our knowledge, this is also the first study to assess the endothelial cell density after SMILE. After this surgical technique, we found no significant cell loss, which was comparable with the outcomes after excimer laser surgery such as LASIK and photorefractive keratectomy,[23,24] or after FLEx.[5] Neither photodisruption for thinner cap making nor photodisruption for deeper lenticule manufacture induced a significant change in the endothelial cell density of the cornea, and the depth of photodisruption does not significantly affect the endothelial cell loss, both after FLEx[7] and also after SMILE.

There are at least two limitations to this study. One is that we included both eyes of the same patient in the current study, although only one eye should be used for statistical analysis. We confirmed the similar outcomes of SMILE, even when only one eye was randomly chosen from each patient, and thus we enrolled both eyes of the same patient

as described in many published studies on refractive surgery. Another limitation is that we did not assess the other aspects of this surgical technique on corneal biomechanics and ocular surface in all eyes. Since SMILE does not require flap making, it may offer benefits in terms of reduced tissue removal, better biomechanical stability, better flap strength, reduced risk of flap dislocation, and milder dry eye symptoms, as compared with LASIK. We are currently conducting a new study on corneal biomechanics and the ocular surface after SMILE.

In conclusion, our results support the view that SMILE is beneficial for the correction of myopia and myopic astigmatism, and the view that neither significant endothelial cell loss nor vision-threatening complications occurred throughout the 1-year follow-up period. This novel surgical approach appears to hold promise as an alternative to LASIK for the correction of myopia and myopic astigmatism.

Footnotes

Contributors: *KK and KS were involved in the design and conduct of the study, KK, AI and HK were involved in collection, management, analysis, and interpretation of data, KK, KS, AI and HK were involved in preparation, review, and final approval of the manuscript.*

Competing Interests: *None.*

Ethics approval: *The study was approved by the Institutional Review Board of Kitasato University.*

Funding: *This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.*

Data Sharing Statement: *No additional data are available.*

REFERENCES

1. Krueger RR, Juhasz T, Gualano A, et al. The picosecond laser for nonmechanical laser in situ keratomileusis. J Refract Surg 1998;14:467-469.

2. Ratkay-Traub I, Ferincz IE, Juhasz T, et al. First clinical results with the femtosecond neodynium-glass laser in refractive surgery. J Refract Surg 2003; 19:94-103.

3. Sekundo W, Kunert K, Russmann C, et al. First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results. J Cataract Refract Surg. 2008;34:1513-1520.

4. Shah R, Shah S. Effect of scanning patterns on the results of femtosecond laser lenticule extraction refractive surgery. J Cataract Refract Surg. 2011;37:1636-1647.

5. Kamiya K, Igarashi A, Ishii R, et al. Early clinical outcomes, including efficacy and endothelial cell loss, of refractive lenticule extraction using a 500 kHz femtosecond laser to correct myopia. J Cataract Refract Surg. 2012;38:1996-2002.

6. Kamiya K, Shimizu K, Igarashi A, et al. Visual and refractive outcomes of femtosecond lenticule extraction and small-incision lenticule extraction for myopia. Am J Ophthalmol. 2014;157:128-134.

7. Shah R, Shah S, Sengupta S. Results of small incision lenticule extraction: All-in-one femtosecond laser refractive surgery. J Cataract Refract Surg. 2011;37:127-137.

8. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol. 2011;95:335-339.

9. Ang M, Tan D, Mehta JS. Small incision lenticule extraction (SMILE) versus laser in-situ keratomileusis (LASIK): study protocol for a randomized, non-inferiority trial. Trials. 2012;13:75.

10. Vestergaard A, Ivarsen AR, Asp S, et al. Small-incision lenticule extraction for moderate to high myopia: Predictability, safety, and patient satisfaction. J Cataract Refract Surg. 2012;38:2003-2010.

11. Hjortdal JØ, Vestergaard AH, Ivarsen A, et al. Predictors for the outcome of small-incision lenticule extraction for Myopia. J Refract Surg. 2012;28:865-871.

12. Riau AK, Ang HP, Lwin NC, et al. Comparison of four different VisuMax circle patterns for flap creation after small incision lenticule extraction. J Refract Surg. 2013;29:236-244.

13. Ozgurhan EB, Agca A, Bozkurt E, et al. Accuracy and precision of cap thickness in small incision lenticule extraction. Clin Ophthalmol. 2013;7:923-926.

14. Agca A, Ozgurhan EB, Demirok A, et al. Comparison of corneal hysteresis and corneal resistance factor after small incision lenticule extraction and femtosecond laser-assisted LASIK: A prospective fellow eye study. Cont Lens Anterior Eye. 2014;37:77-80.

15. Sekundo W, Gertnere J, Bertelmann T, et al. One-year refractive results, contrast sensitivity, high-order aberrations and complications after myopic small-incision lenticule extraction (ReLEx SMILE). Graefes Arch Clin Exp Ophthalmol. 2014;252:837-843.

16. Vestergaard AH, Grauslund J, Ivarsen AR, et al. Efficacy, safety, predictability, contrast sensitivity, and aberrations after femtosecond laser lenticule extraction. J Cataract Refract Surg. 2014;40:403-411.

17. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology. 2014;121:822-828.

18. Lin F, Xu Y, Yang Y. Comparison of the visual results after SMILE and femtosecond laser-assisted LASIK for myopia. J Refract Surg. 2014;30:248-254.

19. Ganesh S, Gupta R. Comparison of visual and refractive outcomes following femtosecond laser- assisted lasik with smile in patients with myopia or myopic astigmatism. J Refract Surg. 2014;30:590-596.

20. Reinstein DZ, Carp GI, Archer TJ, et al. Outcomes of small incision lenticule extraction (SMILE) in low myopia. J Refract Surg. 2014;30:812-818.

21. Xu Y, Yang Y. Small-Incision Lenticule Extraction for Myopia: Results of a 12-Month Prospective Study. Optom Vis Sci. 2014 Nov 13. [Epub ahead of print]

22. Kunert KS, Blum M, Duncker GI, et al. Surface quality of human corneal lenticules after femtosecond laser surgery for myopia comparing different laser parameters. Graefes Arch Clin Exp Ophthalmol. 2011;249:1417-1424.

23. Patel SV, Bourne WM. Corneal endothelial cell loss 9 years after excimer laser keratorefractive surgery. Arch Ophthalmol. 2009;127:1423-1427.

24. Smith RT, Waring GO 4th, Durrie DS, et al. Corneal endothelial cell density after femtosecond thin-flap LASIK and PRK for myopia: a contralateral eye study. J Refract Surg. 2009;25:1098-1102.

FIGURE LEGENDS

Figure 1. Changes in corrected distance visual acuity (CDVA) 1 year after small incision lenticule extraction (SMILE).

Figure 2. Cumulative percentages of eyes attaining specified cumulative levels of uncorrected distance visual acuity (UDVA) 1 year after small incision lenticule extraction (SMILE).

Figure 3. A scatter plot of the attempted versus the achieved manifest spherical equivalent correction 1 year after small incision lenticule extraction (SMILE).

Figure 4. Percentages of eyes within different diopter ranges of the attempted correction (spherical equivalent) 1 year after small incision lenticule extraction (SMILE).

Figure 5. Time course of manifest spherical equivalent after small incision lenticule extraction (SMILE).

TABLES

Table 1. Preoperative demographics of the study population.

Demographic Data	
Age (years)	31.8 ± 6.9 years (range, 20 to 49 years)
Gender (% female)	74 %
LogMAR UDVA	1.12 ± 0.11 (range, 0.52 to 1.52)
LogMAR CDVA	-0.22 ± 0.08 (range, -0.30 to -0.18)
Manifest spherical equivalent (D)	-4.11 ± 1.73 D (range, -1.25 to -8.25 D)
Manifest cylinder (D)	-0.51 ± 0.65 D (range, 0.00 to -2.25 D)
Mean keratometric reading (D)	43.3 ± 1.33 D (range, 40.4 to 46.0 D)
Central corneal thickness (μm)	546.1 ± 32.9 μm (range, 471 to 614 μm)
Endothelial cell density (cells/mm^2)	2804 ± 267 cells/mm^2 (range, 2275 to 3362 cells/mm^2)

LogMAR=logarithm of the minimal angle of resolution, UDVA=uncorrected distance visual acuity, CDVA=corrected distance visual acuity, D=diopter

Table 2. Previous studies on visual and refractive outcomes of small incision lenticule extraction (SMILE).

