EXCIMER LASER REFRACTIVE SURGERY;  
CORNEAL WOUND HEALING AND CLINICAL RESULTS

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ACADEMIC DISSERTATION

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“When you want something, all the universe conspires in helping you to achieve it”
Paulo Coelho, The Alchemist

To Mikaela, Ricardo, Daniela and Manuela
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:


III. Neira Zalentein, W., Tervo, T. M. T., and Holopainen, J. M. A comparative study of correction of moderate-to-high astigmatism by PRK and LASIK. *Submitted.*


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<tr>
<td>ArF</td>
<td>Argon Fluoride</td>
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<tr>
<td>AS</td>
<td>Axis shift</td>
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<td>BB</td>
<td>Broad beam laser</td>
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<tr>
<td>BCVA</td>
<td>Best Corrected (spectacle) Visual Acuity</td>
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<td>CL</td>
<td>Contact lens</td>
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<td>CM</td>
<td>Corneal Confocal Microscopy</td>
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<td>CR</td>
<td>Correction ratio</td>
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<td>D</td>
<td>Diopters</td>
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<td>DLK</td>
<td>Diffuse Lamellar Keratitis</td>
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<td>EA</td>
<td>Error of angle</td>
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<td>ECM</td>
<td>Extracellular matrix</td>
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<td>EM</td>
<td>Error of magnitude</td>
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<td>Error vector</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FS</td>
<td>Femtosecond Laser</td>
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<td>HOA</td>
<td>High order aberration</td>
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<td>LASEK</td>
<td>Laser assisted subepithelial keratomileusis</td>
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<td>LASIK</td>
<td>Laser in-situ keratomileusis</td>
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<td>MRSE</td>
<td>Manifest refraction of spherical equivalent</td>
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<td>NEV</td>
<td>Normalized error vector</td>
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<td>PRK</td>
<td>Photorefractive keratectomy</td>
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<td>PTK</td>
<td>Phototherapeutic keratectomy</td>
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<td>SIRC</td>
<td>Surgically induced refraction correction</td>
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<td>SphEq</td>
<td>Spherical equivalent</td>
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<td>SS</td>
<td>Scanning slit laser</td>
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<td>SSL</td>
<td>Scanning spot laser</td>
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<td>TLSS</td>
<td>Transient light-sensitive syndrome</td>
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<td>TEV</td>
<td>Treatment error vector</td>
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<tr>
<td>UCVA</td>
<td>Uncorrected visual acuity</td>
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<td>Abbreviation</td>
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<tr>
<td>US</td>
<td>Ultrasound pachymetry</td>
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<td>UV</td>
<td>Ultraviolet</td>
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<td>VK</td>
<td>Videokeratography</td>
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<td>WF</td>
<td>Wavefront</td>
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ABSTRACT

Although the first procedure in a seeing human eye using excimer laser was reported in 1988 (McDonald et al. 1989, O'Connor et al. 2006) just three studies (Kymionis et al. 2007, O'Connor et al. 2006, Rajan et al. 2004) with a follow-up over ten years had been published when this thesis was started.

The present thesis aims to investigate 1) the long-term outcomes of excimer laser refractive surgery performed for myopia and/or astigmatism by photorefractive keratectomy (PRK) and laser-in-situ keratomileusis (LASIK), 2) the possible differences in postoperative outcomes and complications when moderate-to-high astigmatism is treated with PRK or LASIK, 3) the presence of irregular astigmatism that depend exclusively on the corneal epithelium, and 4) the role of corneal nerve recovery in corneal wound healing in PRK enhancement.

Our results revealed that in long-term the number of eyes that achieved uncorrected visual acuity (UCVA) $\leq 0.0$ and $\leq 0.5$ (logMAR) was higher after PRK than after LASIK. Postoperative stability was slightly better after PRK than after LASIK. In LASIK treated eyes the incidence of myopic regression was more pronounced when the intended correction was over $> 6.0$ D and in patients aged $< 30$ years. Yet the intended corrections in our study were higher for LASIK than for PRK eyes. No differences were found in percentages of eyes with best corrected visual acuity (BCVA) or loss of two or more lines of visual acuity between PRK and LASIK in the long-term.

The postoperative long-term outcomes of PRK with two different delivery systems broad beam and scanning laser were compared and revealed no differences. Postoperative outcomes of moderate-to-high astigmatism yielded better results in terms of UCVA and less compromise or loss of two more lines of BCVA after LASIK that after PRK. Similar stability for both procedures was revealed.

Vector analysis showed that LASIK outcomes tended to be more accurate than PRK outcomes, yet no statistically differences were found.

Irregular astigmatism secondary to recurrent corneal erosion due to map-dot-fingerprint was successfully treated with phototherapeutic keratectomy (PTK). Preoperative videokeratographies (VK) showed irregular astigmatism. However, postoperatively, all eyes showed a regular pattern. No correlation was found between pre- and postoperative VK patterns.

Postoperative outcomes of late PRK in eyes originally subjected to LASIK showed that all (7/7) eyes achieved UCVA $\leq 0.5$ at last follow-up (range 3 – 11 months), and no eye lost lines of BCVA. Postoperatively all eyes developed and initial mild haze (0.5 – 1) into the first month. Yet, at last follow-up 5/7 eyes showed a haze of 0.5 and this was no longer evident in 2/7 eyes.
Based on these results, we demonstrated that the long-term outcomes after PRK and LASIK were safe and efficient, with similar stability for both procedures. The PRK outcomes were similar when treated by broad-beam or scanning slit laser. LASIK was better than PRK to correct moderate-to-high astigmatism, yet both procedures showed a tendency of undercorrection. Irregular astigmatism was proven to be able to depend exclusively from the corneal epithelium. If this kind of astigmatism is present in the cornea and a customized PRK/LASIK correction is done based on wavefront measurements an irregular astigmatism may be produced rather than treated. Corneal sensory nerve recovery should have an important role in the modulation of the corneal wound healing and post-operative anterior stromal scarring. PRK enhancement may be an option in eyes with previous LASIK after a sufficient time interval that in at least 2 years.
1 INTRODUCTION

Refractive errors have a major impact on public health questions, such as visual requirements at work. It has been calculated that 2.5-4.3 billion dollars are spent each year in the USA only for the inspection and correction of myopia (Sandoval et al. 2005). Spectacles are the most used and safest choice for correcting refractive errors, followed by contact lenses and refractive surgery. The number of corneal refractive surgeries grows every year (Sandoval et al. 2005) despite the fact that risks, such as breaking of the spectacles and infections associated with contact lenses, appear minimal in relation to the risks of refractive surgery even though the complication rates are considered low.

