New Developments in the Lenticule Extraction Procedure

Jesper Hjortdal, MD, PhD[1] and Anders Ivarsen, MD, PhD[2]

1. Clinical Professor; 2. Assistant Professor, Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark

Abstract

For the last 20 years controlled excimer laser ablation of corneal tissue, either directly from the corneal stromal surface or from the corneal interior after creation of a superficial corneal flap, has become widely used to correct myopia, hyperopia, and astigmatism. Recently, an intrastromal refractive procedure whereby a tissue lenticule is cut free in the corneal stroma by a femtosecond laser and removed through a small peripheral incision has been introduced. The procedure avoids creation of a corneal flap and the potential associated risks while avoiding the slow visual recovery of surface ablation procedures. The all-femtosecond-based flap-free intracorneal refractive procedure has been documented to be a predictable, efficient, and safe procedure for correction of myopia and astigmatism. Technologic developments related to further improved cutting quality, hyperopic, and individualized treatments are desirable.

Keywords

Corneal refractive surgery, femtosecond laser, small incision lenticule extraction, myopia, astigmatism

Disclosure: Jesper Hjortdal, MD, PhD, has received travel support from Carl Zeiss Meditec, Jena, Germany. Anders Ivarsen, MD, PhD, has no conflicts of interest to declare.

Received: January 7, 2014 **Accepted**: March 1, 2014 **Citation**: *US Ophthalmic Review,* 2014;7(1):20–5 *DOI: 10.17925/USOR.2014.07.01.20*

Correspondence: Jesper Hjortdal, MD, PhD, Department of Ophthalmology, Aarhus University Hospital, 8000 Aarhus C, Denmark. E: jesper.hjortdal@dadlnet.dk

Over the last few years, surgical extraction of a refractive lenticule, or ReLEx®, has evolved as a new treatment in the field of keratorefractive surgery. Currently, the VisuMax® femtosecond (FS) laser (Carl Zeiss Meditec, Jena, Germany) is the only platform to offer this treatment. The 500 kHz VisuMax laser generates very fast pulses (10^{-15} s range) in the near-infrared spectrum. Depending on the specific laser settings, each pulse conveys approximately 150 nJ, which causes localized photodisruption at the focal point. The generated plasma expands, creating a cavitation bubble, and, as individual cavitation bubbles fuse, the stroma is cut with a minimum of collateral damage. The VisuMax FS laser uses a high numerical aperture and a concave contact glass to focus the laser pulses with very high precision. Thus, laser spots of approximately 1 µm diameter are placed with a defined distance of 2–5 µm in a spiral pattern. To ensure centration on the visual axis, the patient fixates on a blinking light, and suction is applied at the limbus to maintain stability of the eye. Initially, the posterior refractive surface of the lenticule is cut, followed by creation of the plano anterior surface, which is slightly enlarged in diameter to facilitate surgical manipulation.

This review article reviews the current state of the technique, updated clinical results,[1] experimental studies, and, finally, presents some of the challenges that need to be addressed by new technologies.

Depending on the method used to access the lenticule, ReLEx can be split into FLEx, in which a laser-assisted *in situ* keratomileusis (LASIK)-like flap allows surgical removal of the lenticule, and small incision lenticule extraction (SMILE) in which a small incision (approximately 2–4 mm in length) is created for manual lenticule extraction. A blunt spatula is used to break any remaining tissue bridges after the laser treatment, and the lenticule is removed with a pair of forceps (see *Figure 1*). For further details on the surgical approach, please refer to Sekundo et al.,[2] Shah et al.,[3] and Vestergaard et al.[4]

In contrast to LASIK, ReLEx is a one-laser approach, where the critical laser treatment is performed on the intact cornea rather than on exposed corneal stroma. Consequently, the potential variability associated with the excimer laser photoablation is avoided. In addition, the minimally invasive SMILE treatment has several theoretical advantages over flap-based treatments, including little trauma to the corneal surface, less corneal denervation, and better biomechanical strength due to an almost intact anterior stroma. Since the first introduction of ReLEx, the repetition rate of the VisuMax laser has been increased from 200 to 500 kHz, and the settings for laser spot size, energy, and distance have been optimized, changes that may have had a significant impact on the clinical outcome after surgery. Furthermore, the flap-based FLEx represents an evolutionary step before SMILE and is today primarily used as an introductory step for new ReLEx surgeons. Due to these changes, this review focuses primarily on studies concerning SMILE.

Currently, the VisuMax allows myopic corrections up to –10 diopters (D) spherical equivalent (SE) correction, with an astigmatic component of up to 5 D. Hyperopic treatments are not available at the moment, although one study has reported on the outcome of hyperopic FLEx.[5] The VisuMax laser is Conformité Européenne (CE) marked and is currently being evaluated in clinical studies for the approval of SMILE by the US Food and Drug Administration (FDA).