Author	Year	Repetition rate (kHz)	Eyes	Follow-up (months)	Age (years)	Spherical equivalent (D)	Astigmatism (D)	Safety (logMAR CDVA)	Efficacy (logMAR UDVA)	Predictability within ± 0.5D (%)	Predictability within ±1.0D (%)	Stability (D)
Shah et al15	2011	200	51	6	26.0 ± 5.55	-4.87 ± 2.16	-0.76 ± 0.98	70% unchanged 25% gained 1 line or more 6% lost 1 line or more	79% ≤ 0.16 logMAR	91	100	-0.06 ± 0.27 (from 1 month to 6 months)
Sekundo et al16	2011	200	91	6	35.6	-4.75 ± 1.56	-0.78 ± 0.79	49% unchanged 35.6% gained 1 line or more 11% lost 1 line or more	83.5% ≤ 0.00 logMAR	80.2	95.6	0.05 (from 1 week to 6 months)
Vestergaard et al17	2012	500	279	3	38.1 ± 8.7	-7.18 ± 1.57	-0.71 ± 0.50	-0.03 ± 0.07	95% ≤ 0.30 logMAR	77	95	-0.18 (from 1 week to 3 months)
Hjortdal et al18	2012	500	670	3	38.3 ± 8.3	-7.19 ± 1.30	-0.60 ± 0.46	-0.049 ± 0.097	84% ≤ 0.16 logMAR	80.1	94.2	N.A.
Kamiya et al14	2014	500	26	6	31.5 ± 6.2	-4.21 ± 2.63	-0.54 ± 0.74	-0.19 ± 0.07	-0.15 ± 0.20	100	100	0.00 ± 0.30 (form 1 month to 6 months)
Sekundo et al22	2014	500	53	12	29	-4.68 ± 1.29	-0.41 ± 0.51	47% unchanged 42% gained 1 line or	88% ≤ 0.00 logMAR	92	100	-0.08 (from 1 month to 1 year)

								more 11% lost 1 line				
Vestergaard et al23	2014	500	34	6	35 ± 7	-7.56 ± 1.11	N.A.	-0.04 ± 0.06	-0.02 ± 0.08	88	97	-0.02 (from 1 month to 6 months)
Current		500	52	12	31.8 ± 6.9	-4.11 ± 1.73	-0.51 ± 0.65	-0.22 ± 0.07	-0.16 ± 0.11	100	100	-0.05 ± 0.32 (from 1 week to 1 year)

D=diopter, logMAR=logarithm of the minimal angle of resolution, CDVA=corrected distance visual acuity, UDVA=uncorrected distance visual acuity, N.A.=not available.

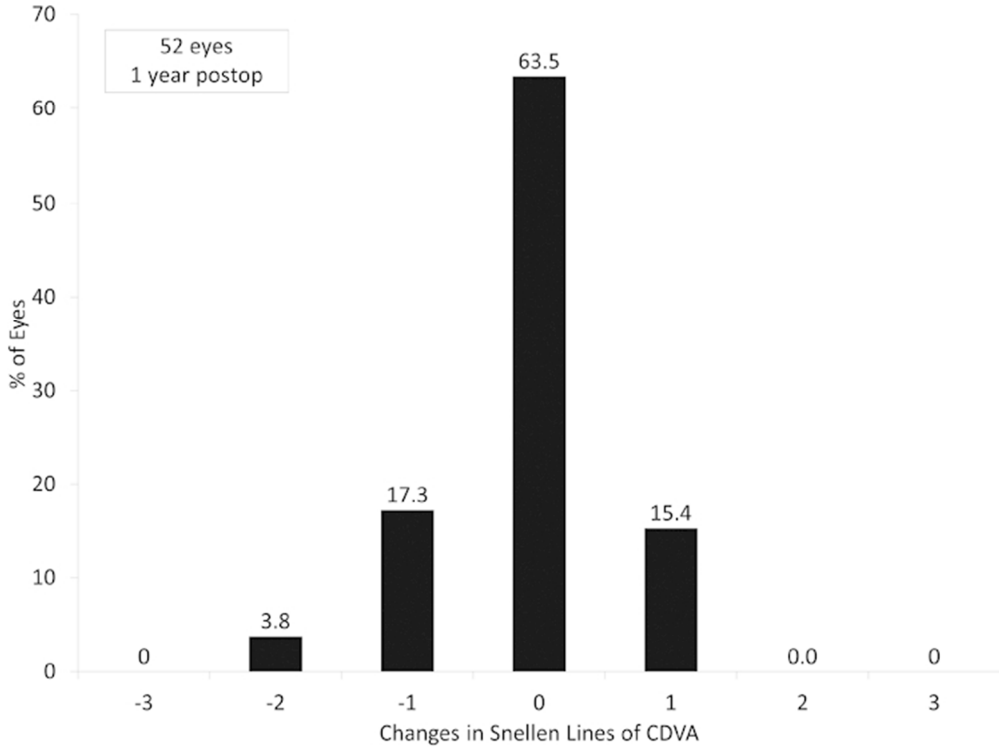

Figure 1. Changes in corrected distance visual acuity (CDVA) 1 year after small incision lenticule extraction (SMILE).
63x47mm (300 x 300 DPI)

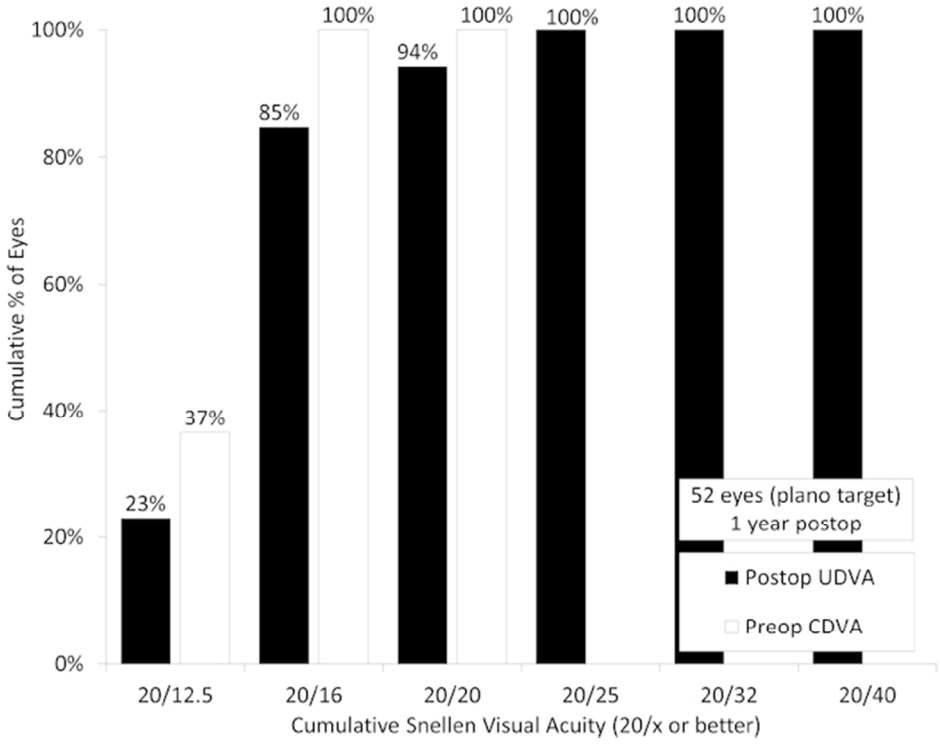

Figure 2. Cumulative percentages of eyes attaining specified cumulative levels of uncorrected distance visual acuity (UDVA) 1 year after small incision lenticule extraction (SMILE).
63x47mm (300 x 300 DPI)