Corneal refractive surgery aims at controlled alteration of the shape of the cornea. Such surgery performed on a completely healthy eye places high demands on the control of wound healing. Corneal refractive procedures are divided into those that change the corneal curvature with relaxing incisions and those that add or remove tissue from the cornea to change its curvature (Barraquer JI 1964). The corneal refractive results are based in the law of thickness introduced by Barraquer in 1964 (Barraquer JI 1964) “changing the thickness of the cornea follows the idea that the cornea is a stable lens, removing tissue in the center or adding tissue on the periphery therefore flattens the cornea.” The argon fluoride (193 nm) excimer laser permits the excision of corneal tissue with minimal damage to the adjacent tissues. It uses high energy ultraviolet radiation to break the covalent bonds between molecules in the corneal stroma without generating high levels of heat (Krauss et al. 1986). This procedure has been termed photoablative process and is the principal reason making laser refractive surgery a relative predictable and safer procedure.

The therapeutic treatment of corneal opacities and irregularities by excimer laser is called phototherapeutic keratectomy (PTK) (Fagerholm 2003). In refractive corrections, photorefractive keratectomy (PRK) modifies the anterior corneal surface ablatting the anterior corneal stroma and generating a new radius of curvature to decrease refractive error. The most popular refractive surgery is Laser in-situ keratomileusis (LASIK) (Sandoval et al. 2005). This uses PRK technology but performs the procedure at the stromal level after the creation of a lamellar flap formed with a mechanical microkeratome (Updegraff and Kritzinger 2000).

The present study was undertaken to assess the long-term postoperative outcomes of the two most common laser refractive surgeries (PRK and LASIK) to treat myopia. The effect of excimer laser surgery in the treatment of regular astigmatism by these two different techniques was analysed. The presence of irregular astigmatism secondary to epithelial irregularities was also evaluated. In addition, it was also of interest to study the correlation of corneal nerve density and postoperative corneal wound healing after excimer laser refractive surgery.
2 REVIEW OF THE LITERATURE

2.1 GROSS CORNEAL ANATOMY

The cornea is an avascular and transparent structure situated in front of the eye. The structural and physiological properties of the cornea determine its optical performance to refract light. The cornea is the most powerful refractive lens of the eye comprising on average 45 D of the approx. 60-70 D total refractive power of the eye. The central thickness of the cornea is between 500 to 550 µm and 600 to 700 µm at the corneal periphery (Doughty and Zaman 2000, Ehlers and Hjortdal 2004, Salvetat et al. 2010). This difference in thickness between the periphery and central corneal generates a disparity in curvature creating an aspheric optical system. The cornea has an elliptical shape when viewed frontally; this configuration arises from an extension of opaque sclera tissue that covers the cornea superiorly and inferiorly. In the adult cornea, the horizontal and vertical average diameters are 12 mm (range 11 to 12.5 mm) and 11 mm (range, 10 to 11.5 mm), respectively (Rufer et al. 2005).

2.1.1 Tear film

The pre-corneal tear film supports and maintains the ocular surface. It lubricates the epithelium, protects the cornea from external agents, modulates wound healing through its components and, secondary to the air-tear interface, creates the first refractive surface.

Three different layers constitute the tear film (Prydal and Campbell 1992, Prydal et al. 1992); a. The inner hydrophilic mucous layer derived from the conjunctival goblet cells and corneal epithelial cells (Chao et al. 1980). This layer is attached to the superficial cells of the corneal epithelium and its essential role is to allow spreading of the tear film, and to prevent the adhesion of foreign pathogens and debris onto the ocular surface. b. The aqueous layer is derived from the main and accessory lacrimal glands. It contains proteins, electrolytes, cytokines and growth factors that modulate the ocular surface and the response to damage. c. The external lipid layer derived from the meibomian glands prevents the evaporation of tears (Mishima and Maurice 1961, Rolando and Refojo 1983) and stabilizes the tear film.

2.1.2 Corneal structure

The cornea is built of around 200 collagen sheets, which are laid at approximately 90 degrees to each other. This collagen structure provides mechanical strength and transparency and allows for undisturbed image formation on the retina. It is composed
from anterior to posterior by the epithelium, Bowman’s layer, stroma, descemet’s membrane and endothelium.

The corneal epithelium is the most external layer of the cornea, with a thickness of approximately 50 µm and an estimated turnover rate of 5 to 7 days (Cenedella and Fleschner 1990, Hanna et al. 1961). Before the time of stems cells Thoft and Friend and others (Buck 1979, Buck 1985, Haddad 2000, Thoft and Friend 1983) proposed that corneal basal epithelial cells moved by a centripetal movement from the periphery to the central area and thereby replaced the exfoliating cells. The finding that the epithelial stem cells are located at the limbus strengthened this view (Dua and Azuara-Blanco 2000, Tseng 1989). Yet new evidence suggests that in some species stem cells are located over the entire ocular surface (Majo et al. 2008).

The corneal epithelium consists of 5 to 6 layers of non-keratinized squamous stratified epithelial cells which are morphologically divided into three different types (Ehlers 1970).

*The apical cells* consist of two to three layers of exfoliating superficial, flat cells joined by desmosomes, intercellular junctions and zonulæ occludentes, tight junctional complexes (Ban et al. 2003, Hsu et al. 1999). These junctions maintain a barrier preventing the flow of substances and impurities into the stroma. The surface of these cells is covered with microvilli and microplicae. These structures promote the absorption of metabolites and oxygen and also stabilize the tear film. The apical surface is coated by the glycocalix, composed of glycoproteins and glycolipid molecules which interact with the mucous layer of the tear film (Ubels et al. 1995). It is believed that the glycocalix plays a role in maintaining the hydrophilic properties of the cornea and smoothing the optical surface required for clear vision.

*The wing cells* consist of 2 to 3 layers of wing-like cells located below the apical cells. They correspond to an intermediate cell type between basal and apical cells.

*The basal cells* form a single, cuboidal, columnar layer of cells above the basement membrane. This layer is the source of wing and apical cells. Neighbouring basal cells are joined by desmosomes, gap junctions and junctional complex. The basal cells secrete and form the *basement membrane* (Hogan MJ et al. 1971), which provides the matrix where cells can attach and migrate. Hemidesmosomes connect the basal cells with the basement membrane (Gipson et al. 1987). Basal cells also secrete anchoring fibrils that penetrate the basement membrane and reach the stroma (Gipson et al. 1987) increasing the adhesion to Bowman’s layer and stroma.

*Bowman’s layer* is located between the epithelium and stroma. It is composed of proteoglycans and collagen fibres I, III, V, and VI (Marshall et al. 1993). This acellular layer, is 8 -12 µm thick (Komai and Ushiki 1991) and does not regenerate. Bowman’s layer increases the biomechanical strength of the cornea, and enhances the adhesions of epithelial cells and stroma secondary to anchoring fibers.