Myopia

Refractive Outcome

Overall, ReLEx has been reported to have high refractive predictability in moderate and high myopia. In the largest report to date on SMILE in 670 myopic eyes 3 months after surgery (preoperative SE refraction was –7.2 D) the mean error in SE refraction was –0.25 ± 0.44 D, with 80 % of eyes within ± 0.50 D and 94 % within ± 1.0 D.[6] We recently extended this evaluation to the first 1,574 eyes 3 months after SMILE and found a similar mean error of –0.15 ± 0.50 D with 77 % of eyes within ± 0.50 D and 95 % within ± 1.0 D.[7] Other reports on SMILE[3,4,8,9] and 500 kHz FLEx[10–14] have found similar refractive outcomes in smaller numbers of patients. Most studies have included patients with moderate and high myopia, while the refractive predictability in treatment of low myopia (less than 2 D) has not been evaluated thoroughly or compared with results after FS-LASIK or photorefractive keratectomy (PRK).

The refractive stability after SMILE has not been extensively investigated. However, in one study on 279 eyes with high myopia, refraction was found to be stable from 1 to 3 months after surgery, although a minor regression of –0.15 D was observed during the first month.[4] Another study on 54 eyes found no regression during the first 6 months after surgery.[8] Similarly, no regression has been found during the first 3–6 months after 500 kHz FLEx[10,11,13,14] or for 1 year after 200 kHz FLEx.[15,16] A prospective, randomized, paired-eye study comparing SMILE and FLEx documented no significant regression between 1 week and 6 months. The procedures were similar in terms of safety, efficacy, predictability, and stability, suggesting that the presence or absence of lifting the flap does not significantly affect these visual and refractive outcomes.[17]

Interestingly, the refractive predictability after SMILE has been found to be unrelated to the degree of the attempted myopic correction.[6] This is in contrast to excimer-based treatments, which show decreasing precision with increasing myopic correction.[18] Furthermore, other parameters including preoperative corneal power, patient age, and gender have been found to have limited impact on the refractive outcome after SMILE.[6]

Visual Outcome

In the first clinical studies, FLEx was reported to have delayed visual recovery in comparison with FS-LASIK.[3,19] Later studies suggested that the laser scanning pattern and energy influenced the lenticule surface quality and the immediate postoperative outcome.[20–22] Subsequent changes in the laser scanning trajectory and energy delivery appear to have reduced the problem with postoperative visual recovery. Several studies have examined the uncorrected distance visual acuity (UDVA) after 500 kHz SMILE for myopia and reported 73–100 % of patients as having an UDVA of 20/25 or better 3–6 months after surgery.[4,6,7] Similar results have been reported for 500 kHz FLEx, and the procedure has been found to be on a par with the outcome after FS-LASIK.[10,14]

Safety

The induced change in corrected distance VA (CDVA) may be used as an indicator for the overall safety of a refractive surgical procedure. In general, loss or gain of two or more lines on the Snellen VA card is considered significant and noticeable for the patient.

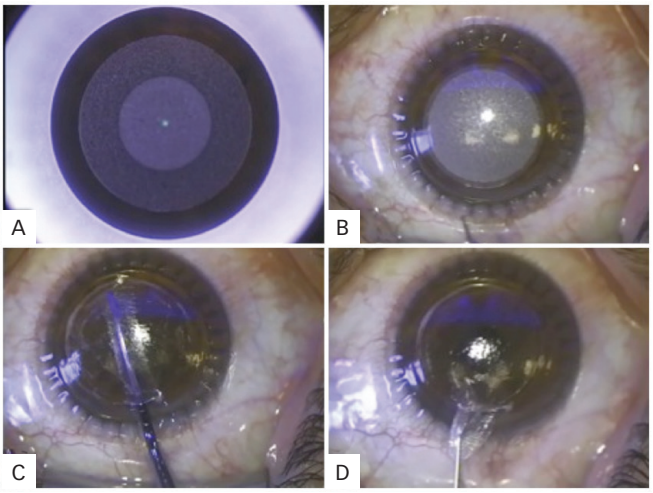
Most studies on FLEx or SMILE are too small to properly evaluate the safety of the procedure, and the frequency of a two-line loss in CDVA has been reported to be between 0 and 8 %.[2,3,8–14] In one study on 279 eyes after SMILE, 0.4 % of eyes were reported to have a loss of two or more lines.[3] By contrast, a 2.4 % risk for a two-line loss was found in 670 eyes by Hjortdal et al.[6] However, in the same study, a safety index (CDVA before/CDVA after surgery) of 1.07 ± 0.22 was found, indicating that CDVA on average increased after surgery, as would be expected because of the image magnification of myopic keratorefractive procedures. In a recent single-center study, the safety and complications of 1,574 SMILE procedures were evaluated after 3 months.[7] CDVA was found to have improved with two or more lines in 3.4 % of eyes, whereas 1.5 % of eyes had experienced a loss of two or more lines. Yet, at a late follow-up visit, all patients with a loss in VA had recovered to within one line of the preoperative value. The surgeon learning curve and the laser settings were found to be important parameters for the postoperative visual recovery. In a study using a double-pass instrument, FLEx induced a transient decrease in optical quality in association with an increase in intraocular scattering in the early postoperative period, possibly due to mild interface haze formation, but gradually recovered with time.[23] It was suggested that this transient degradation in optical quality relate may result in a slight delay of CDVA recovery in the early postoperative period. Using high-resolution optical coherence tomography, presence of microdistorsions in Bowman's layer after SMILE and FS-LASIK has been compared. Microdistorsions in Bowman's layer were more common after SMILE 1 day after surgery and were associated with the refractive lenticule thickness and surgery order. The microdistorsions remained stable after 1 week but had no apparent impact on long-term visual performance.[24] In summary, safety after SMILE appears to be comparable with that reported after FS-LASIK,[25,26] although recovery may be prolonged in a few cases.