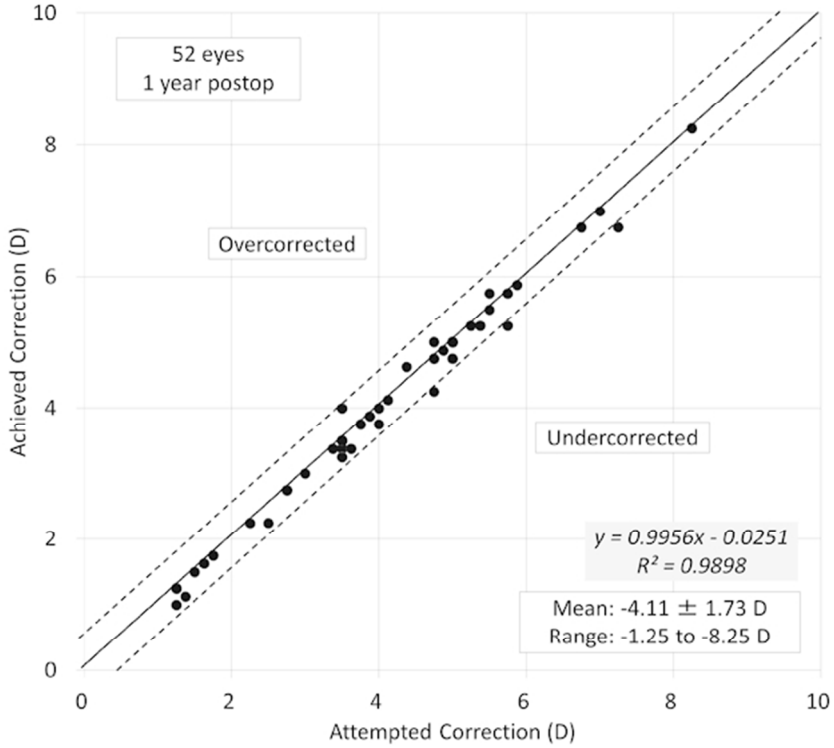

Figure 3. A scatter plot of the attempted versus the achieved manifest spherical equivalent correction 1 year after small incision lenticule extraction (SMILE).
63x47mm (300 x 300 DPI)

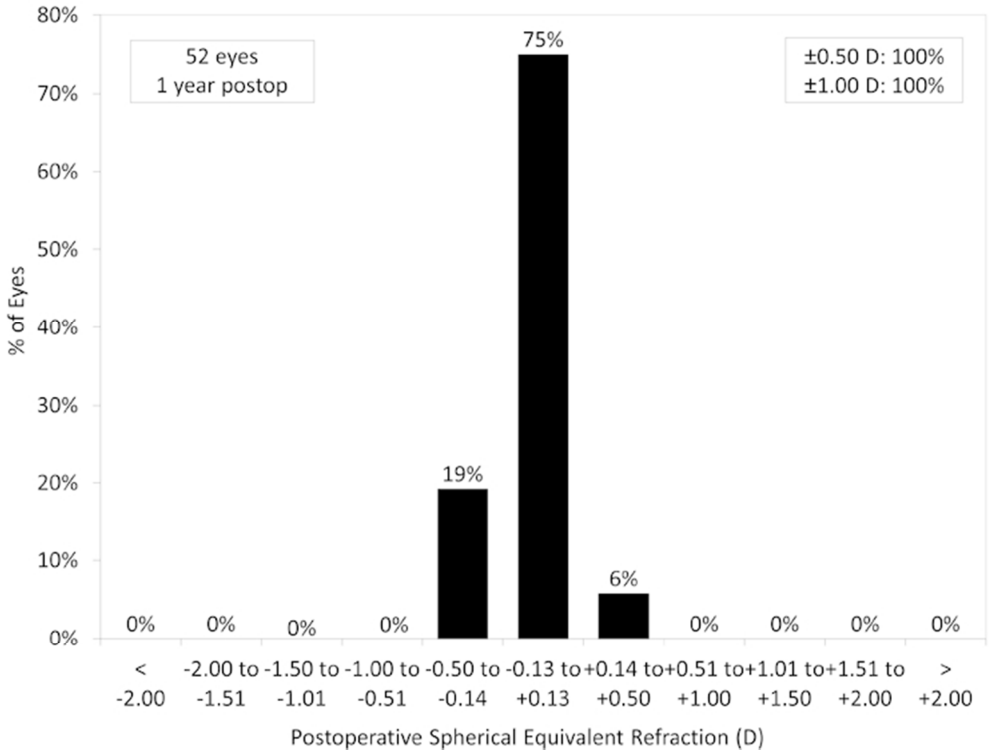

Figure 4. Percentages of eyes within different diopter ranges of the attempted correction (spherical equivalent) 1 year after small incision lenticule extraction (SMILE).
63x47mm (300 x 300 DPI)

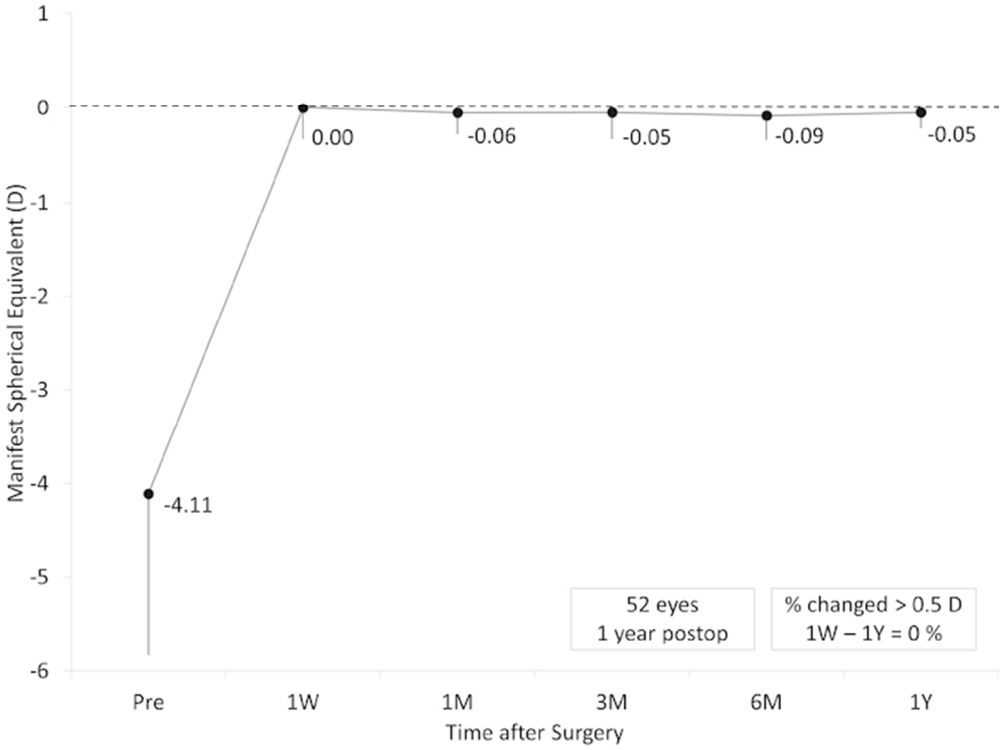

Figure 5. Time course of manifest spherical equivalent after small incision lenticule extraction (SMILE).

63x47mm (300 x 300 DPI)

BMJ Open

Visual and Refractive Outcomes of Small-Incision Lenticule Extraction for the Correction of Myopia: One-Year Follow-Up.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008268.R1
Article Type:	Research
Date Submitted by the Author:	12-Aug-2015
Complete List of Authors:	Kamiya, Kazutaka; University of Kitasato School of Medicine, Department of Ophthalmology Shimizu, Kimiya; Kitasato University, Ophthalmology Igarashi, Akihito; Kitasato University, Ophthalmology Kobashi, Hidenaga; University of Kitasato School of Medicine, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology
Keywords:	OPHTHALMOLOGY, Cataract and refractive surgery < OPHTHALMOLOGY, Corneal and external diseases < OPHTHALMOLOGY

Title Page:

Title: Visual and Refractive Outcomes of Small-Incision Lenticule Extraction for the Correction of Myopia: One-Year Follow-Up.

Authors: Kazutaka Kamiya, MD, PhD; Kimiya Shimizu, MD, PhD; Akihito Igarashi, MD, PhD; Hidenaga Kobashi, MD.

Author Affiliations: Department of Ophthalmology, University of Kitasato School of Medicine, Kanagawa, Japan.

Short title: Clinical outcomes of small incision lenticule extraction

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Competing interest: *The authors have no commercial or propriety interest in the product or company described in the current article.*

The study was approved by the Institutional Review Board at Kitasato University

School of Medicine.

Key words: *femtosecond laser; small-incision lenticule extraction; safety; efficacy; predictability; stability; myopia.*

Correspondence: Kazutaka Kamiya, MD, PhD, Associate Professor, Department of Ophthalmology, University of Kitasato School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa, 252-0374, Japan; kamiyak-tky@umin.ac.jp

ABSTRACT

OBJECTIVE: To assess the 1-year clinical outcomes of small-incision lenticule extraction (SMILE) for the correction of myopia and myopic astigmatism using a 500-kHz femtosecond laser system.

