Corneal refractive surgery: Is intracorneal the way to go and what are the needs for technology?

Jesper Hjortdal*[a], Anders Ivarsen[a]
[a]Dept. of Ophthalmology, Aarhus University Hospital, 8000 Aarhus C, Denmark

*jesper.hjortdal@dadlnet.dk; phone +45 23346770; fax +45 86121653; auh.dk

ABSTRACT

Corneal refractive surgery aims to reduce or eliminate refractive errors of the eye by changing the refractive power of the cornea. 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. This procedure avoids creation of a corneal flap and the potential associated risks while avoiding the slow visual recovery of surface ablation procedures. Precise intrastromal femtosecond laser cutting of the fine lenticule requires very controlled laser energy delivery in order to avoid lenticule irregularities, which would compromise the refractive result and visual acuity. This newly introduced 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. Technological developments related to further improved cutting quality, hyperopic and individualized treatments are desirable.

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

1. INTRODUCTION

During the last 20 years, the excimer laser has dominated the arena of keratorefractive surgery initially with surface ablation procedures such as photorefractive keratectomy (PRK) and later with the flap-based laser in situ keratomileusis (LASIK). Due to excellent patient satisfaction, high precision, and very good safety[1,2], LASIK has become one of the most frequently performed surgical procedures. LASIK is performed as a two-stage procedure, which involves the cutting of a flap in the anterior stroma of the cornea followed by excimer laser photoablation of stromal tissue.

Within the last decade, femtosecond lasers have mostly replaced manual microkeratomes for cutting of the LASIK flap (FS-LASIK). Although this may have improved the clinical outcome[3], the procedure still has potential disadvantages. First, flap-related complications such as traumatic flap dislocation[4], reduced corneal sensitivity due to severed stromal nerves[5], and surgically induced ectasia due to loss of biomechanical strength[6] remain significant challenges. Second, several factors may influence the precision of the photoablative procedure, including corneal hydration, room humidity, patient age, parallax error, and laser fluency[7,8]. In surface ablation procedures, postoperative wound healing may cause stromal haze formation and affect the long-term stability of the obtained refractive correction, with myopic regression as a well-known complication of high myopic corrections[9].

2. INTRACORNEAL LASER SURGERY

Within the last few years, surgical extraction of a refractive lenticule, ReLEx®, has evolved as a new treatment in the field of keratorefractive surgery. Presently, the VisuMax® femtosecond laser system (Carl Zeiss Meditec, Jena, Germany) is the only platform to offer this treatment. The 500-kHz VisuMax generates very fast pulses (10^{-15} s) 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 femtosecond laser uses a high numerical aperture and 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 cornea to maintain

Ophthalmic Technologies XXIV, edited by Fabrice Manns, Per G. Söderberg, Arthur Ho, Proc. of SPIE Vol. 8930, 89300B · © 2014 SPIE · CCC code: 1605-7422/14/$18 · doi: 10.1117/12.2054449

stability of the eye. Initially, the posterior surface of the lenticule is cut, followed by creation of the anterior surface, which is slightly enlarged in diameter to facilitate surgical manipulation.

The present proceeding reviews the current state of the technique, initial clinical results based on a recent review[10], 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 divided into FLEx, in which a LASIK-like flap allows surgical removal of the lenticule, and SMILE, in which a small incision (approximately 2–4 mm in length) is created for manual lenticule extraction, so SMILE opens up the 3rd generation of laser vision correction procedures. 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 (Figure 1). For further details on the surgical approach, please refer to Sekundo et al.[11], Shah et al.[12], and Vestergaard et al.[13].