Endothelial changes after ReLEx have not been systematically evaluated. One study with 38 FLEX-treated eyes reported that the procedure did not result in significant changes in endothelial cell density.[11]

Complications

A variety of peri- and postoperative complications have been reported after SMILE. The most frequently reported perioperative complications include

Figure 1: Small Incision Lenticule Extraction Procedure



A) Image obtained during femtosecond laser cutting of lenticule. Posterior side of lenticule has been cut and anterior cut has been approximately 50 % completed. B) Immediately after completion of femtosecond laser cutting. C) Through a small peripheral incision, remaining tissue-bridges are broken with a blunt spatula. D) Lenticule is removed through the peripheral incision.

tears at the incision and minor abrasions. Decentration, suction loss, difficulties removing the lenticule, and cap perforation occur rarely.[3,4,9,10,19] Frequent postoperative complications include dry eye, microstriae, and increased interface scatter, whereas rare complications include keratitis, interface inflammation, epithelial ingrowth, and monocular ghost images.[10,11,19] Recently, we found irregular postoperative topography in 18 of 1,574 eyes, giving rise to ghost images in six cases.[23] Topography-guided PRK was performed in four of these eyes, ameliorating the symptoms in three cases. In another recent paper, a lenticule remnant was documented to be the cause of postoperative monocular double vision.[27] Postoperative ectasia has not been reported after SMILE; however, one case has been described after a flap-based FLEx treatment.[15]

Overall, SMILE appears to be a technically more demanding surgical procedure than LASIK, introducing specific potential complications related to the extraction of the refractive lenticule, while eliminating some specific LASIK complications. Still, despite a relatively high frequency of peri- and postoperative complications, the visual outcome is reported to be good, with minimal risk for loss in CDVA on the long term.

Astigmatism

Correction of high astigmatism has not yet been systematically evaluated after ReLEx. Only one paper on 200 kHz FLEx included a detailed evaluation of the outcome after cylinder correction.[28] An undercorrection of approximately 10 % was reported; however, the average preoperative cylinder was only 0.96 ± 0.87 D, and the population skewed toward low corrections, making it difficult to extrapolate to high astigmatisms. Recently, we evaluated correction of myopic astigmatism with SMILE in 775 eyes, of which 106 eyes had astigmatism of 2.50 D or more. On average, 95 % were within ± 1.0 D of the attempted SE correction 3 months after surgery. However, a significant astigmatic undercorrection was observed, with an average error of treatment of 0.17 ± 0.42 D in low astigmatism and 0.59 ± 0.65 D in high astigmatism.[29]

Hyperopia

At present, only one study has examined hyperopic treatment (average SE refraction + 2.8 ± 1.3 D) with 200 kHz FLEx.[5] After 9 months, only 64 % of patients had a postoperative refraction within ± 1.0 D of that attempted, and there was significant regression of the effect during the first 6 months after surgery. Thus, it still remains to be determined whether ReLEx eventually will allow safe and predictable hyperopic treatments.

Presbyopia

Many options have been proposed for surgical presbyopia correction of which a monovision or blended vision correction is one possibility.[30] Results after aiming for SMILE monovision has, however, not been published.