METHODS: This prospective study evaluated fifty-two eyes of 39 consecutive patients (31.8 ± 6.9 years, mean age ± standard deviation) with spherical equivalents of -4.11 ± 1.73 D (range, -1.25 to -8.25 D) who underwent SMILE for myopia and myopic astigmatism. Preoperatively, and 1 week and 1, 3, 6, and 12 months postoperatively, we assessed the safety, efficacy, predictability, stability, corneal endothelial cell loss, and the adverse events of the surgery.

RESULTS: The logMAR uncorrected distance visual acuity (UDVA) and LogMAR corrected distance visual acuity (CDVA) were -0.16 ± 0.11 and -0.22 ± 0.07, respectively, 1 year postoperatively. At 1 year, all eyes were within ± 0.5 D of the targeted correction. Manifest refraction changes of -0.05 ± 0.32 D occurred from 1 week to 1 year postoperatively (p=0.20, Wilcoxon signed-rank test). The endothelial cell density was not significantly changed from 2804 ± 267 cells/mm^2 preoperatively to 2743 ± 308 cells/mm^2 1 year postoperatively (p=0.12). No vision-threatening complications occurred during the observation period.

CONCLUSIONS: SMILE performed well in the correction of myopia and myopic astigmatism, and no significant change in endothelial cell density or any other serious complications occurred throughout the 1-year follow-up period, suggesting its viability as a surgical option for the treatment of such eyes.

Strengths and limitations of this study.

Early visual and refractive outcomes of small incision lenticule extraction (SMILE) are encouraging, but most of these postoperative follow-up are spanning 3 to 6 months.

Moreover, the endothelial cell loss after this surgical procedure, which is a major concern in the prognosis of the patient, has not so far fully elucidated.

Although we did not assess the other aspects of this surgical technique on corneal biomechanics and ocular surface in this study, this is one of the long-term studies to assess the safety, efficacy, predictability, stability, and adverse events of SMILE.

SMILE was beneficial in all measures of safety, efficacy, predictability, and stability for the correction of myopia and myopic astigmatism, and neither significant endothelial cell loss nor vision-threatening complications occurred throughout the 1-year follow-up period.

INTRODUCTION

The femtosecond laser allows very precise cuts with less thermal damage to the tissues than seen with other lasers, and it is therefore one of the most revolutionary technologies to be seen in medical care in recent years. In ophthalmology, it has been used mainly for the creation of corneal flaps for laser in situ keratomileusis (LASIK) with high precision, as an alternative to the mechanical microkeratome. A recent breakthrough of this technology has resulted in a novel refractive procedure called refractive lenticule extraction (ReLEx), which requires neither a microkeratome nor an excimer laser, but uses only the femtosecond laser system, as an all-in-one device for flap and lenticule preparation. The first clinical results with laser-induced extraction of a refractive lenticule were reported in highly myopic eyes,[1] and in blind or amblyopic eyes.[2] Additionally, the ReLEx technique, which can be used for femtosecond lenticule extraction (FLEx) [3-6] by lifting the flap and by small-incision lenticule extraction (SMILE) [4,6-21] without lifting the flap, has been proposed as an alternative to conventional LASIK for the correction of refractive errors.

Early visual and refractive outcomes of SMILE are encouraging, but most of these postoperative follow-ups span 3 to 6 months,[6-14,16-19] except in a few studies.[15,20,21] In consideration of the prevalence of this new technique, more studies of long duration

using different groups are necessary for confirmation of these preliminary findings. The purpose of this study is to prospectively assess the 1-year clinical outcomes, including the endothelial cell loss, of SMILE for the correction of myopia and myopic astigmatism.

MATERIALS AND METHODS

Study Population

Fifty-two eyes of 39 consecutive patients (10 men and 29 women) who underwent SMILE for the correction of myopia and myopic astigmatism, using the VisuMax femtosecond laser system (Carl Zeiss Meditec, Jena, Germany) with a 500 kHz repetition rate at the Kitasato University Hospital were included in this prospective study. The mean patient age at the time of surgery was 31.8 ± 6.9 years (range, 20 to 49 years). The sample size in this study offered 94% statistical power at the 5% level in order to detect a 0.10-difference in logarithm of the minimal angle of resolution (logMAR) of visual acuity, when the standard deviation (SD) of the mean difference was 0.20, and offered 81% statistical power at the 5% level in order to detect a 80-cells/mm^2 difference in the endothelial cell density before and after surgery, when the SD of the mean difference was 200 cells/mm^2. The inclusion criteria for this surgical

technique in our institution were as follows: unsatisfaction with spectacle or contact lens correction, manifest spherical equivalent of -1.25 to -9 diopters (D), manifest cylinder of 0 to 4 D, sufficient corneal thickness (estimated total postoperative corneal thickness > 400 μm and estimated residual thickness of the stromal bed > 250 μm), endothelial cell density ≥ 1800 cells/mm^2, no history of ocular surgery, severe dry eye, progressive corneal degeneration, cataract, or uveitis. Eyes with keratoconus were excluded from the study by using the keratoconus screening test of Placido disk videokeratography (TMS-2, Tomey, Nagoya, Japan). In all eyes, the preoperative manifest refraction was selected as the target correction. Routine postoperative examinations were performed at 1 day, 1 week, and 1, 3, 6, and 12 months after surgery. Preoperatively, and 1 week and 1, 3, 6, and 12 months postoperatively, we determined the following: logarithm of the minimal angle of resolution (logMAR) of uncorrected distance visual acuity (UDVA), logMAR of corrected distance visual acuity (CDVA), manifest spherical equivalent refraction, and endothelial cell density (preoperatively and 1-year postoperatively), in addition to the usual slit-lamp biomicroscopic and funduscopic examinations. Before surgery, the mean keratometric readings and the central corneal thickness were measured using an autorefractometer (ARK-700A, Nidek, Gamagori, Japan) and an ultrasound pachymeter (DGH-500, DGH Technologies,

Exton, US), respectively. The endothelial cell density was determined with a non-contact specular microscope (SP-8800, Konan, Nishinomiya, Japan). The manufacturer's software automatically produced an endothelial cell density measurement by visually comparing the cell size in the image with the predefined patterns on the screen. Each measurement was repeated at least 3 times, and the average value was used for analysis. The study was approved by the Institutional Review Board of Kitasato University and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients after explanation of the nature and possible consequences of the study.

Surgical Procedure

SMILE was performed using the VisuMax femtosecond laser system with a 500 kHz repetition rate. The laser was visually centered on the pupil. A small (S) curved interface cone was used in all cases. In order, the main refractive and nonrefractive femtosecond incisions were performed in the following automated sequence: the posterior surface of the lenticule (spiral in pattern), the anterior surface of the lenticule (spiral out pattern), followed by a side cut of cap. The femtosecond laser parameters were as follows: 120 µm cap thickness, 7.5 mm cap diameter, 6.5 mm lenticule diameter, 140 nJ power for lenticule making, a 3-mm side cut for the access to the lenticule with angles of 90°. A

spatula was inserted through the side cut over the top of the refractive lenticule dissecting this plane followed by the bottom of the lenticule. The lenticule was subsequently grasped with modified McPherson forceps (Geuder, GmbH, Heidelberg, Germany), and removed. After the removal of the lenticule the intrastromal space was flushed with balanced salt solution using a cannula. All surgeries were uneventful and no definite intraoperative complication was observed. No adjustments to the manufacturer's nomograms were done. After surgery, steroidal (0.1% betamethasone, Rinderon ^{TM}, Shionogi, Osaka, Japan) and antibiotic (0.3% levofloxacin, Cravit^{TM}, Santen, Osaka, Japan) medications were topically administered 4 times daily for 2 weeks, and then the frequency was steadily reduced.

Statistical Analysis

All statistical analyses were performed using a commercially available statistical software (Ekuseru-Toukei 2010, Social Survey Research Information Co, Ltd., Tokyo, Japan). The normality of all data samples was first checked by the Kolmogorov-Smirnov test. Since the data did not fulfill the criteria for normal distribution, the Wilcoxon signed-rank test was used for statistical analysis to compare the pre- and post-surgical data. The relationship between two sets of data was analyzed by Spearman's rank correlation test. Unless otherwise indicated, the results are

expressed as mean ± SD, and a value of $p<0.05$ was considered statistically significant.

RESULTS

Patient Population

Preoperative patient demographics of the study population are summarized in Table 1. No eyes were lost during the 1-year follow-up in this series.