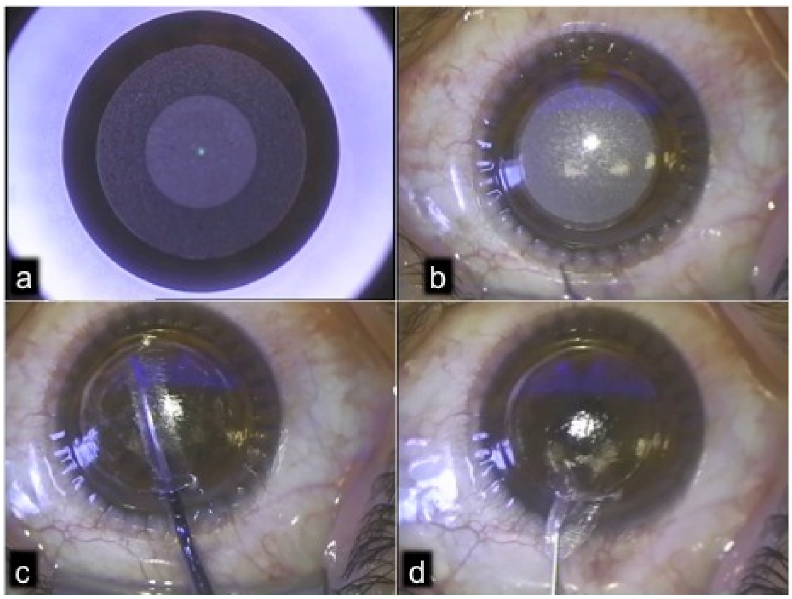

Figure 1. SMILE procedure. a) Image obtained during femtosecond laser cutting of lenticule. Posterior side of lenticule have been cut and anterior cut have been approximately 50% completed. b) Immediately after completion of femtosecond laser cutting. c) Through a small peripheral incision, remaining tissue-bridges are broken with a blunt spatula. d) Lenticule is removed through the peripheral incision.

In contrast to LASIK, FLEx and SMILE represent 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 microinvasive SMILE treatment have several theoretical advantages over flap-based treatments, including very 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 femtosecond 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, the present review focuses primarily on studies concerning SMILE.

At present, 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[14]. The VisuMax laser is CE (Conformité Européenne) marked and is currently being evaluated in clinical studies for the approval of SMILE by the FDA (US Food and Drug Administration).

3. CLINICAL RESULTS

3.1 Refractive outcome

Overall, ReLEx has been reported to have high refractive predictability (Table 1). In the largest report to date on SMILE in 670 myopic eyes 3 months after surgery, 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 [15]. 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[32]. Other reports on SMILE[12, 13, 16, 17] and 500-kHz FLEx[18–22] have found very similar refractive outcomes in smaller numbers of patients.

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[13]. One other study on 54 eyes found no regression during the first 6 months after surgery[16]. Similarly, no regression has been found during the first 3–6 months after 500-kHz FLEx[18, 19, 21, 22] or for 1 year after 200-kHz FLEx[23, 24].

Interestingly, the refractive predictability after SMILE has been found to be unrelated to the degree of the attempted myopic correction[15]. This is in contrast to excimer-based treatments, which show decreasing precision with increasing myopic correction[25]. Furthermore, other parameters including preoperative corneal power, patient age, and gender have been found to have very limited impact on the refractive outcome after SMILE[15].

Correction of high astigmatism has not yet been systematically evaluated after ReLEx. Only one paper on 200-kHz FLEx contains a detailed evaluation of the outcome after cylinder correction[26]. 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 spherical equivalent correction three 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[27]. At present, only one study has examined hyperopic treatment (average SE refraction + 2.8 ± 1.3 D) with 200-kHz FLEx[14]. 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.

3.2 Visual outcome

In the first clinical studies, FLEx was reported to have delayed visual recovery in comparison with FS-LASIK[12,28]. However, later studies suggested that the laser scanning pattern and energy had an impact on the lenticule surface quality and the immediate postoperative outcome [29,30,31]. Subsequent changes in the laser scanning trajectory and energy delivery appear to have eliminated the problem with postoperative visual recovery. Three studies have examined the uncorrected distance visual acuity (UDVA) after 500-kHz SMILE for myopia and report 73–100 % of patients as having an UDVA of 20/25 or better 3–6 months after surgery[13,15,16]. Similar results have been reported for 500-kHz FLEx, and the procedure has been found to be on par with the outcome after FS-LASIK[18,22]. The efficacy index 3 months after SMILE (postoperative UDVA/preoperative CDVA) has been found to be 0.90 ± 0.25, indicating that a patient on average can expect a postoperative UDVA of 90 % of their preoperative CDVA[15].