Possible Advantages of Intrastromal Treatments

Sensitivity and Tear Production

Several recent studies have examined the corneal sensitivity after SMILE in comparison with a flap-based treatment.[31–35] In a randomized paired-eye study, Demirok et al. demonstrated less reduction in corneal sensitivity after SMILE than after FS-LASIK, although sensitivity had fully normalized in both groups by 6 months.[32] Similar findings have been documented in a non-paired study of SMILE and FS-LASIK.[35] In another randomized paired-eye study, the corneal nerve density and number of long nerve fibers were higher after SMILE than after FLEx;[31] accordingly, sensitivity was better after SMILE. In comparative studies on SMILE, FLEx, and FS-LASIK, better sensitivity was found at all time points for up to 3 months after SMILE.[33,34]

Studies based on a paired-eye evaluation of the postoperative tear secretion after SMILE in comparison with a flap-based treatment[31,32] were not able to document significant differences in tear osmolarity, tear secretion rate, and tear meniscus height. However, one study found a slight difference in the postoperative tear-film break-up time in favor of SMILE.[27] In a non-randomized study, SMILE surgeries resulted in a short-term increase in dry eye symptoms, tear film instability, and loss of corneal sensitivity, but corneal staining was less compared with patients undergoing FS-LASIK.[35]

Overall, the minimally invasive SMILE causes less damage to corneal nerves than flap-based treatments, resulting in better postoperative sensitivity. These changes appear to have only minimal measurable impact on the postoperative tear secretion.

Corneal Biomechanics and Sublayer Thickness

In SMILE, most of the anterior stroma remains intact after surgery. Since the cornea is biomechanically stronger in the anterior part,[36] it would theoretically be more robust after SMILE than after a flap-based treatment where most of the anterior lamellae are severed. Thus, SMILE-treated corneas may be more resistant to trauma and less prone to developing postoperative keratectasia, and SMILE-treated corneas have been suggested to be even stronger than a PRK-treated corneas.[37] It has recently been speculated that the refractive lenticule should be removed deeper within the stroma to increase the postoperative corneal strength.[37] Although this might be advantageous from a biomechanical point of view, many factors could affect the outcome, including endothelial safety, the quality of the laser cut in deeper stroma, and the relative front- and back-surface changes. Thus, the optimal depth of the refractive lenticule still remains to be determined.

At present, only few studies has been published on the biomechanical properties after SMILE in comparison with FS-LASIK using the Ocular Response Analyzer.[38] This paired-eye, randomized study found no differences in corneal hysteresis (CH) or corneal resistance factor (CRF) 6 months after surgery. In a comparable study on SMILE and FLEx, we similarly found no difference between the methods regarding CH and CRF.[39] However, in a small comparative study on SMILE, FLEx, and FS-LASIK, we recently found the biomechanical response, as measured with the Corvis ST, to be more abnormal after a flap-based treatment than after SMILE. (Bach-Pedersen I, et al., Corneal biomechanical properties after LASIK, ReLEx FLEx, and ReLEx SMILE by Scheimpflug-based dynamic tonometry. Submitted for publication, 2014.) Overall, the biomechanical changes after SMILE are still unclear, and there is a considerable need for further studies.

A planar and uniform flap is generally considered important in flap-based keratorefractive surgery, and three studies have found the cap to be of nearly uniform thickness and similar to the flap after FLEx or FS-LASIK.[8,40–42] Furthermore, in one study, no significant changes were observed in central cap or stromal bed thickness for 6 months after surgery.[41] We recently evaluated corneal sublayer thicknesses after SMILE and FLEx[39] and found

no significant difference in cap or stromal bed thickness 6 months after surgery. As seen after other myopic keratorefractive procedures,[43,44] a compensatory epithelial hyperplasia was observed.

Wound Healing

In excimer laser keratorefractive surgery, the energy delivered to the cornea may promote subsequent inflammation and wound repair.[45] In contrast to the excimer laser, FS lasers deliver only minimal amounts of energy to surrounding tissue,[46] suggesting that the FS laser may induce less postoperative wound repair. In accordance, a study in rabbits has demonstrated FLEx to induce less wound healing and inflammation than FS-LASIK, particularly after high myopic corrections.[47] In another recent study in rabbits, SMILE also induced less keratocyte apoptosis, proliferation, and inflammation compared with FS laser LASIK.[46] Whether these observations have any clinical relevance remains to be determined; wound repair after LASIK and, in particular, PRK has been extensively investigated and is known to influence the postoperative outcome.[45,48,49]

Unique Perspectives for Intrastromal Lenticule Extraction

Extracting an intact stromal lenticule from the cornea opens new interesting possibilities in keratorefractive surgery. First, if the extracted tissue can be successfully preserved, the surgical procedure may in theory be reversed at a later time point by re-implantation of the lenticule. Second, the lenticule has been used to change the refraction in another individual by implanting a myopic lenticule in the stromal pocket of a hyperopic patient.[50] Such a procedure would, at least in Europe, require permission from national authorities, as this would be considered a corneal transplantation.

In a recent study, refractive lenticules from rabbit eyes were demonstrated to have an intact collagen structure and viable keratocytes after 1-month cryopreservation.[51] Other studies in rabbits and primates have shown successful cryopreservation and later re-implantation of a stromal lenticule.[52–55] Furthermore, in primates, the procedure was shown to induce little postoperative wound repair, and keratocyte repopulation could be observed after 16 weeks.[52] Although further studies are needed, lenticule re-implantation or transplantation from one patient to another may become reality in the near future.

