New Developments in the Lenticule Extraction Procedure

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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

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 less 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).
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Myopia Refractive Outcome

Overall, RefLEx 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. 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. Other reports on SMILE and 500 kHz FLEx 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. Another study on 54 eyes found no regression during the first 6 months after surgery. Similarly, no regression has been found during the first 3–6 months after 500 kHz FLEx or for 1 year after 200 kHz FLEx. 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.

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

Visual Outcome

In the first clinical studies, FLEx was reported to have delayed visual recovery in comparison with FS-LASIK. Later studies suggested that the laser scanning pattern and energy influenced the lenticule surface quality and the immediate postoperative outcome. 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. 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.

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. A loss in VA had recovered to within one line of the preoperative value. 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. 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 microdistortions in Bowman's layer after SMILE and FS-LASIK has been compared. Microdistortions 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 microdistortions remained stable after 1 week but had no apparent impact on long-term visual performance. In summary, safety after SMILE appears to be comparable with that reported after FS-LASIK, 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.

Complications

A variety of peri- and postoperative complications have been reported after SMILE. The most frequently reported perioperative complications include...
tears at the incision and minor abrasions. Decentration, suction loss, difficulties removing the lenticule, and cap perforation occur rarely.\textsuperscript{24,30,31} Frequent postoperative complications include dry eye, microstriae, and increased interface scatter, whereas rare complications include keratitis, interface inflammation, epithelial ingrowth, and monocular ghost images.\textsuperscript{31,32,33} Recently, we found irregular postoperative topography in 18 of 1,574 eyes, giving rise to ghost images in six cases.\textsuperscript{25} 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.\textsuperscript{26} Postoperative ectasia has not been reported after SMILE; however, one case has been described after a flap-based FLEX treatment.\textsuperscript{34}

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.\textsuperscript{24} 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.\textsuperscript{27}

**Hyperopia**
At present, only one study has examined hyperopic treatment (average SE refraction + 2.8 ± 1.3 D) with 200 kHz FLEX.\textsuperscript{28} 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.\textsuperscript{35,36} 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.\textsuperscript{21–23} 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.\textsuperscript{37} Similar findings have been documented in a non-paired study of SMILE and FS-LASIK.\textsuperscript{38} In another randomized paired-eye study, the corneal nerve density and number of long nerve fibers were higher after SMILE than after FLEX;\textsuperscript{39} 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.\textsuperscript{33,34}

Studies based on a paired-eye evaluation of the postoperative tear secretion after SMILE in comparison with a flap-based treatment\textsuperscript{29,30,32} 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{37} It has recently been speculated that the refractive lenticule should be removed deeper within the stroma to increase the postoperative corneal strength.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
no significant difference in cap or stromal bed thickness 6 months after surgery. As seen after other myopic keratorefractive procedures, 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. In contrast to the excimer laser, FS lasers deliver only minimal amounts of energy to surrounding tissue, 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. In another recent study in rabbits, SMILE also induced less keratocyte apoptosis, proliferation, and inflammation compared with FS laser LASIK. 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.

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. 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. Other studies in rabbits and primates have shown successful cryopreservation and later re-implantation of a stromal lenticule. Furthermore, in primates, the procedure was shown to induce little postoperative wound repair, and keratocyte repopulation could be observed after 16 weeks. 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. 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. 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 the optimizing 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 spherocylindrical 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. 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.

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. In flap-based treatments, an excimer-based enhancement procedure can be performed after lifting the flap. Retreatment after SMILE is, however, more complicated.

Possible approaches may include PRK or LASK. 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, and another has reported on successful FS-LASIK in a patient with perioperative suction loss. In a rabbit model, the conversion of a SMILE cap to a flap has been demonstrated, allowing subsequent intrastromal photobleaching. 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 are 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 posterior 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. ■
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