3.3 Safety and complications

The induced change in corrected distance visual acuity (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 visual acuity 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 lie between 0 and 8 % [11,12,16–22]. In one study on 279 eyes after SMILE, 0.4 % of eyes were reported to have a loss of two or more lines[12]. In contrast, a 2.4 % risk of a two-line loss was found in 670 eyes by Hjortdal et al.[15]. 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[32]. 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 visual acuity 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. Overall, safety after SMILE appears to be comparable with that reported after FS-LASIK[1,3], although recovery may be prolonged in a few cases.

Endothelial changes after FLEx and SMILE have not been systematically evaluated. Only one study on 38 eyes has reported endothelial cell counts and found that FLEx induced no significant changes in endothelial cell density[19].

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, whereas decentration, suction loss, difficulties removing the lenticule, and cap perforation may rarely occur[12,13,17,18,26]. Frequent postoperative complications include dry eye, microstriae, and increased interface scatter, whereas rare complications include keratitis, interface inflammation, epithelial ingrowth, and monocular ghost images[18,19,26]. Recently, we found irregular postoperative topography in 18 of 1,574 eyes, giving rise to ghost images in six cases[32]. 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[33]. Postoperative ectasia has not been reported after SMILE; however, one case has been documented after a flap-based FLEx treatment[23].

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 typical LASIK complications. Still, despite a relatively high frequency of peri- and postoperative complications, the visual outcome is reported to be good, with minimal risk of loss in CDVA on the long term.

3.4 Higher order aberrations (HOAs) and contrast acuity

Few studies have compared the induced HOAs after FLEx and LASIK[20] or FS-LASIK[18,24]. In these studies, both FLEx and LASIK were found to increase the total corneal or whole-eye HOAs; however, FLEx induced less spherical aberration than FS-LASIK. Furthermore, in LASIK the induced HOAs were found to increase with the degree of attempted refractive correction, whereas in FLEx no such correlation was found[20].

Parallax error during excimer laser photoablation has been suggested as an explanation for the observed differences in induced spherical aberration after LASIK and FLEx[20]. As of yet, no studies have reported changes in HOAs after SMILE with the 500-kHz VisuMax laser.

Contrast sensitivity after ReLEx has been examined in a retrospective, comparative study on 200-kHz FLEx and FS-LASIK. Both procedures showed a similar increase in photopic contrast sensitivity after 1 year; however, FLEx also showed an improvement in mesopic contrast that was not found after FS-LASIK[24]. Presently, changes in contrast sensitivity have not been evaluated after SMILE.

Based on the few comparative studies on HOAs and contrast sensitivity, ReLEx appears to be similar or better than LASIK; however, studies on SMILE are lacking.

3.5 Corneal sensitivity and tear secretion

Three studies have examined the corneal sensitivity after SMILE in comparison with a flap-based treatment[34,35,36]. 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[35]. In another randomized paired-eye study, the corneal nerve density and number of long nerve fibers were higher after SMILE than after FLEx[34]; accordingly, sensitivity was better after SMILE. Finally, in a comparative study on SMILE, FLEx, and FSLASIK, better sensitivity was found at all time points for up to 3 months after SMILE[36].

Studies based on a paired-eye evaluation of the postoperative tear secretion after SMILE in comparison with a flap-based treatment[34,35] 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[34].