Safety Outcomes

LogMAR CDVA was -0.15 ± 0.07, -0.19 ± 0.07, -0.20 ± 0.08, -0.20 ± 0.07, and -0.22 ± 0.07, 1 week, and 1, 3, 6 and 12 months after surgery, respectively. We found no significant difference between preoperative CDVA and 1-year postoperative CDVA ($p=0.48$, Wilcoxon signed-rank test). The safety index was 0.86 ± 0.17, 0.95 ± 0.24, 0.97 ± 0.21, 0.97 ± 0.21, and 1.00 ± 0.20, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively. Thirty-three eyes (63.5%) showed no change in CDVA, 8 eyes (15.4%) gained 1 line, while 9 eyes (17.3 %) lost 1 line, and 2 eyes (3.8%) lost 2 lines 1year postoperatively (Figure 1). Although two eyes lost 2 lines, possibly because of a very mild interface haze formation and/or irregular astigmatism, the eyes had a CDVA of 20/20 or more.

Effectiveness Outcomes

LogMAR UDVA was -0.08 ± 0.13, -0.12 ± 0.11, -0.13 ± 0.13, -0.14 ± 0.12, and -0.16 ± 0.11, 1 week and 1, 3, 6 and 12 months after surgery, respectively. We found a significant difference between preoperative UDVA and 1-year postoperative UDVA ($p<0.001$, Wilcoxon signed-rank test). The efficacy index was 0.75 ± 0.21, 0.83 ± 0.24, 0.84 ± 0.25, 0.86 ± 0.25, and 0.91 ± 0.25, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively. The cumulative percentages of eyes attaining specified cumulative levels of UDVA 1 year postoperatively are shown in Figure 2. One week and 1, 3, 6 and 12 months after surgery, 100%, 100%, 100%, 100%, and 100% of eyes, and 81%, 85%, 90%, 92%, and 94% of eyes had a UDVA of 20/40, and of 20/20 or better, respectively.

Predictability

A scatter plot of the attempted versus the achieved manifest spherical equivalent correction at 1 year postoperatively is shown in Figure 3. The percentages of eyes within different diopter ranges of the attempted spherical equivalent correction and refractive astigmatism are shown in Figures 4 and 5. One week, and 1, 3, 6 and 12 months after surgery, 94%, 98%, 96%, 96%, and 100% of eyes, and 98%, 100%, 100%, 100%, and 100% of eyes were within ± 0.5, and ± 1.0 D of the attempted spherical equivalent correction, respectively.

Stability

The change in the manifest spherical equivalent is shown in Figure 6. One week and 1, 3, 6 and 12 months after surgery, the mean manifest spherical equivalent was 0.00 ± 0.32, -0.06 ± 0.21, -0.05 ± 0.28, -0.09 ± 0.25, and -0.05 ± 0.16 D, respectively. Manifest spherical equivalent was not significantly decreased, from 0.00 ± 0.35 D 1 week postoperatively, to -0.05 ± 0.16 D 1 year postoperatively (p=0.201, Wilcoxon signed-rank test).

Endothelial Cell Density

The endothelial cell density was decreased, but not significantly, from 2804 ± 267 cells/mm^2 preoperatively to 2743 ± 308 cells/mm^2 1 year postoperatively (p=0.12, Wilcoxon signed-rank test). The preoperative and postoperative endothelial cell density and the lenticule thickness according to the degree of myopia are shown in Table 2. The mean percentage of endothelial cell loss was 2.0 % 1 year after surgery. We found no significant correlation of the endothelial cell loss, with the amount of spherical equivalent correction (Spearman correlation coefficient r=0.14, p=0.34), or with the lenticule thickness (r=0.12, p=0.38).

Secondary Surgeries / Adverse Events

A suction loss occurred in 1 eye (2%), but we successfully completed the procedure

after the contact glass was immediately reattached. This eye had UDVA and CDVA of 20/16 1 year postoperatively. Otherwise, all surgeries were uneventful and no significant intraoperative complication was observed. Transient interface haze and optically insignificant peripheral microstriae developed in 6 eyes (12 %) and 2 eyes (4 %), respectively, during the first postoperative month. All these eyes were followed without additional surgical intervention, and gradually resolved thereafter. No epithelial ingrowth, diffuse lamellar keratitis, keratectasia, or any other vision-threatening complications were seen at any time during the 1-year observation period.

DISCUSSION

In the present study, our results showed that SMILE was beneficial in all measures of safety, efficacy, predictability, and stability for the correction of myopia throughout the 1-year follow-up period. Previous studies on the visual and refractive outcomes of SMILE are summarized in Table 3.

With regard to the safety and efficacy of the procedure, Shah et al[7] demonstrated that 70%, 25%, and 6% of eyes had an unchanged CDVA, gained 1 line or more, and lost 1 line or more, respectively, and the 79% of all eyes in which the full refractive correction was attempted had a UDVA of 20/25 or better. Sekundo et al[8] reported that 53% of eyes

remained unchanged, 32.3% gained one line, 3.3% gained two lines, 8.8% lost one line and 1.1% lost 2 lines of CDVA, and that 97.6% and 83.5% of treated eyes had a UCVA of 20/40, and of 20/20 or better 6 months postoperatively. In a different study, they stated that the safety and efficacy indices were 1.08 and 0.99, respectively.[15] Vestergaard et al[10] reported that logMAR CDVA was -0.03 ± 0.07, and that 95% of eyes had a UDVA of 10/20 or more 3 months postoperatively. Hjortdal et al[11] also demonstrated that the safety and efficacy indices were 1.07 ± 0.22 and 0.90 ± 0.25 3 months postoperatively, respectively. In another study, we reported that logMAR CDVA and UDVA were -0.19 ± 0.22 and -0.15 ± 0.20 6 months postoperatively, respectively.[6] Reinstein et al[20] and Xu et al[21] reported that 91% and 99% of eyes had an unchanged CDVA or gained lines, and that 96% and 83% of eyes had a UDVA of 20/20 1 year postoperatively, respectively. Our current findings were comparable with the results of these previous studies in terms of safety, but the efficacy achieved in the current study was slightly better than that of previous studies, presumably because of the slightly lower myopic correction and/or the use of the newer generation femtosecond laser with its higher repetition rate in this study. There was a tendency for a slight delay in UDVA recovery in the early postoperative period (especially 1 week postoperatively) after SMILE, which were in line with that after FLEx.[5,6] Kunert et al[22] showed that the

surface regularity index decreased as pulse energy increased, and that cases of interface haze were uncommon, since they had begun to apply lower energies. Further refinement of the energy settings of the femtosecond laser is necessary to improve visual outcomes not only after FLEx[5,6], but also after SMILE.

With regard to predictability, 77 to 100% and 94.2 to 100% of eyes have been reported to be within ± 0.5 and 1.0 D of the targeted correction, respectively.[6-8,10,11,15-21] Hjortdal et al[11] stated that the average difference between achieved correction and attempted correction was 0.25 D of undercorrection, which may be added when planning SMILE. The predictability achieved in this study was comparable to, or slightly higher than, that in other previous studies.[6-8,10,11,15-21] The discrepancy may be also attributed to the slightly lower myopic correction and the use of the newer generation femtosecond laser with its higher repetition rate in the current study.

With regard to the stability, Shah et al[7] showed that the mean change in refraction from 1 month postoperatively was -0.02 ± 0.18 and -0.06 ± 0.27 D at 3 and 6 months postoperatively, respectively. Sekundo et al[8] demonstrated that the mean refraction was 0.05 D, 0.14 D, and 0.10 D, 1 week, 1 and 6 months after surgery, respectively. They also stated that the mean spherical equivalent gradually regressed by 0.08 D, from -0.11 D at 1 month postoperatively to -0.19 D at 1 year postoperatively.[15] Vestergaard et al[10]

found a slight, but significant, regression from 1 week to 1 month, but no significant regression from 1 month to 3 months after SMILE. In another study, we showed that changes of 0.00 ± 0.30 D occurred in manifest refraction from 1 week to 6 months after SMILE.[6] Reinstein et al[20] reported that the mean refraction was 0.10 D, -0.05 D, and -0.05 D, 1, 3, and 12 months after surgery, respectively. Xu et al[21] showed that the change in manifest refraction from 1 day to 1 year was -0.06 ± 0.37 D. We found no significant refractive regression from 1 week to 1 year after SMILE in the current study. A careful long-term follow-up is still necessary for confirming whether refractive regression occurs in the late postoperative period.