*The stroma* composes almost 90% of the thickness of the cornea. It is formed of collagen (types I, III, IV, and VI), extracellular matrices, nerve fibers and cells (Ihanamaki et al. 2004). Keratan sulfates are the major proteoglycans, helping to regulate the hydration and structural properties of the stroma. The corneal transparency has been related to the distance and regular arrangement of collagen fibers (Maurice 1957). Stromal
fibroblasts (keratocytes) are the primary cellular elements of the stroma (Hay 1979, West-Mays and Dwivedi 2006); they lie between the collagen lamellae organized in a clockwise, spiral arrangement (Muller et al. 1995). Keratocyte density is higher in the anterior stroma than in the posterior stroma (Erie et al. 2006, Moller-Pedersen et al. 1997, Patel et al. 2001). These cells constantly maintain the stromal structure interacting through gap junctions and similar innervations. After stromal damage keratocytes begin to migrate to restore the tissue (Fini and Stramer 2005, Jester et al. 1999, West-Mays and Dwivedi 2006). Depending on the extent and type of stromal damage an activation of fibroblast can lead to the loss of corneal transparency (Fini and Stramer 2005, Jester et al. 1999).

Descement’s membrane is the basement membrane of the corneal endothelium. It is composed mainly of collagen type IV (Marshall et al. 1991), laminins and glycoproteins (Beuerman and Pedroza 1996, Marshall et al. 1993). Similarly to Bowman’s layer, it does not regenerate, but shows an age-dependent increase in thickness.

The endothelium is composed by a single layer of endothelial cells. At birth the cell density is about 3500 cells/mm$^2$ (Waring 1982, Waring et al. 1982). The endothelial cell count decreases with age by ~2% per year. The major function of the endothelium is to regulate the hydration level of the corneal stroma and maintain the corneal transparency. This hydration level is regulated by ionic pumps located on the endothelial plasma membrane. The “pump leak” hypothesis established that the amount of water and solutes that leak into the stroma are compensated by the rate of pumping of excess water from the stroma back to the aqueous humor (Maurice 1972, Waring et al. 1982). Furthermore, the endothelial cells control the transport of nutrients from the aqueous humor to the other corneal layers by active transport mechanisms.

2.1.3 Corneal innervation

The sensory innervation of the cornea derives principally from the ophthalmic division of the trigeminal nerve via the nasociliary nerves. In some cases, the second branch of the trigeminal nerve, the maxillary nerve through the infraorbital nerve, carries sensory innervations for the inferior cornea (Rozsa and Beuerman 1982, Ruskell 1974, Zander and Weddell 1951).

Nerve bundles from the two long ciliary nerves, which are branches of the nasociliary portion of the trigeminal nerve, enter the cornea in the middle third of the stroma in a radial fashion. Once they enter the stromal cornea, the peripheral bundles lose the myelin sheaths retaining only their Schwann cells sheaths and run toward the centre of the cornea (Muller et al. 1996, Muller et al. 2003). In their trajectory some fibres innervate individual keratocytes. The stromal nerve sub divides extensively into smaller branches bending 90 degrees toward the surface of the cornea. After penetrating Bowman’s layer they lose the remaining Schwann cell sheath and bend 90 degree another time forming the subbasal nerve plexus located between the Bowman’s layer and the basal epithelial cells (Muller et al. 1997). Nerve terminals then protrude between the epithelial cells and terminate in the superficial layers of the corneal epithelium (Chan-Ling 1989, Muller et al. 1997, Zander and Weddell 1951). Electrophysiological studies (Belmonte and Giraldez 1981, Belmonte
et al. 1991, Gallar et al. 1993, Tanelian and Beuerman 1984) have found three different types of corneal sensory fibres: a) mechano-nociceptors (20% of fibres) that react to mechanical forces. b) polymodal nociceptors (70% of fibres) that react to mechanical energy, heat and chemical irritants, and c) cold-sensitive receptors (10-15% of fibres) that react to a decrease in corneal temperature.

2.2 REFRACTIVE ERRORS

The different anatomical parts of the eye can be compared to a camera, where the cornea, lens, iris and retina have a function similar to that of the lenses, diaphragm and film to refract the rays of light at a determined point. The refractive state where the focus parallels rays of light from a distant point to the retina is called emmetropia. Yet the point of focus can also be located in front (myopia) or behind (hypermetropia) the retina, causing ametropia. A balance between the refractive power and axial length of the eye is required to focus the light on a desired point of the retina.

A long axial length of the eye or a steep cornea that increases the refractive power of the eye is the principle cause of myopia. By contrast, hypermetropia eyes have a short axial length of the eye or a too flat cornea. In myopia the image is formed anterior to the retina and in hypermetropia at a point posterior to the retina.

Spherical refracting surfaces have constant curvature in all meridians, yet with astigmatism, disparity in the curvature of the refractive surface of the eye at different meridians causes the refractive surface of the eye to assume a cylindrical shape avoiding the rays of light to focus on a single point of the retina. Cylinders show a maximum curvature along their circumferential direction and zero curvature along their length. The zero curvature is 90 degrees to the maximum curvature. This toric form creates two line images of a point at right angles to each other and at different distances along the axis.

In regular astigmatism the meridians’ directions are constants and located at 90 degrees to each other. This type of astigmatism is correctable with a cylindrical lens. The corneal toric shape explains most astigmatisms. If the vertical meridian is steepest (the principal meridian lies at close to 90 degrees), the astigmatism is with-the-rule, and it is correctable with a plus cylinder near to 90 degrees or a minus cylinder close to 180 degrees. If the horizontal meridian is the steepest (the principal meridian lies is close to 180 degrees), the astigmatism is against-the-rule and a plus cylinder close to 180 degrees or a minus cylinder close to 90 degrees can be used. Oblique astigmatism will occur when the principal meridians lie between 30 to 60 degrees, or 120 – 150 degrees.

Irregular astigmatism shows a disparity in the principal meridians, not being located at 90 degrees to each other. This was defined by Duke-Elder as a refractive condition in which the refraction in meridians conforms to no geometrical plan and the refracted rays have no planes of symmetry (Duke-Elder S 1970). The refractive surfaces might present multiple zones of increased or decreased surface power, depending on the cause of the astigmatism. Cylindrical lenses cannot correct these types of defects. In the topography there may be multiples zones of flat or steep areas at least 2 mm in diameter in any area of the cornea.
2.3 EXCIMER LASER

2.3.1 Principle

The corneal refractive procedures can be divided into those that change the corneal curvature with relaxing incisions or radio frequency energy (conductive keratoplasty) and those that add or remove tissue from the cornea to change its curvature (Barraquer JI 1964, Barraquer JI 1989). Since its introduction in the 1980’s and its first application to the human eye the excimer laser has changed the world of refractive surgery. The term excimer arises from “excited dimer” that describes an energized molecule with two identical components. Rare gas atoms interact with a halogen molecule when they are stimulated by an electrical discharge (about 30,000 electron volts) within the laser cavity (Tasman W 2001). These energized atoms emit photons of ultraviolet light which, when released, emit the laser light.