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

3.6 Corneal biomechanics and sublayer thickness

In SMILE, most of the anterior stroma remains intact after surgery. Since the cornea is biomechanically strongest in the anterior part[37], 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 they have been suggested to be even stronger than PRK-treated corneas[37]. Furthermore, it has recently been speculated that the refractive lenticule should be removed deeper within the stroma to increase the postoperative corneal strength[38]. 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 one study has been published on the biomechanical properties after SMILE in comparison with FS-LASIK using the Ocular Response Analyzer[39]. 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[40]. 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[41]. 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 keratorefrative surgery, and three studies have found the cap to be of nearly uniform thickness and similar to the flap after FLEx or FS-LASIK[16,42,43]. Furthermore, in one study, no significant changes were observed in central cap or stromal bed thickness for 6 months after surgery[43]. We recently evaluated corneal sublayer thicknesses after SMILE and FLEx[40] and found no significant difference in cap or stromal bed thickness 6 months after surgery. As seen after other myopic keratorefractive procedures[44,45], a compensatory epithelial hyperplasia was observed.

4. EXPERIMENTAL STUDIES

In excimer laser keratorefractive surgery, the energy delivered to the cornea may promote subsequent inflammation and wound repair[49]. In contrast to the excimer laser, femtosecond lasers deliver only minimal amounts of energy to surrounding tissue[50], suggesting that the femtosecond laser may induce less postoperative wound repair. In accordance, a recent study in rabbits has demonstrated FLEx to induce less wound healing and inflammation than FS-LASIK, particularly after high myopic corrections[50]. Whether this observation has 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[49,51,52].

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 can be used to change the refraction in another individual, for example, by implanting a myopic lenticule in the stromal pocket of a hyperopic patient[53]. Such a procedure would 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[54]. Other studies in rabbits and primates have shown successful cryopreservation and later re-implantation of a stromal lenticule[55–57]. Furthermore, in primates, the procedure was shown to induce little postoperative wound repair, and keratocyte repopulation could be observed after 16 weeks[47]. Thus, although further studies are needed, lenticule re-implantation or transplantation from one patient to another may become reality in the near future.

5. NEEDS FOR TECHNOLOGY IMPROVEMENT

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

5.1 Laser cut quality

The femtosecond 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 du to non-linear effects within a certain range that is approx. given be the Rayleigh length (z_R) (Figure 2):

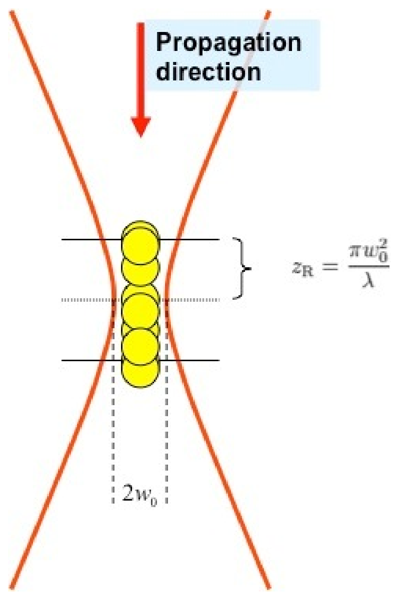

Figure 2. The actual point of focus of the femtosecond laser is associated with some degree of imprecision and is characterized by the Rayleigh length (z_R). The Rayleigh length is dependent on the wavelength (λ) and the beam waist (w_0). (Courtesy: Dirk Mühlhoff, Carl Zeiss Meditec, Jena, Germany).

The VisuMax femtosecond laser operates with a wavelength of 1043 nm (λ) and a beam waist (w_0) of 1 µm. The beam waist is dependent on a number of optical factors related to the femtosecond laser system. From the known parameters the Rayleigh length can be calculated to be about 3 µm. This shows that the axial position of individual points of interaction is stable within a range of about 3µm. One can see why the VisuMax technology fulfills the applicative requirements if one takes into account that a cut surface is defined by millions of adjacent points of interaction. Electron microscopy pictures of the lenticule show that the cut quality is high[58]. Similarly, clinical investigations document that the cap thickness in SMILE can be created accurate and reproducible[59].

Sometimes the Rayleigh length is discussed in relation to the central profile thickness for a 1-diopter correction that is approximately 13 µm. This is misleading because not the central profile thickness but the corresponding overall corneal curvature change is the relevant parameter. This again is supported by the high predictability of the SMILE procedure[15].