Further Improvements to Intrastromal Laser Surgery

Although intrastromal refractive surgery as performed with the SMILE technique seems to be predictable, efficient, and safe, there are concerns that could be improved.

Laser Cut Quality

The FS laser used in ReLEx is a 1,043 nm solid-state Nd:glass laser. At the laser focus point, the laser energy increases above a critical level and plasma formation and cavitation takes place. The actual point of focus is associated with some degree of imprecision that is determined by lateral and axial beam scanning imprecision. However the axial point of interaction between laser pulse and corneal tissue may fluctuate due to non-linear effects within a certain range.

Further optimization of the FS laser in terms of wavelength and scanning imprecision is maybe possible. If the wavelength could be reduced to one-third and/or the lateral beam imprecision could be lowered further, the actual fluctuation in laser precision would be reduced. However, it is unknown whether such technologic modifications are actually useful and possible, especially considering laser safety.

Extractability is another aspect of cut quality that is clinically interesting. This parameter is closely related to the number of laser spots that are used to separate the lenticule from its surrounding tissue with only a reasonably low number of tissue bridges. With its 500 kHz laser pulse repetition rate the VisuMax is able to produce a well-separated lenticule within about 30 seconds. The current level of speed and extractability is acceptable but still keeps room for future improvements.

Centration and Cyclotorsion

The optimal exact centration of laser refractive procedures with respect to the various lines and axes that can be defined in the human eye has been debated for years.[56] Some authors argue that refractive procedures should be centered at the pupil center, other argues that centration should be at the corneal vertex, and others that the correct centering is somewhere between these fairly easily identifiable landmarks, as this will correspond to the visual axis.

In FS lasers, the eye is fixed by suction to an applicator attached to the laser in order to keep the cornea stable during laser cutting. The operating surgeon has to put on suction and fixate the eye manually. After the eye is stabilized, it is not possible to translate the center of laser cutting into a more ideal position. Similarly, the eye may undergo cyclotorsion from the upright to the supine position. As refraction is performed when patients are upright, but surgery is performed with patients supine, this may induce errors when astigmatism is treated. Modern excimer lasers are equipped with very fast image tracking and processing software, which allows the laser to compensate for cyclotorsion automatically. Excimer lasers also allows the surgeon to adjust the center of the treatment to the position best corresponding to the visual axis.

Development of similar tracking solutions and capabilities for automatic adjustment of centration and cyclotorsion possibly may further improve the outcome of FS-based intrastromal procedures.

Treatment of Astigmatism and Hyperopia

Geometrically, correction of myopia is fairly simple and the necessary lenticule shape to be removed was calculated many years ago by Munnerlyn et al.[57] Although this calculation ignores aspects related to the aspheric shape of the cornea, the formula has been widely used, also as a basis for intrastromal refractive surgery. In correction of astigmatism and hyperopia, the actual correcting tissue removal will end abruptly. For astigmatic corrections, the ends of the removed tissue cylinder will give rise to symmetric discontinuities in the meridian of the cylinder, and in hyperopic corrections, the doughnut-shaped tissue will end with a rotational symmetric discontinuity. Although such discontinuities may seem dramatic, the overlying corneal stroma and epithelium will act as smoothing factors, but at the expense of less refractive effect.

In excimer laser surgery, transition zones have been used to smooth these gaps, and similar transitions have been used in FS laser surgery. Further research is needed to explore the optimum size of these transition zones,

and also to optimize the cutting sequence between the refractive deep cut, cap cut, transition zones, and side cuts.

Topography and Wave-front-guided Treatments

Laser refractive treatments are normally based on standard sphero-cylindrical treatments defined by meticulous refraction of the patient before surgery. As the optics of the eye is not perfect, all eyes have some degree of higher-order optical aberrations of which spherical aberrations and coma are the dominant. Aberrations can be measured in individual eyes by whole-eye aberrometry.[58] Some eyes have very large aberrations caused by imperfections in the shape of the cornea, which is typically called irregular astigmatism and can be measured by corneal topography. Topographic as well as whole-eye aberrations may be corrected by excimer laser surgery, and successful correction of such aberrations result in better VA.[58]

At present, FS laser-based surgery of the cornea cannot correct higher-order aberrations or irregular astigmatism. Development of interfaces from aberrometers and topographers into individualized lenticule cutting patterns will possibly improve the outcome of intrastromal procedures in patients with high levels of such optical imperfections.

Retreatments

Although ReLEx has been found to have a high refractive predictability, some patients have a postoperative residual refractive error due to over- or undercorrection.[6] In flap-based treatments, an excimer-based enhancement procedure can be performed after lifting the flap.[59] Retreatment after SMILE is, however, more complicated.