In 1981, Taboada and Archibald (1981) reported that the argon fluoride (ArF) excimer laser emits high-power ultraviolet (UV) radiation at 193 nm that could reshape the corneal epithelium. Trokel et al. (1983) reported in 1983, that the excimer laser permits the excision of corneal stromal tissue with minimal damage to the adjacent tissues. Later studies (Krauss et al. 1986, Puliafito et al. 1985, Seiler and Wollensak 1986, Srinivasan and Sutcliffe 1987) showed that the excimer laser uses this high energy ultraviolet radiation to break the covalent bonds between molecules in the corneal stroma without generating heat. This has been termed a photoablative process and is the principal reason making refractive surgery a more predictable and safe procedure. In 1985, Seiler performed the first procedure on a human blind eye (Seiler and Wollensak 1986), yet it was only in 1988 that McDonald and co-workers performed the first procedure on a seeing human eye (McDonald et al. 1989).

To date several different excimer laser systems have been developed:

a. Broad-beam laser (BB): This system can adjust the spot size between 0.6 mm to 8 mm. It starts at the centre and moves to the periphery of the cornea. A shorter operating time, and less need for eye-tracking systems are the relative advantages of this system. However, higher incidence of central islands and a higher energy output are considered its disadvantages.

b. Scanning slit laser (SS): This system uses a rectangular beam. The size of the rectangular spot can be adjusted up to 2 x 9 mm. Improvement in beam homogeneity and uniformity as well as a decreased incidence of central islands are the advantages of this type of laser. Longer operating times and lack of more accurate tracking systems are considered disadvantages of this laser instrument.

c. Scanning-spot lasers (SSL): This system uses a spot beam between 0.5 and 2.0 mm that travels across the cornea reducing the need for laser energy. The advantage of this type of laser is also that it permits custom-design ablations, but such laser delivery systems require an accurate tracking system.
2.3.2 Interaction of excimer laser with the cornea

The photoablative process is a reduction procedure involving the excision of tissue. Once the 193 nm UV energy emitted by the ArF excimer laser is absorbed by the solid component of the cornea (Krauss et al. 1986), it breaks the carbon-carbon and carbon–nitrogen bonds that form the corneal collagen molecule generating a decomposing ablative process that produces minimal thermal damage in the corneal tissue (Bende et al. 1988). Immediately after the breakage the kinetic energy created ejects the molecular fragments from the place on impact (Krauss et al. 1986, Trokel et al. 1983). The energy emitted by the laser is inversely proportional to the pulse repetition, the higher the repetition rate, the smaller the energy emitted by the pulse. The available lasers have a repetition rate between 10 (BB) and 750 (SSL) Hz. Several studies (Krueger and Trokel 1985, Krueger et al. 1985, Puliafito et al. 1987, Seiler et al. 1990) have calculated the laser fluence or energy density per unit area projected (irradiance) necessary to ablate the cornea. The threshold to ablate the corneal surface with the ArF excimer laser is 50 mJ/cm$^2$, yet the most efficient fluence in human eyes should be higher than 120 mJ/cm$^2$. Commercially available excimer lasers work with a fluence between 120 and 180 mJ/cm$^2$ (Duffey and Leaming 2002). The amount of corneal tissue ablated by the pulse of the laser is directly proportional to the amount of energy and the depth of ablation increases in proportion to the square of the ablation diameter (Munnerlyn et al. 1988). Using a fluence of 160 – 180 mJ/cm$^2$ an ablation rate between 0.21 and 0.27 microns per pulse is obtained (Seiler et al. 1993).

2.3.3 Phototherapeutic keratectomy (PTK)

The therapeutic treatment of corneal opacities and irregularities by excimer laser is called phototherapeutic keratectomy (PTK) (Fagerholm 2003). It refers to a regular and sequential ablation of the anterior layers of the cornea. In general, PTK has been used to remove superficial opacities, treat surface irregularities, and correct complications after photorefractive keratectomy (PRK) and Laser in-situ keratomileusis (LASIK). The best candidates for PTK are patients with anterior opacities or anterior elevated stromal changes; deep stromal changes do not response positively to PTK. Reshaping of a surface irregularity has been performed using masking fluids (Kornmehl et al. 1991). Commonly hyperopic postoperative changes in refractive error are found after PTK (Fagerholm et al. 1993, Sher et al. 1991, Stark et al. 1992, Starr et al. 1996). Stability of the mean refraction and best corrected visual acuity (BCVA) is usually achieved by the third postoperative month (Fagerholm 2003, Maloney et al. 1996, Ohman et al. 1994). Long-term studies after PTK have reported statistically improved corneal clarity, BCVA, and reduced surface irregularity (Fagerholm et al. 1993, Fagerholm 2003, Maloney et al. 1996, Rapuano 1997).

PTK is effective for the relief of pain and cure of spontaneous epithelial detachments in recurrent corneal erosion syndrome (Cavanaugh et al. 1999, Dinh et al. 1999, Maini and Loughman 2002, Rapuano and Laibson 1993, Rapuano and Laibson 1994, Rapuano 1997, Zuckerman et al. 1996), as it stimulates the formation of new anchoring fibrils in the
stroma and results in enhanced epithelial adhesion (Davis and Lindstrom 2001, Wu et al. 1991). However, postoperative pain during the first 48 hours may be severe, and the recurrence rate of erosion has been reported to be 13.8% to 26.3% during a 12-month follow-up period (Cavanaugh et al. 1999, Rapuano 1997, Reidy et al. 2000).

2.3.4 Photorefractive keratectomy (PRK)

Photorefractive keratectomy (PRK) modifies the anterior corneal surface after removal of the corneal epithelium ablating the anterior corneal stroma and generating a new radius of curvature to decrease refractive error. Attempts to restore the epithelium on top of the stromal wound have led to alternative techniques, such as Laser-Assisted Sub-Epithelial Keratomileusis (LASEK). In this procedure dilute alcohol suspension is used to detach the epithelium which can thereafter be lifted. Alternatively, in Epi-LASIK a mechanical microkeratome is used to scrape the epithelium. In 1995, the US Food and Drug Administration (FDA) approved the use of PRK for spherical myopic correction, followed by myopic astigmatism in 1997. In 1998, the FDA approved hyperopic correction pursued by hyperopic astigmatism in 2000. A wide spectrum of PRK corrections has been approved by the FDA, myopic corrections up to -12.0 D, hyperopic corrections up to +6.0 D and astigmatism corrections up to 4.0 D, yet for PRK myopic manifest refraction of spherical equivalent (MRSE) correction between -1.0 diopters (D) to -7.0 (D) are, however, closer to today’s criteria (Waring 2008). After Bowman’s layer exposure the laser is directed to ablate the corneal surface. Myopic treatments primarily ablate the central cornea, and hyperopic treatments perform an annular shape ablation at the periphery. Astigmatism treatments have different approaches depending on type of astigmatism. Earlier, smaller optical ablations zones (4 to 4.5 mm) were used to reduce the depth of ablation, yet the presence of glare and halos led to an increase in the size of the ablation (Epstein et al. 1994, Kalski et al. 1996, Kim et al. 1996, Morris et al. 1996). Large ablation diameters and the use of transition zones have improved the postoperative results (Dausch et al. 1993, O'Brart et al. 1995, O'Brart et al. 1996, Rajan et al. 2006). Nowadays, the most commonly used optical zones of 6.5 mm and 7 mm are used for myopic and hyperopic treatments respectively, both of them surrounded by a transition zone of 9 mm (Albert and Jakobiec's. 2008).