Further optimization of the femtosecond laser with respect to wavelength and beam waist is discussed today. If the wavelength could be reduced to one-third and/or the beam waist could be lowered further, the Rayleigh length would be reduced. However, it seems questionable whether such technological modifications actually are 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.

5.2 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[60]. Some authors argue that refractive procedures should be centered at the pupil center, other argues that centration should be at the corneal vertex, and other that the correct centering is somewhere between these fairly easily identifiable landmarks, as this will correspond to the visual axis.

In femtosecond 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 would improve the outcome of femtosecond based intrastromal procedures.

5.3 Astigmatic and hyperopic treatment

Geometrically, correction of myopia is fairly simple and the necessary lenticule shape to be removed was calculated many years ago by Munnerlyn et al.[61]. 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 toric 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 smoothen these gaps, and similar transitions have been used in femtosecond 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, and transition zones, and side cuts.

5.4 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[62]. Some eyes have very large aberrations caused by imperfections in the shape of the cornea; this 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 visual acuity[62].

At present, femtosecond 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.

5.5 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[15]. In flap-based treatments, an excimer-based enhancement procedure can be performed after lifting the flap[46]. 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[32], and another has reported on successful FS-LASIK in a patient with perioperative suction loss[47].

In a rabbit model, the conversion of a SMILE cap to a flap has been demonstrated, allowing subsequent intrastromal photoablation[48]. Still, the optimal approach for SMILE enhancements needs to be established.

Performing a new conventional SMILE procedure is typically referred from, as most surgeons are afraid to interfere with the original incision plane that 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 superficial, in the cap.

In both situations, further development and clinical testing of this variation of the technique is necessary.

5.6 Corneal biomechanics test

One considerable advantage of SMILE is that no corneal flap is created. Intuitively, this would leave the cornea considerably stronger than after a LASIK procedure. Mathematical modeling suggests that this feature is the case[38]. Real clinical documentation for the biomechanical advantage of SMILE compared with LASIK is, however, not available.

Our knowledge on the biomechanical properties of the human cornea comes from in vitro testing of corneal strips or whole globes[63]. During the last 10 years, devices based on pneumatic force application have been introduced. Unfortunately, neither Corneal Hysteresis as measured by the Ocular Response Analyzer[40] or more recently, techniques based on dynamic Scheimpflug visualization of corneal deformation have be able to document fundamental differences between flap-based and cap-based laser surgery[41].

As a spin-off conclusion, it is clear that there is considerable need for technological development of clinically usable devices that more precisely can evaluate biomechanical properties of the cornea. Such devices would also have significant interest as a diagnostic tool to identify patients with sub-clinical keratoconus.

6. CONCLUSION

Several studies have shown that the refractive and visual outcomes after SMILE and FLEx are as good as after FS-LASIK, and ReLEx has even been indicated to induce fewer HOAs. Furthermore, SMILE has been shown to be as safe as LASIK, although the procedure may be technically more demanding and have a different variety of complications.

The minimal impact on the anterior stroma in SMILE represents the most interesting aspect of the new procedure. Thus, stromal nerves are spared, and SMILE has been convincingly demonstrated to cause less denervation and have better sensitivity than flap-based treatments. Yet, 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. However, 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 myopic corrections. Correction of myopic astigmatism also appears promising, but hyperopic treatments need further evaluation, and the long-term outcome and biomechanical properties of SMILE remain undetermined. 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. In contrast, ReLEx may allow exciting new treatments including reimplantation or transplantation of refractive lenticules, and it is of considerable interest to see the further evolution of the technique over the coming years.

REFERENCES

[1] 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. 39(10), 1543–9 (2013).

[2] Brown MC, Schallhorn SC, Hettinger KA, Malady SE. "Satisfaction of 13,655 patients with laser vision correction at 1 month after surgery," J Refract Surg. 25(7 Suppl), S642–6 (2009).