Possible approaches may include PRK or LASIK, whereas a new ReLEx procedure may be more unpredictable due to multiple dissection planes within the cornea. Presently, no systematic clinical evaluation of SMILE enhancements has been published. One study has reported on successful topography-guided PRK in SMILE patients with postoperative irregular astigmatism,[27] and another has reported on successful FS-LASIK in a patient with perioperative suction loss.[60] In a rabbit model, the conversion of a SMILE cap to a flap has been demonstrated, allowing subsequent intrastromal photoablation.[21] Still, the optimal approach for SMILE enhancements needs to be established.

Performing a new conventional SMILE procedure close to the original intrastromal cutting plane is typically avoided as interference with the original incision plane may result in difficult or incomplete lenticule removal. A possible option would be to perform a new SMILE procedure in a different plane, either deeper in the cornea, or more superficially, in the cap. In both situations, further development and clinical testing of this variation of the technique is necessary.

Conclusion

Several studies have shown that the refractive and visual outcomes after SMILE and FLEx for moderate and high myopia are as good as after FS-LASIK. SMILE has also been shown to be as safe as LASIK, although the procedure may be technically more demanding and have a specific variety of complications.

The minimal impact on the anterior stroma in SMILE represents the most interesting aspect of the new procedure. Thus, more stromal nerves are spared, and SMILE has been convincingly demonstrated to cause less denervation and have better sensitivity than flap-based treatments. The impact on postoperative tear secretion and dry-eye symptoms remains unclear. Due to the intact anterior stromal lamellae, the cornea may be stronger after SMILE than after a flap-based treatment, but biomechanical differences have proven elusive and have not yet been positively confirmed.

In its current state, SMILE has been shown to be a reliable, efficient, and safe procedure for correction of moderate and high myopia. Correction of myopic astigmatism also appears promising, but hyperopic treatments need further evaluation. Furthermore, compensation for eye rotation as well as aspheric or custom lenticule profiles is still not available. Thus, in complicated cases with irregular corneas, the excimer laser is still the only valid option. By contrast, ReLEx may allow exciting new treatments including re-implantation or transplantation of refractive lenticules, and it is of considerable interest to see the further evolution of intrastromal lenticule extraction surgery. ■

1. Ivarsen A, Hjortdal J, All-femtosecond laser keratorefractive surgery, *Curr Ophthalmol Rep*, 2014;2:26–33.
2. 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;34:1513–20.
3. Shah R, Shah S, Sengupta S, Results of small incision lenticule extraction: all-in-one femtosecond laser refractive surgery, *Cataract Refract Surg*, 2011;37:127–37.
4. Vestergaard A, Ivarsen AR, Asp S, Hjortdal JØ, Small-incision lenticule extraction for moderate to high myopia: predictability, safety, and patient satisfaction, *J Cataract Refract Surg*, 2012;38:2003–10.
5. Blum M, Kunert KS, Voßmerbäumer U, Sekundo W, Femtosecond lenticule extraction (ReLEx) for correction of hyperopia – first results, *Graefes Arch Clin Exp Ophthalmol*, 2013 251:349–55
6. Hjortdal JØ, Vestergaard AH, Ivarsen A, et al., Predictors for the outcome of small-incision lenticule extraction for myopia, *J Refract Surg*, 2012;28:865–71.
7. Ivarsen A, Asp S, Hjortdal J, Safety and complications of more than 1500 small-incision lenticule extraction procedures, *Ophthalmology*, 2013 [Epub ahead of print).
8. Zhao J, Yao P, Li M, et al., The morphology of corneal cap and its relation to refractive outcomes in femtosecond laser small incision lenticule extraction (SMILE) with anterior segment optical coherence tomography observation, *PLoS ONE*, 2013;8:e70208.
9. 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;95:335–9.
10. Vestergaard A, Ivarsen A, Asp S, Hjortdal JØ, Femtosecond (FS) laser vision correction procedure for moderate to high myopia: a prospective study of ReLEx FLEx and comparison with a retrospective study of FS-laser *in situ* keratomileusis, *Acta Ophthalmol*, 2013;91:355–62.
11. 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.
12. Kamiya K, Shimizu K, Igarashi A, et al., Comparison of visual acuity, higher-order aberrations and corneal asphericity after refractive lenticule extraction and wavefront guided laser-assisted *in situ* keratomileusis for myopia, *Br J Ophthalmol*, 2013;97:968–75.
13. Ang M, Chaurasia SS, Angunawela RI, et al., Femtosecond lenticule extraction (FLEx): clinical results, interface evaluation, and intraocular pressure variation, *Invest Ophthalmol Vis Sci*, 2012;53:1414–21.
14. Demirok A, Agca A, Ozgurhan EB, et al., Femtosecond lenticule extraction for correction of myopia: a 6 month follow-up study, *Clin Ophthalmol*, 2013;7:1041–7.
15. Blum M, Kunert KS, Engelbrecht C, et al., Femtosecond lenticule extraction (FLEx)—results after 12 months in myopic astigmatism, *Klin Monbl Augenheilkd*, 2010;227:961–5.
16. Gertnere J, Solomatin I, Sekundo W, Refractive lenticule extraction (ReLEx FLEx) and wavefront-optimized Femto-LASIK: comparison of contrast sensitivity and high-order aberrations at 1 year, *Graefes Arch Clin Exp Ophthalmol*, 2013;251:1437–42.
17. Kamiya K, Shimizu K, Igarashi A, Kobashi H, Visual and refractive outcomes of femtosecond lenticule extraction and small-incision lenticule extraction for myopia, *Am J Ophthalmol*, 2014;157:128–34.
18. Gazieva L, Beer MH, Nielsen K, Hjortdal J, A retrospective comparison of efficacy and safety of 680 consecutive lasik treatments for high myopia performed with two generations of flying-spot excimer lasers, *Acta Ophthalmol*, 2011;89:729–33.
19. Blum M, Kunert K, Schröder M, Sekundo W, Femtosecond lenticule extraction for the correction of myopia: preliminary 6-month results, *Graefes Arch Clin Exp Ophthalmol*, 2010;248:1019–27.
20. Shah R, Shah S, Effect of scanning patterns on the results of femtosecond laser lenticule extraction refractive surgery, *J Cataract Refract Surg*, 2011;37:1636–47.
21. 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;29:236–44.
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;249:1417–24.
23. Kamiya K, Shimizu K, Igarashi A, Kobashi H, Time course of optical quality and intraocular scattering after refractive lenticule extraction. *PLoS One*, 2013;8:e76738.
24. Yao P, Zhao J, Li M, et al., Microdistortions in Bowman's layer following femtosecond laser small incision lenticule extraction observed by Fourier-Domain OCT, *J Refract Surg,* 2013;29:668–74.
25. Tomita M, Waring GO 4th, Magnago T, Watabe M, Clinical results of using a high-repetition-rate excimer laser with an optimized