2.3.5 Laser assisted in situ keratomileusis (LASIK)

LASIK uses the same PRK laser technology but performs the procedure at the stromal level after the creation of a lamellar flap consisting of epithelium, Bowman's layer and anterior stroma (Updegraff and Kritzinger 2000). Corneal lamellar dissection was first described in 1949 by Jose Barraquer (Barraquer JI 1949) known to many as “the father of modern refractive surgery.” At that time Professor Barraquer introduced the microkeratome, a high precision surgical device that enabled the creation of a flap of corneal tissue. In 1964, Barraquer performed the first successful reported lamellar surgery,
at that time an extracorporeal treatment that he called keratomileusis (Barraquer JI 1964) derived from the Greek root keratos (cornea) and mileusis (carving) for sculpture. After the manual dissection of a corneal cap with a microkeratome, a cutting machine modelled after a carpenter’s plane, the corneal cap was reshaped in a laboratory. During the 1980s, Luis A. Ruiz developed the first automated microkeratome that made it possible to create a corneal cap, and to remove a second corneal disc performing the first keratomileusis in situ or automatic lamellar keratoplasty (ALK) (Ruiz and Rowsey 1988). In 1990, Pallikaris (Pallikaris et al. 1990) described the use of a microkeratome in junction with the excimer laser, and coined the term Laser in-situ keratomileusis (LASIK). Later advances included the use of laser to create a corneal flap. The femtosecond lasers (FS) use an infrared (1053 nm) scanning pulses to cut the corneal stroma creating precise lamellar flaps for LASIK (Nordan et al. 2003, Sugar 2002).

LASIK has become the most widely performed refractive surgery nowadays (Sandoval et al. 2005). This preference over PRK is based in less postoperative pain, haze formation and regression and faster visual recovery (Azar and Farah 1998, el Danasoury et al. 1999, Helmy et al. 1996, Shortt and Allan 2006, Steinert and Hersh 1998).

2.3.5.1 Microkeratome

Manual microkeratomes evolved from the Barraquer device. This apparatus performs a manual horizontal lamellar cut using a translational movement across the cornea, yet it required high surgical skills to create reproducible flaps, making them obsolete. In 1986 Ruiz and Rowsey (Ruiz and Rowsey 1988) introduced the automated mechanical microkeratome that performed constant flaps with smooth surfaces. Since then, several microkeratomes have been developed and are currently available, each of them with different specifications in oscillation, blade angle, hinge location and flap thickness. Basically, the microkeratome consists of a corneal shaper head, a motor, and a pneumatic fixation ring. Once these parts are assembled they are connected to a control unit that contains the electrical source power and a suction pump. A blade (stainless steel or plastic) is inserted inside the corneal shape head that oscillates in a range of 2000 to 20000 rpm depending of the microkeratome (Belin and Schultze 2000). The suction rings which allow the ocular globe to be hold have different diameters varying from 8 to 10.75 mm. The diameter of the flap has a direct relation to the size of the suction ring and the keratometric values (Belin and Schultze 2000). Large ring diameters or steeper corneas (high K values) result in larger flaps, small ring diameters or flatter corneas (low K values) generate smaller flaps. Yet the microkeratome footplate is the most important factor that influences flap thickness. Hinge location can be nasally or superiorly, yet less compromise of the corneal sensitivity has been found with superior hinge flaps (Kumano et al. 2003).

In 2000, the FDA approved the IntraLase femtosecond laser (FS) for corneal surgery. This solid state laser creates lamellar flaps using infrared scanning pulses that create small cavitations burbles (Ratkay-Traub et al. 2003) without damage of the adjacent tissue with an accuracy of 1 µm. It employs a suction ring, with an applanating glass contact lens that creates low pressure (between 10 and 35 mmHg) (Sugar 2002). Initially it used pulse rates
of 10 kHz requiring relatively a long time of flap creation, but, nowadays the current FS laser fires at a rate of 60 kHz resulting in much lower times for flap creation. Fifth generation FS have even reached a firing rate of 150 kHz further reducing the flap creation time and decreasing the energy needed. The major advantages of FS laser systems over microkeratomes are increase in flap homogeneity and a higher rate of reproducibility. A capacity to create flaps of different diameters and thicknesses, even under 90 µm have decrease the flaps related complications (Durrie and Kezirian 2005, Kezirian and Stonecipher 2004) and increases postoperative flap adhesion (Knorz and Vossmerbaeumer 2008). Complications with FS are rare, being most commonly transient light-sensitive syndrome (TLSS) and diffuse lamellar keratitis (DLK). The mechanism of TLSS is still unknown, yet it seems to be secondary to an inflammatory response to the gas bubbles or keratocytes’ response to laser ablation.

Postoperative visual outcomes between microkeratomes and FS have not shown any differences (Javaloy et al. 2007, Montes-Mico et al. 2007a), although the contrast sensitivity seems to be better after FS (Montes-Mico et al. 2007b), yet the complication rate between both groups is similar (Moshirfar et al. 2010).

2.4 CORNEAL WOUND HEALING

Wound healing is essential to maintain the transparency and optical properties of the cornea. Physiology diversity in response to injury is a major factor in outcome results after refractive surgery. PRK and LASIK differ in the intensity of corneal wound healing. This difference seems to be secondary to the preservation of epithelium and Bowman’s layer after LASIK (Ambrosio and Wilson 2003, Helena et al. 1998, Mohan et al. 2003, Tervo and Moilanen 2003, Wilson et al. 2007) and the amount of depth of photoablation in both procedures (Moller-Pedersen et al. 1998, Moller-Pedersen et al. 2000).

The mechanisms behind corneal wound healing response form a complex cascade of events involving epithelial cells, keratocytes, corneal nerves, lacrimal glands, tear film, and cells of the immune system. Cytokines and growth factors are the soluble factors that mediate the signals and interaction between different cells and components to restore corneal functionality. In the following I will describe corneal wound response in different layers of the cornea in more detail.