[3] Farjo AA, Sugar A, Schallhorn SC, Majmudar PA, Tanzer DJ, Trattler WB, Cason JB, Donaldson KE, Kymionis GD. "Femtosecond lasers for LASIK flap creation: a report by the American Academy of Ophthalmology," Ophthalmology. 120(3), e5–20 (2013).

[4] Iskander NG, Peters NT, Anderson Penno E, Gimbel HV. "Late traumatic flap dislocation after laser in situ keratomileusis," J Cataract Refract Surg. 27(7), 1111–4 (2001).

[5] Pérez-Santonja JJ, Sakla HF, Cardona C, Chipont E, Alio´ JL. "Corneal sensitivity after photorefractive keratectomy and laser in situ keratomileusis for low myopia," Am J Ophthalmol. 127(10), 497–504 (1999).
[6] Geggel HS, Talley AR. "Delayed onset keratectasia following laser in situ keratomileusis," J Cataract Refract Surg. 25(4), 582–6 (1999)
[7] Ang EK, Couper T, Dirani M, Vajpayee RB, Baird PN. "Outcomes of laser refractive surgery for myopia," J Cataract Refract Surg. 35(5), 921–33 (2009).
[8] Walter KA, Stevenson AW. "Effect of environmental factors on myopic LASIK enhancement rates," J Cataract Refract Surg. 30(4), 798–803 (2004).
[9] Vestergaard AH, Hjortdal JØ, Ivarsen A, Work K, Grauslund J, Sjølie AK. "Long-term outcomes of photorefractive keratectomy for low to high myopia: 13 to 19 years of follow-up," J Refract Surg. 29(5), 312–9 (2013).
[10] Ivarsen A, Hjortdal J. "All-Femtosecond Laser Keratorefractive Surgery," in Current Ophthalmology Reports (Refractive surgery - From laser to intraocular lenses). Springer (e-ISSN 2167-4868). Doi 10.1007/s40135-013-0032-2 (2013)
[11] Sekundo W, Kunert K, Russmann C, Gille A, Bissmann W, Stobrawa G, Sticker M, Bischoff M, Blum M. "First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results," J Cataract Refract Surg. 34(9), 1513–20 (2008).
[12] Shah R, Shah S, Sengupta S. "Results of small incision lenticule extraction: all-in-one femtosecond laser refractive surgery," Cataract Refract Surg. 37(1), 127–37 (2011).
[13] 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. 38(11), 2003–10 (2012)
[14] Blum M, Kunert KS, Voßmerbäumer U, Sekundo W. "Femtosecond lenticule extraction (ReLEx) for correction of hyperopia - first results," Graefes Arch Clin Exp Ophthalmol. 251(1), 349–55 (2013)
[15] Hjortdal JØ, Vestergaard AH, Ivarsen A, Ragunathan S, Asp S. "Predictors for the outcome of small-incision lenticule extraction for myopia," J Refract Surg. 28(12), 865–71 (2012).
[16] Zhao J, Yao P, Li M, Chen Z, Shen Y, Zhao Z, Zhou Z, Zhou X. "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. 8(8), e70208 (2013).
[17] 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. 95(3), 335–9 (2011)
[18] 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. 91(4), 355–62 (2013).
[19] Kamiya K, Igarashi A, Ishii R, Sato N, Nishimoto H, Shimizu K. "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. 38(11), 1996–2002 (2012)
[20] Kamiya K, Shimizu K, Igarashi A, Kobashi H, Komatsu M. "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. 97(8), 968–75 (2013).
[21] Ang M, Chaurasia SS, Angunawela RI, Poh R, Riau A, Tan D, Mehta JS. "Femtosecond lenticule extraction (FLEx): clinical results, interface evaluation, and intraocular pressure variation," Invest Ophthalmol Vis Sci. 53(3), 1414–21 (2012)
[22] Demirok A, Agca A, Ozgurhan EB, Bozkurt E, Celik U, Demircan A, Guleryuz NB, Cankaya KI˙, Yilmaz OF. "Femtosecond lenticule extraction for correction of myopia: a 6 month follow-up study," Clin Ophthalmol. 7, 1041–7 (2013).
[23] Blum M, Kunert KS, Engelbrecht C, Dawczynski J, Sekundo W. "Femtosecond lenticule extraction (FLEx)—results after 12 months in myopic astigmatism," Klin Monbl Augenheilkd. 227(12), 961–5 (2010).
[24] 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. 251(5), 1437–42 (2013).
[25] 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. 89(8), 729–33 (2011).