After this surgical technique, we found no significant cell loss, which was comparable with the outcomes after excimer laser surgery such as LASIK and photorefractive keratectomy,[23,24] or after FLEx.[5] Ganesh et al recently reported that the endothelial cell density was not significantly changed, from 2695.13 ± 222.8 cells/mm^2 preoperatively, to 2682.5 ± 231.8 cells/mm^2 1 year postoperatively, in eyes undergoing SMILE with accelerated cross-linking.[25] Neither photodisruption for thinner cap making nor photodisruption for deeper lenticule manufacture induced a significant change in the endothelial cell density of the cornea, and the depth of photodisruption does not significantly affect the endothelial cell loss, both after FLEx[7] and also after SMILE.

There are at least two limitations to this study. One is that we included both eyes of the same patient in the current study, although only one eye should be used for statistical analysis. We confirmed the similar outcomes of SMILE, even when only one eye was randomly chosen from each patient, and thus we enrolled both eyes of the same patient as described in many published studies on refractive surgery. Another limitation is that we did not assess the other aspects of this surgical technique on corneal biomechanics or ocular surface in all eyes. Since SMILE does not require flap making, it may offer benefits in terms of reduced tissue removal, better biomechanical stability, better flap strength, reduced risk of flap dislocation, and milder dry eye symptoms, as compared with LASIK. We are currently conducting a new study on corneal biomechanics and the ocular surface after SMILE.

In conclusion, our results support the view that SMILE is beneficial for the correction of myopia and myopic astigmatism, and the view that neither significant endothelial cell loss nor vision-threatening complications occurred throughout the 1-year follow-up period. This novel surgical approach appears to hold promise as an alternative to LASIK for the correction of myopia and myopic astigmatism.

Footnotes

Contributors: *KK and KS were involved in the design and conduct of the study, KK, AI and HK were involved in collection, management, analysis, and interpretation of data, KK, KS, AI and HK were involved in preparation, review, and final approval of the manuscript.*

Competing Interests: *None.*

Ethics approval: *The study was approved by the Institutional Review Board of Kitasato University.*

Funding: *This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.*

Data Sharing Statement: *No additional data are available.*

REFERENCES

1. Krueger RR, Juhasz T, Gualano A, et al. The picosecond laser for nonmechanical laser in situ keratomileusis. J Refract Surg 1998;14:467-469.

2. Ratkay-Traub I, Ferincz IE, Juhasz T, et al. First clinical results with the femtosecond neodynium-glass laser in refractive surgery. J Refract Surg 2003; 19:94-103.

3. Sekundo W, Kunert K, Russmann C, et al. First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results. J Cataract Refract Surg. 2008;34:1513-1520.

4. Shah R, Shah S. Effect of scanning patterns on the results of femtosecond laser lenticule extraction refractive surgery. J Cataract Refract Surg. 2011;37:1636-1647.

5. Kamiya K, Igarashi A, Ishii R, et al. Early clinical outcomes, including efficacy and endothelial cell loss, of refractive lenticule extraction using a 500 kHz femtosecond laser to correct myopia. J Cataract Refract Surg. 2012;38:1996-2002.

6. Kamiya K, Shimizu K, Igarashi A, et al. Visual and refractive outcomes of femtosecond lenticule extraction and small-incision lenticule extraction for myopia. Am J Ophthalmol. 2014;157:128-134.

7. Shah R, Shah S, Sengupta S. Results of small incision lenticule extraction: All-in-one femtosecond laser refractive surgery. J Cataract Refract Surg. 2011;37:127-137.

8. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol. 2011;95:335-339.

9. Ang M, Tan D, Mehta JS. Small incision lenticule extraction (SMILE) versus laser in-situ keratomileusis (LASIK): study protocol for a randomized, non-inferiority trial. Trials. 2012;13:75.

10. Vestergaard A, Ivarsen AR, Asp S, et al. Small-incision lenticule extraction for moderate to high myopia: Predictability, safety, and patient satisfaction. J Cataract Refract Surg. 2012;38:2003-2010.

11. Hjortdal JØ, Vestergaard AH, Ivarsen A, et al. Predictors for the outcome of small-incision lenticule extraction for Myopia. J Refract Surg. 2012;28:865-871.

12. Riau AK, Ang HP, Lwin NC, et al. Comparison of four different VisuMax circle patterns for flap creation after small incision lenticule extraction. J Refract Surg. 2013;29:236-244.

13. Ozgurhan EB, Agca A, Bozkurt E, et al. Accuracy and precision of cap thickness in small incision lenticule extraction. Clin Ophthalmol. 2013;7:923-926.

14. Agca A, Ozgurhan EB, Demirok A, et al. Comparison of corneal hysteresis and corneal resistance factor after small incision lenticule extraction and femtosecond laser-assisted LASIK: A prospective fellow eye study. Cont Lens Anterior Eye. 2014;37:77-80.

15. Sekundo W, Gertnere J, Bertelmann T, et al. One-year refractive results, contrast sensitivity, high-order aberrations and complications after myopic small-incision lenticule extraction (ReLEx SMILE). Graefes Arch Clin Exp Ophthalmol. 2014;252:837-843.

16. Vestergaard AH, Grauslund J, Ivarsen AR, et al. Efficacy, safety, predictability, contrast sensitivity, and aberrations after femtosecond laser lenticule extraction. J Cataract Refract Surg. 2014;40:403-411.

17. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology. 2014;121:822-828.

18. Lin F, Xu Y, Yang Y. Comparison of the visual results after SMILE and femtosecond laser-assisted LASIK for myopia. J Refract Surg. 2014;30:248-254.

19. Ganesh S, Gupta R. Comparison of visual and refractive outcomes following femtosecond laser- assisted lasik with smile in patients with myopia or myopic astigmatism. J Refract Surg. 2014;30:590-596.

20. Reinstein DZ, Carp GI, Archer TJ, et al. Outcomes of small incision lenticule extraction (SMILE) in low myopia. J Refract Surg. 2014;30:812-818.

21. Xu Y, Yang Y. Small-Incision Lenticule Extraction for Myopia: Results of a 12-Month Prospective Study. Optom Vis Sci. 2014 Nov 13. [Epub ahead of print]

22. Kunert KS, Blum M, Duncker GI, et al. Surface quality of human corneal lenticules after femtosecond laser surgery for myopia comparing different laser parameters. Graefes Arch Clin Exp Ophthalmol. 2011;249:1417-1424.

23. Patel SV, Bourne WM. Corneal endothelial cell loss 9 years after excimer laser keratorefractive surgery. Arch Ophthalmol. 2009;127:1423-1427.

24. Smith RT, Waring GO 4th, Durrie DS, et al. Corneal endothelial cell density after femtosecond thin-flap LASIK and PRK for myopia: a contralateral eye study. J Refract Surg. 2009;25:1098-1102.

25. Ganesh S, Brar S. Clinical Outcomes of Small Incision Lenticule Extraction with Accelerated Cross-Linking (ReLEx SMILE Xtra) in Patients with Thin Corneas and Borderline Topography. J Ophthalmol. 2015;2015:263412.

FIGURE LEGENDS

Figure 1. Changes in corrected distance visual acuity (CDVA) 3 months and 1 year after small incision lenticule extraction (SMILE).

Figure 2. Cumulative percentages of eyes attaining specified cumulative levels of uncorrected distance visual acuity (UDVA) 3 months and 1 year after small incision lenticule extraction (SMILE).

Figure 3. A scatter plot of the attempted versus the achieved manifest spherical equivalent correction 1 year after small incision lenticule extraction (SMILE).

Figure 4. Percentages of eyes within different diopter ranges of the attempted correction (spherical equivalent) 3 months and 1 year after small incision lenticule extraction (SMILE).

Figure 5. Percentages of eyes within different diopter ranges of refractive astigmatism before and 1 year after small incision lenticule extraction (SMILE).

Figure 6. Time course of manifest spherical equivalent after small incision lenticule extraction (SMILE).

TABLES

Table 1. Preoperative demographics of the study population.

Demographic Data	
Age (years)	31.8 ± 6.9 years (range, 20 to 49 years)
Gender (% female)	74 %
LogMAR UDVA	1.12 ± 0.11 (range, 0.52 to 1.52)
LogMAR CDVA	-0.22 ± 0.08 (range, -0.30 to -0.18)
Manifest spherical equivalent (D)	-4.11 ± 1.73 D (range, -1.25 to -8.25 D)
Manifest cylinder (D)	-0.51 ± 0.65 D (range, 0.00 to -2.25 D)
Mean keratometric reading (D)	43.3 ± 1.33 D (range, 40.4 to 46.0 D)
Central corneal thickness (μm)	546.1 ± 32.9 μm (range, 471 to 614 μm)
Endothelial cell density (cells/mm^2)	2804 ± 267 cells/mm^2 (range, 2275 to 3362 cells/mm^2)

LogMAR=logarithm of the minimal angle of resolution, UDVA=uncorrected distance visual acuity, CDVA=corrected distance visual acuity, D=diopter

Table 2. Preoperative and postoperative endothelial cell density and lenticule thickness according to the degree of myopia.in eyes undergoing small incision lenticule extraction (SMILE).