ablation profile for myopic correction in 10,235 eyes, *J Cataract Refract Surg*, 2013;39:1543–9.
26. Farjo AA, Sugar A, Schallhorn SC, et al., Femtosecond lasers for LASIK flap creation: a report by the American Academy of Ophthalmology, *Ophthalmology*, 2013;120:e5–20.
27. Dong Z, Zhou X, Irregular astigmatism after femtosecond laser refractive lenticule extraction, *J Cataract Refract Surg*, 2013;39:952–4.
28. Kunert KS, Russmann C, Blum M, Sluyterman VLG, Vector analysis of myopic astigmatism corrected by femtosecond refractive lenticule extraction, *J Cataract Refract Surg*, 2013;39:759–69.
29. Ivarsen A, Hjortdal J, Correction of myopic astigmatism with small incision lenticule extraction, *J Refract Surg*, (accepted for publication, 2014).
30. Reinstein DZ, Carp GI, Archer TJ, Gobbe M. LASIK for presbyopia correction in emmetropic patients using aspheric ablation profiles and a micro-monovision protocol with the Carl Zeiss Meditec MEL 80 and VisuMax, *J Refract Surg,* 2012;28:531–41.
31. Vestergaard AH, Grønbech KT, Grauslund J, et al., Subbasal nerve morphology, corneal sensation, and tear film evaluation after refractive femtosecond laser lenticule extraction, *Graefes Arch Clin Exp Ophthalmol,* 2013;251:2591–2600.
32. Demirok A, Ozgurhan EB, Agca A, et al., Corneal sensation after corneal refractive surgery with small incision lenticule extraction, *Optom Vis Sci*, 2013;90:1040–7.
33. Wei S, Wang Y, Comparison of corneal sensitivity between FS-LASIK and femtosecond lenticule extraction (ReLEx flex) or small-incision lenticule extraction (ReLEx SMILE) for myopic eyes, *Graefes Arch Clin Exp Ophthalmol,* 2013;251:1645–54.
34. Li M, Niu L, Qin B, et al., Confocal comparison of corneal reinnervation after small incision lenticule extraction (SMILE) and femtosecond laser *in situ* keratomileusis (FS-LASIK), *PLoS One*, 2013;8:e81435.
35. Li M, Zhao J, Shen Y, et al., Comparison of dry eye and corneal sensitivity between small incision lenticule extraction and femtosecond LASIK for myopia, *PLoS One*, 2013;8:e77797.
36. Randleman JB, Dawson DG, Grossniklaus HE, et al., Depth-dependent cohesive tensile strength in human donor corneas: implications for refractive surgery, *J Refract Surg*, 2008;24;S85–9.
37. Reinstein DZ, Archer TJ, Randleman JB, Mathematical model to compare the relative tensile strength of the cornea after PRK, LASIK, and small incision lenticule extraction, *J Refract Surg*, 2013;29:454–60.
38. 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.
39. Vestergaard A, Grauslund J, Ivarsen A, Hjortdal J, Central corneal sublayer pachymetry and biomechanical properties after refractive femtosecond laser lenticule extraction, *J Refract Surg*, (accepted for publication, 2013).
40. Ozgurhan EB, Agca A, Bozkurt E, et al., Accuracy and precision of cap thickness in small incision lenticule extraction, *Clin Ophthalmol*, 2013;7:923–6.
41. Tay E, Li X, Chan C, et al., Refractive lenticule extraction flap and stromal bed morphology assessment with anterior segment optical coherence tomography, *J Cataract Refract Surg*, 2012;38:1544–51.
42. Reinstein DZ, Archer TJ, Gobbe M, Accuracy and reproducibility of cap thickness in small incision lenticule extraction, *J Refract Surg*, 2013;29:810–8.