[26] Kunert KS, Russmann C, Blum M, Sluyterman VLG. "Vector analysis of myopic astigmatism corrected by femtosecond refractive lenticule extraction," J Cataract Refract Surg. 39(5), 759–69 (2013)
[27] Ivarsen A, Hjortdal J. "Correction of myopic astigmatism with small incision lenticule extraction," J Refract Surg. (accepted for publication) (2014).
[28] 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. 248(7), 1019–27 (2010).
[29] Shah R, Shah S. "Effect of scanning patterns on the results of femtosecond laser lenticule extraction refractive surgery," J Cataract Refract Surg. 37(9), 1636–47 (2011)
[30] Riau AK, Ang HP, Lwin NC, Chaurasia SS, Tan DT, Mehta JS. "Comparison of four different VisuMax circle patterns for flap creation after small incision lenticule extraction," J Refract Surg. 29(4), 236–44 (2013).
[31] Kunert KS, Blum M, Duncker GI, Sietmann R, Heichel J. "Surface quality of human corneal lenticules after femtosecond laser surgery for myopia comparing different laser parameters," Graefes Arch Clin Exp Ophthalmol. 249(9), 1417–24 (2011).
[32] Ivarsen A, Asp S, Hjortdal J. "Safety and complications of more than 1500 small-incision lenticule extraction procedures," Ophthalmology 2014 (doi: 10.1016/j.ophtha.2013.11.006, e-pub ahead of print).
[33] Dong Z, Zhou X. "Irregular astigmatism after femtosecond laser refractive lenticule extraction," J Cataract Refract Surg. 39(6), 952–4 (2013).
[34] Vestergaard AH, Grønbech KT, Grauslund J, Ivarsen AR, Hjortdal JO. "Subbasal nerve morphology, corneal sensation, and tear film evaluation after refractive femtosecond laser lenticule extraction," Graefes Arch Clin Exp Ophthalmol. 251 (11), 2591–2600 (2013).
[35] Demirok A, Ozgurhan EB, Agca A, Kara N, Bozkurt E, Cankaya KI, Yilmaz OF. "Corneal sensation after corneal refractive surgery with small incision lenticule extraction," Optom Vis Sci. 90(10), 1040–7 (2013).
[36] 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. 251(6), 1645–1654 (2013).
[37] Randleman JB, Dawson DG, Grossniklaus HE, McCarey BE, Edelhauser HF. "Depth-dependent cohesive tensile strength in human donor corneas: implications for refractive surgery," J Refract Surg. 24(1); S85–9. (2008)
[38] 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. 29(7), 454–60 (2013).
[39] Agca A, Ozgurhan EB, Demirok A, Bozkurt E, Celik U, Ozkaya A, Cankaya I, Yilmaz OF. "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. doi:10.1016/j.clae.2013. 05.003. (2013)
[40] 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).
[41] Bach-Pedersen I, Bak-Nielsen S, Vestergaard A, Ivarsen A, Hjortdal J. "Corneal biomechanical properties after LASIK, ReLEx flex, and ReLEx smile by Scheimpflug-based dynamic tonometry," Graefes Arch. (submitted).
[42] Ozgurhan EB, Agca A, Bozkurt E, Gencer B, Celik U, Cankaya KI, Demirok A, Yilmaz OF. Accuracy and precision of cap thickness in small incision lenticule extraction. Clin Ophthalmol. 7, 923–6 (2013).
[43] Tay E, Li X, Chan C, Tan DT, Mehta JS. "Refractive lenticule extraction flap and stromal bed morphology assessment with anterior segment optical coherence tomography," J Cataract Refract Surg. 38(9), 1544–51 (2012).
[44] 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. 50(5), 2061–6 (2009).
[45] 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. 23(4), 385–92 (2007).
[46] Netto MV, Wilson SE. "Flap lift for LASIK retreatment in eyes with myopia," Ophthalmology. 111(7), 1362–7 (2004).
[47] Sharma R, Vaddavalli PK. "Implications and management of suction loss during refractive lenticule extraction (ReLEx)," J Refract Surg. 29(7), 502–3 (2013).