Epithelial corneal debridment from its basement membrane generates apoptosis in keratocytes followed by simple epithelial replacement by mitosis without any fibrosis. If epithelial injury compromises the basement membrane it stimulates a fibrotic response (Zieske et al. 2001). In the case of PRK the fibrotic response involves a higher area compared to LASIK in which the fibrosis response is limited to the edges of the flap created by the microkeratome.

Immediately after an epithelial injury an anterior stromal keratocyte apoptosis can be observed (Dupps and Wilson 2006, Wilson et al. 1996). This continues for at least one week. This response is mediated by the release of cytokines such as Interleukin (IL)-1(Wilson et al. 1996), tumour necrosis factor (TNF)-α (Wilson et al. 2001), epidermal growth factor (EGF) and platelet derived growth factor (PDGF) (Tuominen et al. 2001).
Twelve to 24 hours after the onset of keratocyte apoptosis keratocytes start to migrate and proliferate in the anterior stroma along with differentiation in myofibroblasts more posteriorly (Helena et al. 1998, Jester et al. 1992, Mohan et al. 2003, van Setten et al. 1992). These events are probably mediated by various tear fluid and tissue-derived growth factors such as transforming growth factor beta (TGF-B), hepatocyte growth factor (HGF) and other cytokines that increase in tears following corneal wounding (Tervo et al. 1997). Inflammatory cells (macrophages/monocytes, T cells and polymorphonuclear cells) are attracted into the corneal stroma from the limbal blood supply and the tear film (Helena et al. 1998) to eliminate the apoptotic cells and necrotic debris. Activated keratocytes start to deposit new extracellular matrix (ECM) that can be observed as early as seven days after injury (Linna and Tervo 1997) followed by a stromal re-growth already documented in three-dimensional images (Jester et al. 1999, Moller-Pedersen et al. 1997). Different factors (Moller-Pedersen et al. 1997, Netto et al. 2006, Tuunanen et al. 1997) such as the volume of stromal tissue removed or irregularities of the stroma have been shown to act in concert and to regulate the stromal repair and formation of scar tissue or “haze”.

After an epithelial injury, the first observable change at the stroma is the keratocyte apoptosis followed by the activation of quiescent keratocytes. Helena et al. (Helena et al. 1998) showed that the extension and location of epithelial injury correlates with the keratocytes response. Anterior stromal fibrosis (haze) is caused by a synthesis of a new ECM by activated keratocytes (Moller-Pedersen et al. 1997, West-Mays and Dwivedi 2006) that lose their ability to express corneal crystalline proteins (Pei et al. 2004) and a secondary increase in cellular reflectivity (Moller-Pedersen et al. 2000) that decreases the normal corneal transparency.

The central keratocyte density measured by corneal confocal microscopy (CM) reported a density of $22 \pm 2 \text{ 981 cells/mm}^3$ (mean ± SD) in normal corneas (Moilanen et al. 2008, Patel et al. 2001) with a higher density in the anterior than in the posterior stroma (Erie et al. 2006, Moilanen et al. 2008, Moller-Pedersen et al. 1997, Prydal et al. 1998). Earlier reports (Muller et al. 1996, Muller et al. 2003) have demonstrated the direct innervations of individual keratocytes by nerve bundles at the central stroma. Six months postoperatively the keratocyte apoptosis is more extensive in the anterior stroma after PRK than after LASIK. CM after PRK has shown that there is a concomitant decrease in the number of keratocytes in the anterior corneal stroma that continues as long as five years after the procedure and starts to compromise the middle and posterior stroma after this time (Erie et al. 2006, Moilanen et al. 2008). In the case of LASIK, the keratocyte density is also decreased in the anterior and posterior stromal flap and in the anterior retroablation zone (Erie et al. 2006, Moilanen et al. 2008, Vesaluoma et al. 2000a) even after five years (Erie et al. 2006). Flap denervation (Mitooka et al. 2002, Vesaluoma et al. 2000a) and chronic liberation of cytokines secondary to arrested corneal epithelial cells located in the flap interface (Erie et al. 2006, Wilson et al. 2001) have been proposed to explain the chronic decrease of keratocytes in the anterior flap. A question that remains unanswered is the clinical significance of this decrease in keratocytes as well the minimum number of keratocytes required to keep the cornea viable.

Both PRK and LASIK damage corneal nerves and generate changes in corneal sensitivity (Benitez-del-Castillo et al. 2001, Campos et al. 1992, Erie et al. 2005, Ishikawa...

PRK injures the epithelial nerve ends, epithelial and subepithelial plexuses, and anterior stromal nerves. Histological (Tervo et al. 1994, Trabucchi et al. 1994) and CM studies (Erie et al. 2005, Tervo and Moilanen 2003) have assessed information on nerve regeneration after PRK. These findings showed regenerated fibres at one day post-PRK in histological sections, and visible by CM by seven days post-PRK. Corneal sensitivity correlated with the changes observed. Sensitivity begins to recover after one week and reached almost normal values three months later (Matsui et al. 2001, Perez-Santonja et al. 1999). However, long-term morphological alterations were visible even one year later (Tervo et al. 1994) and subbasal nerve density examined by CM was not reached until two years after PRK (Erie et al. 2005, Moilanen et al. 2008).

In LASIK, the lamellar incision cuts the bundles of nerve fibres of the superficial stroma and the subbasal nerve plexus. Yet postoperatively in the flap, the epithelial and basal epithelial/subepithelial nerves took a few days to disappear except for the hinge (Lee et al. 2002, Tervo and Moilanen 2003). Regeneration of anterior stromal, subbasal and epithelial fibres occurred approximately three months later although deep stromal nerves showed abnormal morphology five months after LASIK (Latvala et al. 1996, Linna et al. 1998). Corneal sensitivity after LASIK measured by mechanical aesthesiometers reported a decrease of sensitivity one to two weeks after LASIK (Donnenfeld et al. 2004, Linna et al. 2000a) which recovered to normal level six to 12 months later. New noncontact aesthesiometers reported hypersensitivity one week post-LASIK followed by a decrease in sensitivity three to five months later. Near normal values has been reported two years after the procedure (Gallar et al. 2004, Tuisku et al. 2007). Post-LASIK corneal subbasal nerve density measured by CM showed a slower regeneration compared to PRK reaching nearly preoperative values five years after LASIK (Erie et al. 2005). An earlier study (Tuunanen et al. 1997) stressed the importance of corneal nerve density and nerve recovery to avoid haze. LASIK-induced neurotrophic epitheliopathy (LINE) is a term proposed by Wilson and Ambrosio (Wilson and Ambrosio 2001, Wilson 2001) to describe an entity in post-LASIK patients complaining of ocular discomfort resembling dry eye symptoms although corneal sensitivity and dry eye are normal (Tuisku et al. 2007). Transection of afferent sensory nerve fibres and aberrant regenerated corneal nerves are likely to be among the most important factors associated with this entity (Ambrosio et al. 2008). Some studies (Tuunanen et al. 1997, Wilson 2001, Tuisku et al. 2007) suggest that the modulation of corneal wound healing, post-operative anterior stromal scarring, or even symptoms showed a direct relation with corneal subbasal nerve plexus to maintain corneal healing and transparency.