43. Ivarsen A, Fledelius W, Hjortdal JØ, Three-year changes in epithelial and stromal thickness after PRK or LASIK for high myopia, *Invest Ophthalmol Vis Sci*, 2009;50:2061–6.
44. Patel SV, Erie JC, McLaren JW, Bourne WM, Confocal microscopy changes in epithelial and stromal thickness up to 7 years after LASIK and photorefractive keratectomy for myopia, *J Refract Surg*, 2007;23:385–92.
45. Alio JL, Javaloy J, Corneal inflammation following corneal photoablative refractive surgery with excimer laser, *Surv Ophthalmol*, 2013;58:11–25.
46. Dong Z, Zhou X, Wu J, et al., Small incision lenticule extraction (SMILE) and femtosecond laser LASIK: comparison of corneal wound healing and inflammation, *Br J Ophthalmol*, 2014;98:263–9.
47. Riau AK, Angunawela RI, Chaurasia SS, et al., Early corneal wound healing and inflammatory responses after refractive lenticule extraction (ReLEx), *Invest Ophthalmol Vis Sci*, 2011;52:6213–21.
48. Moller-Pedersen T, Cavanagh HD, Petroll WM, Jester JV, Stromal wound healing explains refractive instability and haze development after photorefractive keratectomy: a 1-year confocal microscopic study, *Ophthalmology*, 2000;107:1235–45.
49. Ivarsen A, Laurberg T, Møller-Pedersen T, Characterisation of corneal fibrotic wound repair at the LASIK flap margin, *Br J Ophthalmol*, 2003;87:1272–8.
50. Pradhan KR, Reinstein DZ, Carp GI, et al., Femtosecond laser-assisted keyhole endokeratophakia: correction of hyperopia by implantation of an allogeneic lenticule obtained by SMILE from a myopic donor, *J Refract Surg*, 2013;29:777–82.
51. Mohamed-Noriega K, Toh KP, Poh R, Bet al., Cornea lenticule viability and structural integrity after refractive lenticule extraction (ReLEx) and cryopreservation, *Mol Vis*, 2011;17:3437–49.
52. Riau AK, Angunawela RI, Chaurasia SS, et al., Reversible femtosecond laser-assisted myopia correction: a non-human primate study of lenticule re-implantation after refractive lenticule extraction, *PLoS ONE*, 2013;8:e67058.
53. Angunawela RI, Riau AK, Chaurasia SS, et al., Refractive lenticule re-implantation after myopic ReLEx: a feasibility study of stromal restoration after refractive surgery in a rabbit model, *Invest Ophthalmol Vis Sci*, 2012;53:4975–85.
54. Liu H, Zhu W, Jiang AC, et al., Femtosecond laser lenticule transplantation in rabbit cornea: experimental study, *J Refract Surg*, 2012;28:907–11.
55. Lim CH, Riau AK, Lwin NC, et al., LASIK following small incision lenticule extraction (smile) lenticule re-implantation: a feasibility study of a novel method for treatment of presbyopia, *PLoS One*. 2013;8:e83046.
56. Reinstein DZ, Gobbe M, Archer TJ, Coaxially sighted corneal light reflex versus entrance pupil center centration of moderate to high hyperopic corneal ablations in eyes with small and large angle kappa, *J Refract Surg*, 2013;29:518–25.
57. Munnerlyn CR, Koons SJ, Marshall J, Photorefractive keratectomy: a technique for laser refractive surgery, *J Cataract Refract Surg*, 1988;14:46–52.
58. Maeda N, Clinical applications of wavefront aberrometry – a review, *Clin Experiment Ophthalmol*, 2009;37:118–29.
59. Netto MV, Wilson SE, Flap lift for LASIK retreatment in eyes with myopia, *Ophthalmology*, 2004;111:1362–7.
60. Sharma R, Vaddavalli PK, Implications and management of suction loss during refractive lenticule extraction (ReLEx): *J Refract Surg*, 2013;29:502–3.