[48] Riau AK, Ang HP, Lwin NC, Chaurasia SS, Tan DT, Mehta JS. "Comparison of four different VisuMax circle patterns for flap creation after small incision lenticule extraction," J Refract Surg. 29(4), 236–44 (2013).
[49] Alio JL, Javaloy J. "Corneal inflammation following corneal photoablative refractive surgery with excimer laser," Surv Ophthalmol. 58(1), 11–25 (2013).
[50] Riau AK, Angunawela RI, Chaurasia SS, Lee WS, Tan DT, Mehta JS. "Early corneal wound healing and inflammatory responses after refractive lenticule extraction (ReLEx)," Invest Ophthalmol Vis Sci. 52(9), 6213–21 (2011).
[51] 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. 107(7), 1235–45 (2000).
[52] Ivarsen A, Laurberg T, Møller-Pedersen T. "Characterisation of corneal fibrotic wound repair at the LASIK flap margin," Br J Ophthalmol. 87(10), 1272–8 (2003).
[53] Pradhan KR, Reinstein DZ, Carp GI, Archer TJ, Gobbe M, Gurung R. Femtosecond laser-assisted keyhole endokeratophakia: correction of hyperopia by implantation of an allogeneic lenticule obtained by SMILE from a myopic donor. J Refract Surg. 29(11): 777-82 (2013).
[54] Mohamed-Noriega K, Toh KP, Poh R, Balehosur D, Riau A, Htoon HM, Peh GS, Chaurasia SS, Tan DT, Mehta JS. "Cornea lenticule viability and structural integrity after refractive lenticule extraction (ReLEx) and cryopreservation," Mol Vis. 17, 3437–49 (2011).
[55] Riau AK, Angunawela RI, Chaurasia SS, Lee WS, Tan DT, Mehta JS. "Reversible femtosecond laser-assisted myopia correc- tion: a non-human primate study of lenticule re-implantation after refractive lenticule extraction," PLoS ONE. 8(6), e67058 (2013).
[56] Angunawela RI, Riau AK, Chaurasia SS, Tan DT, Mehta JS. "Refractive lenticule re-implantation after myopic ReLEx: a fea- sibility study of stromal restoration after refractive surgery in a rabbit model," Invest Ophthalmol Vis Sci. 53(8), 4975–85 (2012).
[57] Liu H, Zhu W, Jiang AC, Sprecher AJ, Zhou X. "Femtosecond laser lenticule transplantation in rabbit cornea: experimental study," J Refract Surg. 28(12), 907–11 (2012).
[58] Riau AK, Ang HP, Lwin NC, Chaurasia SS, Tan DT, Mehta JS. Comparison of four different VisuMax circle patterns for flap creation after small incision lenticule extraction. J Refract Surg. 29(4): 236-44 (2013).
[59] Reinstein DZ, Archer TJ, Gobbe M. Accuracy and reproducibility of cap thickness in small incision lenticule extraction. J Refract Surg. 29(12): 810-8 (2013).
[60] 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. 29(8), 518-25 (2013).
[61] Munnerlyn CR, Koons SJ, Marshall J. "Photorefractive keratectomy: a technique for laser refractive surgery," J Cataract Refract Surg. 14(1), 46-52 (1988).
[62] Maeda N. "Clinical applications of wavefront aberrometry - a review," Clin Experiment Ophthalmol. 37(1), 118-29 (2009).
[63] Hjortdal J. "Regional elastic performance of the human cornea," J Biomech. 29(7), 931-42 (1996).