Several factors have been associated with more severe compromise of sensitivity after LASIK compared to PRK, including lamellar cut, thickness, (Nassaralla et al. 2005) orientation and width of the flap, (Donnenfeld et al. 2004) and ablation depth (Bragheeth and Dua 2005, De Paiva et al. 2006, Kim and Kim 1999, Shoja and Besharati 2007). Thin, nasally placed flaps, broader hinge and smaller ablations are associated with less compromise of corneal sensitivity.
2.5 PREOPERATIVE ASSESSMENT OF REFRACTIVE SURGERY

Corneal curvature by videokeratography needs to be measured. Pathology in corneal curvature is a contraindication to corneal refractive surgery, unless the procedure has a therapeutic aim. Different reported scales are available, yet the absolute and the normalized colour-scale are the most used.

Pupil size under different light conditions, bright and dim, should be tested. Large pupil size under scotopic conditions has been associated with postoperative complaints of glare and halos (O’Brart et al. 1995, O’Brart et al. 1996, Rajan et al. 2006). Accordingly, the laser ablation zone should be 6 - 9 mm. Yet widening the ablation diameter increases the depth of ablation and thus the risk of post operative corneal ectasia (Rabinowitz 2006).

Proper measure of central corneal thickness is crucial before refractive surgery. A residual corneal thickness between 300 and 250 µm should be left untouched in the posterior cornea after flap creation in LASIK patients to prevent the risk of postoperative ectasia (Randleman et al. 2003, Randleman et al. 2008, Wang et al. 1999). To date, the most commonly used method of measuring corneal thickness is ultrasound pachymetry (US). Some other optical techniques such as slit scanning elevation topography or hybrid slit-scanning topography, Scheimpflug imaging, or optical coherence tomography (OCT) have gained popularity (Rabinowitz 2006). Yet some of these techniques report thicker corneas than US (Cairns and McGhee 2005).

Wavefront (WF) techniques measure the complete refractive status of the eye. WF aberration is defined as a deviation between an ideal optical system and the WF that originates from the measured optical system (Maeda 2001). These aberrations are classified as low order aberrations (sphere, cylinder aberrations) than can be corrected by spectacles and the high order aberration (HOA) that cannot. It also gives reason to suspect early corneal pathologies, such as keratoconus. In terms of vision, HOA can blur the quality of vision having a greater effect in scotopic conditions being a potential source of reduced image quality (Wang et al. 2003). Postoperative results after wavefront customized corneal ablations have shown excellent results (Kim et al. 2004, Kohnen et al. 2004, Mastropasqua et al. 2004, Phusitphoykai et al. 2003). However, the superior results of customized ablations vs. traditional corrections are still a matter of discussion.

Dry eye is one of the most common complications after laser refractive surgery (De Paiva et al. 2006, Lui et al. 2003, Quinto et al. 2008). Tear production usually decreases after refractive surgery (Ozdamar et al. 1999, Siganos et al. 2000). Preoperative dry eye condition is a major risk factor for more severe or symptomatic dry eye after surgery. Lower tear function is a factor for postoperative dry eye, and thus tear production and quality should be assessed prior to surgery. Surface ablations present a lower risk of developing dry eye (Lee et al. 2000) than intrastromal ablations (Albietz et al. 2004, Battat et al. 2001, Toda et al. 2001). PRK and LASIK seem to generate a tear deficient dry eye which is mediated by neural- mechanisms, with a recovery rate more delayed after LASIK than after PRK (Ang et al. 2001, Lee et al. 2000). Postoperative dry eye symptoms after LASIK have been suggested to be secondary to a neurotrophic epitheliopathy rather than a true dry eye (Ambrosio et al. 2008, Wilson 2001) probably as a consequence to aberrantly
regenerate corneal nerves. Direct connections between postoperative dry eye symptoms and deep ablations have been suggested (Tuisku et al.). Patients should be informed of the possibility of developing chronic dry eye symptoms after laser refractive surgery, especially after deep ablations by LASIK.

2.6 VISUAL ACUITY AND REFRACTIVE RESULTS AFTER EXCIMER LASER SURGERY

In general the results of excimer laser corneal surgery are good, although measured parameters after refractive surgery differ in most publications, making direct comparisons difficult. Since the end of the 1990s standard guidelines for reporting outcomes after refractive surgery have been proposed by the editorial staffs of the Journal of Cataract and Refractive Surgery and the Journal of Refractive Surgery (Koch et al. 1998, Waring 2000). Since then, most studies have reported results based on range groups of manifest refraction of spherical equivalent (MRSE) corrections and treatment modalities or laser platforms. The guidelines recommended assessing the efficacy, safety and stability of postoperative outcomes.

The efficacy of refractive surgery is assessed by determining the proportion of eyes achieving a postoperative UCVA \( \leq 0.0 \) (logMAR scale) or \( \geq 20/20 \) (Snellen scale), which corresponds to the statistical mean visual acuity of the population, and/or the proportion of eyes achieving a UCVA \( \leq 0.5 \) (logMAR scale) or \( \geq 20/40 \) (Snellen scale), which corresponds to the threshold to measure the functional visual ability to drive in some Western countries, and the percentage of eyes with MRSE within ±1.00 diopters (D) or ±0.50 D of the attempted correction.

The safety of refractive surgery is determined by the percentage of patients with postoperative loss of 2 or more lines of BCVA after surgery, and also by the incidence of surgical and postoperative complications.

The stability of refractive surgery is determined by the mean change in MRSE over a certain interval of time.

2.6.1 PRK outcomes

2009, Stephenson et al. 1998) have demonstrated that these results persist over time (Table 1).