	Low myopia (≥ -3 D)	Moderate myopia (-3 D>, ≥-6 D)	High Myopia (<-6 D)
Number of eyes (%)	14 (27%)	32 (62%)	6 (12%)
Lenticule thickness (μm)	48.6 ± 10.2	91.0 ± 13.1	128.3 ± 8.6
Preoperative ECD (cells/mm^2)	2859 ± 191	2804 ± 300	2676 ± 215

Postoperative ECD (1 year)(cells/mm^2)	2834 ± 229	2736 ± 332	2564 ± 289
Endothelial cell loss (%)	0.8 ± 5.9	2.1 ± 10.1	4.3 ± 6.1

ECD=endothelial cell density.

Table 3. Previous studies on visual and refractive outcomes of small incision lenticule extraction (SMILE).

Author	Year	Repetition rate (kHz)	Eyes	Follow-up (months)	Age (years)	Spherical equivalent (D)	Astigmatism (D)	Safety (logMAR CDVA)	Efficacy (logMAR UDVA)	Predictability within ± 0.5D (%)	Predictability within ±1.0D (%)	Stability (D)
Shah et al7	2011	200	51	6	26.0 ± 5.55	-4.87 ± 2.16	-0.76 ± 0.98	70% unchanged 25% gained 1 line or more 6% lost 1 line or more	79% ≤ 0.16 logMAR	91	100	-0.06
Sekundo et al8	2011	200	91	6	35.6	-4.75 ± 1.56	-0.78 ± 0.79	49% unchanged 35.6% gained 1 line or more 11% lost 1 line or more	83.5% ≤ 0.00 logMAR	80.2	95.6	0.05
Vestergaard et al10	2012	500	279	3	38.1 ± 8.7	-7.18 ± 1.57	-0.71 ± 0.50	-0.03 ± 0.07	95% ≤ 0.30 logMAR	77	95	-0.18
Hijordal et al11	2012	500	670	3	38.3 ± 8.3	-7.19 ± 1.30	-0.60 ± 0.46	-0.049 ± 0.097	84% ≤ 0.16 logMAR	80.1	94.2	-0.25 ± 0.44 (undercorrection)
Kamiya et al6	2014	500	26	6	31.5 ± 6.2	-4.21 ± 2.63	-0.54 ± 0.74	-0.19 ± 0.07	-0.15 ± 0.20	100	100	0.00 ± 0.30
Sekundo et al15	2014	500	53	12	29	-4.68 ± 1.29	-0.41 ± 0.51	47% unchanged 42% gained 1 line or more 11% lost 1 line	88% ≤ 0.00 logMAR	92	100	-0.08

Vestergaard et al16	2014	500	34	6	35 ± 7	-7.56 ± 1.11	-	-0.08 ± 0.08	-0.04 ± 0.06	88	97	-0.17 ± 0.34
Ivarsen et al17	2014	500	1574	3	38 ± 8	-7.25 ± 1.84	-0.93 ± 0.90	-0.05 ± 0.10	-	-	-	-0.15 ± 0.50
Lin et al18	2014	-	60	3	25.9 ± 6.4	-5.13 ± 1.75	-0.57 ± 0.47	96.7% unchanged 3.3% lost 1 line or more	85% ≤ 0.00 logMAR	-	98.3	-0.09 ± 0.38
Ganesh et al19	2014	-	50	3	27.4 ± 5.6	-4.95 ± 2.09	-0.53 ± 0.93	88% unchanged 12% gained 1 line	84% ≤ 0.00 logMAR	-	-	-0.14 ± 0.28
Reinstein et al20	2014	500	110	12	32.4 ± 5.7	-2.61 ± 0.54	-0.55 ± 0.38	66% unchanged 25% gained 1 line or more 9% lost 1 line	96% ≤ 0.00 logMAR	84	99	-0.05 ± 0.36
Xu et al21	2015	-	52	12	24.5 ± 6.0	-5.53 ± 1.70	-0.64 ± 0.51	67% unchanged 32% gained 1 line or more 1% lost 1 line	83% ≤ 0.00 logMAR	90.4	98.1	-0.06 ± 0.37
Current		500	52	12	31.8 ± 6.9	-4.11 ± 1.73	-0.51 ± 0.65	-0.22 ± 0.07	-0.16 ± 0.11	100	100	-0.05 ± 0.32

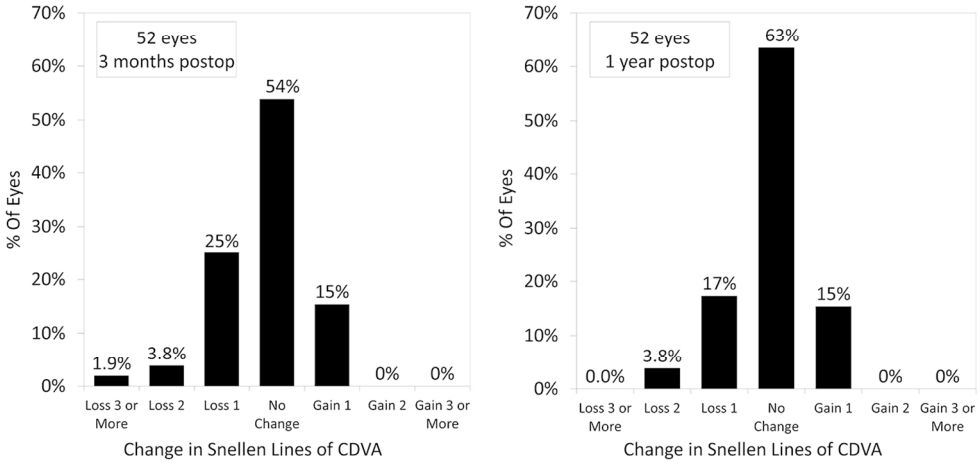

Figure 1. Changes in corrected distance visual acuity (CDVA) 3 months and 1 year after small incision lenticule extraction (SMILE).
127x95mm (300 x 300 DPI)

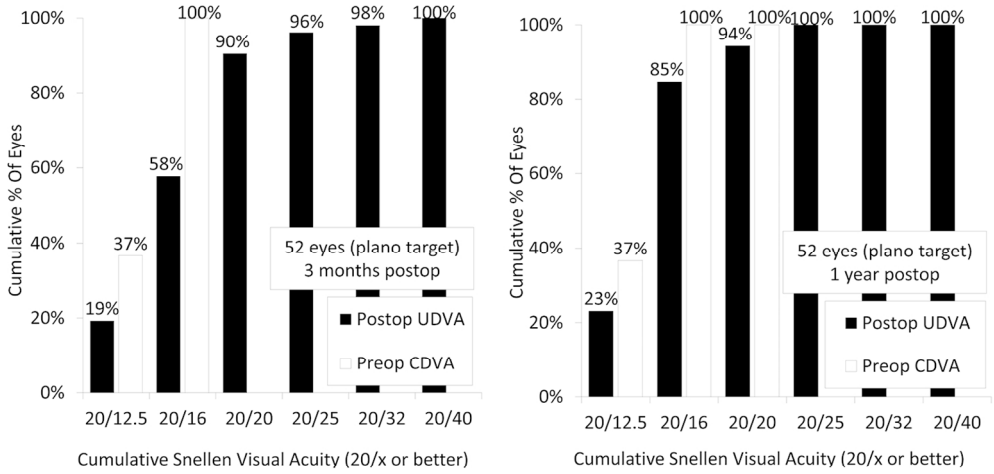

Figure 2. Cumulative percentages of eyes attaining specified cumulative levels of uncorrected distance visual acuity (UDVA) 3 months and 1 year after small incision lenticule extraction (SMILE).
127x95mm (300 x 300 DPI)

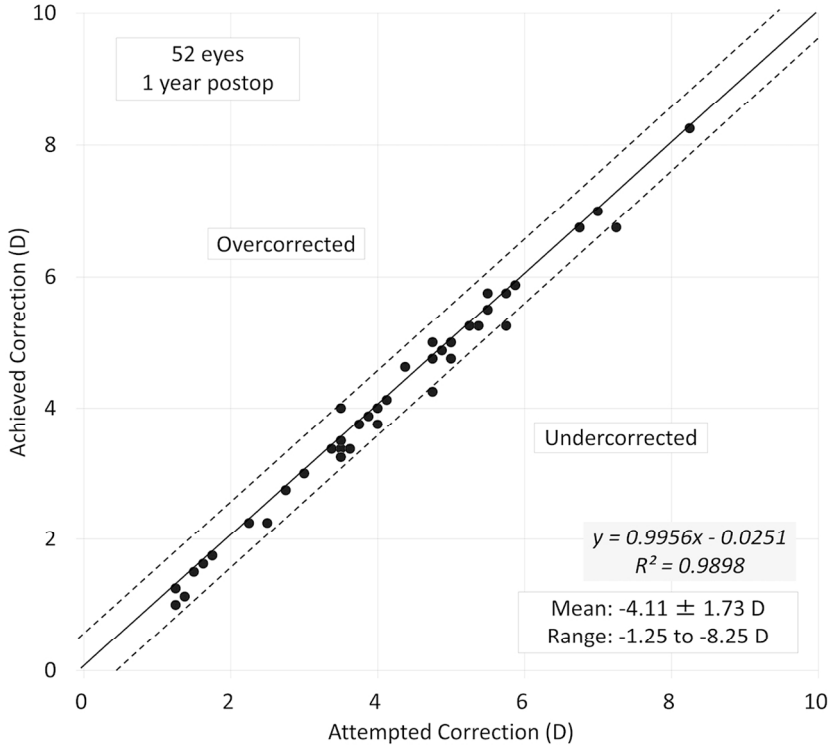

Figure 3. A scatter plot of the attempted versus the achieved manifest spherical equivalent correction 1 year after small incision lenticule extraction (SMILE).
127x95mm (300 x 300 DPI)

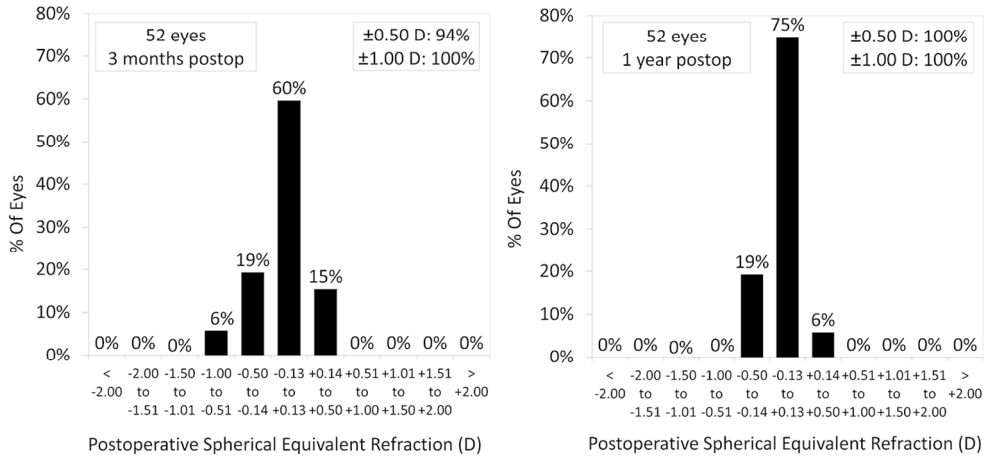

Figure 4. Percentages of eyes within different diopter ranges of the attempted correction (spherical equivalent) 3 months and 1 year after small incision lenticule extraction (SMILE).
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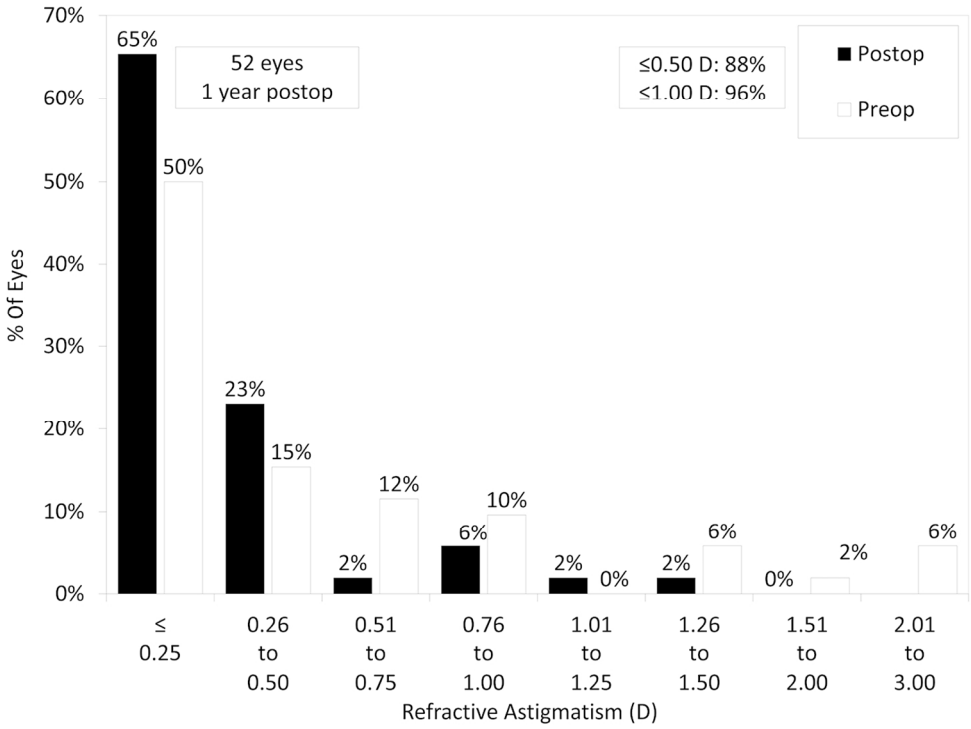

Figure 5. Percentages of eyes within different diopter ranges of refractive astigmatism before and 1 year after small incision lenticule extraction (SMILE).
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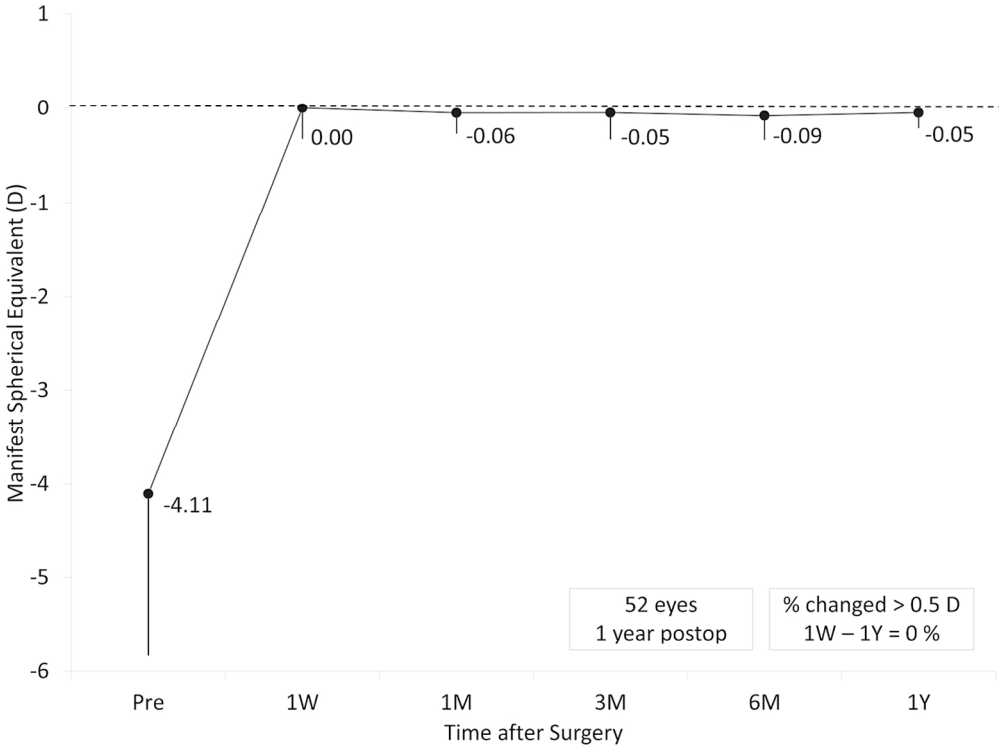

Figure 6. Time course of manifest spherical equivalent after small incision lenticule extraction (SMILE).
127x95mm (300 x 300 DPI)