Most studies with short follow-up reported a postoperative UCVA ≥20/50 (logMAR 0.4) in more that 80% of eyes. This value in long-term follow-up studies continues, yet attempted corrections (over 6 D) tend to decline in efficacy (Alio et al. 2008a, Alio et al. 2008b). Predictability of MRSE within ± 1.00 D after one to three years postoperatively has been reported in ~ 70% of eyes (Bricola et al. 2009, Honda et al. 2004, Kim et al. 1997, Koshimizu et al. 2010, Pietila et al. 2004, Rajan et al. 2004, Shojaei et al. 2009, Stephenson et al. 1998). In long-term follow-up studies predictability of MRSE within ± 1.00 D varies between 34 to 91%. These differences can be explained by the inclusion criteria used, the postoperative goal, the amount of correction attempted, and even the parameters reported to have been used in the studies. This is the case, for instance, in Rajan et al. (Rajan et al. 2004), who reported a variation of MRSE within ± 1.00 D in 75% and 22% of eyes who underwent an attempted correction of -2 D and -7 D respectively. Yet long-term follow-up studies including and reporting correction less that -7.5 D without subgroups (Alio et al. 2008a, O’Connor et al. 2006, Pietila et al. 2004) (325 eyes) reported MRSE within ±1.00 D in more than 75% of the eyes at last follow-up round. On average, the postoperative loss of 2 or more lines of BCVA seems to be less than 4% (Steinert and Bafna 1998). This percentage has been reported to increase in corrections over 6 D (Alio et al. 2008b). Corneal postoperative haze, that could explain loss of lines of BCVA, has been reported to have cleared within 12 months in low correction and within 24 months in moderate –high corrections (Fagerholm 2000, Moilanen et al. 2003). Some of the losses of BCVA in long-term studies were reported to be secondary to ocular pathologies instead of postoperative complications. PRK studies have previously demonstrated that stability tends to be reached in the first 6-12 months (Klyce and Smolek 1993, Kremer and Dufek 1995, Pallikaris and Siganos 1994). A positive correlation has been found between regression and high myopic attempted correction (Rajan et al. 2004, Seiler and McDonnell 1995, Steinert and Bafna 1998, Stephenson et al. 1998), and inverse correlation with age (Rajan et al. 2004, Stephenson et al. 1998). The highest myopic regression reported in PRK studies was 1.60 D (Amano and Shimizu 1995). In long-term studies no significant difference was found in change of MRSE at one, six, and 12 year follow-up (Rajan et al. 2004). However, a slight but continuous myopic regression has been reported in all other long-term follow-up studies (Alio et al. 2008a, Alio et al. 2008b, Bricola et al. 2009, Honda et al. 2004, Kim et al. 1997, Koshimizu et al. 2010, Pietila et al. 2004, Shojaei et al. 2009, Stephenson et al. 1998).
Table 1 Postoperative outcomes of myopic long-term PRK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (Eyes)</th>
<th>Male/Female</th>
<th>Mean Age (Range) (Y)</th>
<th>Follow-up Period (Y)</th>
<th>Range of Pre-operative myopic MRSE</th>
<th>UCVA ≥ 20/40 (%)</th>
<th>MRSE Within ±1.0 D (%)</th>
<th>Loss of 2 or More Lines of BCVA (%)</th>
<th>Mean Myopic Regression (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pietila et al. 2004</td>
<td>69</td>
<td>30/39</td>
<td>31 (19–54)</td>
<td>8</td>
<td>≤6.0</td>
<td>78.3</td>
<td>78.3</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>O'Connor et al. 2006</td>
<td>58</td>
<td>18/21</td>
<td>32 (20–54)</td>
<td>12</td>
<td>1.8–7.3</td>
<td>91.3</td>
<td>81.1</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Honda et al. 2004</td>
<td>15</td>
<td>7/1</td>
<td>29 (20–42)</td>
<td>5</td>
<td>3.0 – 9.0</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>0.9</td>
</tr>
<tr>
<td>Kim et al. 1997</td>
<td>201</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
<td>2.3–12.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Koshimizu et al. 2010</td>
<td>42</td>
<td>13/16</td>
<td>33.4 (21–60)</td>
<td>10</td>
<td>2.5-14.1</td>
<td>81</td>
<td>55</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Alio et al. 2008a</td>
<td>225</td>
<td>72/66</td>
<td>30.1 (17–66)</td>
<td>10</td>
<td>1.0-5.9</td>
<td>77</td>
<td>75</td>
<td>3.1</td>
<td>0.2</td>
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<tr>
<td>Alio et al. 2008d</td>
<td>267</td>
<td>89/192</td>
<td>32.1 (8 - 66)</td>
<td>10</td>
<td>6.0-17.8</td>
<td>63</td>
<td>58</td>
<td>11.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Rajan et al. 2004</td>
<td>118</td>
<td>NR</td>
<td>46 (34-70)</td>
<td>12</td>
<td>2.0 -7.0</td>
<td>NA</td>
<td>34</td>
<td>1.4</td>
<td>0.3 (30-40 Y) 0.1 (40- 50 Y) 0.2 (50- 60 Y)</td>
</tr>
<tr>
<td>Shojai et al. 2009</td>
<td>194</td>
<td>69/38</td>
<td>33.4 (20-58)</td>
<td>8</td>
<td>4.7-14.5</td>
<td>73.1</td>
<td>79.3</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Stephenson et al. 1998</td>
<td>83</td>
<td>NR</td>
<td>NR (27-63)</td>
<td>6</td>
<td>1.5-17.5</td>
<td>91 – 0*</td>
<td>Range (91-50)</td>
<td>3</td>
<td>Higher in higher correction.</td>
</tr>
</tbody>
</table>

- NR: not reported
- * Values changed with increase of correction
2.6.2 LASIK outcomes

Although LASIK is the most common laser refractive surgery currently performed in the world, long-term studies are scarce. LASIK short-term studies (Bahar et al. 2007, Kawesch and Kezirian 2000, Lindbohm et al. 2009, Lyle and Jin 2001, Magallanes et al. 2001, Maldonado-Bas and Onnis 1998, Neeracher et al. 2004, Rashad 1999, Salchow et al. 1998, Sugar et al. 2002) have shown that the procedure is effective and predictable in terms of obtaining good UCVA and that it is also safe with minimal loss of visual acuity.

In terms of efficacy, short-term follow-up studies have reported that about 95% of eyes reached UCVA ≥20/50 (logMAR 0.4) when attempted myopic correction was less than ≤7 D. However, this value tends to decline when attempted corrections are higher (Ang et al. 2009, Sakimoto et al. 2006). Predictability of MRSE within ± 1.00 D was reported in about 95% of eyes with attempted correction less than 6 D, and this decreased to 80-85% with higher corrections (Sakimoto et al. 2006). Safety after LASIK with loss of 2 or more lines of BCVA has been reported to be ~ one % for low-moderate and high corrections. Regression up to 1.00 D in high corrections has been found post-LASIK (Kawesch and Kezirian 2000).

Long-term studies (Table 2) with a follow-up longer than five years (Alio et al. 2008c, Alio et al. 2008d, Kato et al. 2008, Kymionis et al. 2007, Liu et al. 2008, O'Doherty et al. 2006, Sekundo et al. 2003) after LASIK have focused on high corrections, with modest results. One of these reports (Alio et al. 2008d) have studied postoperative outcomes in eyes with less than 10 D corrections and reported that 90% of eyes were within UCVA ≥20/50 and MRSE within ±1.00 D in 75% of eyes at 10 years. Loss of lines of BCVA seems to be around three %, but its rose to a very alarming 27% when high corrections were analysed (Kymionis et al. 2007).

Stability at long-term is reached at around 3 months after surgery. A faster regression in the first two years followed by a slower rate of regression has been reported (Alio et al. 2008d, Liu et al. 2008, O'Doherty et al. 2006).

2.6.3 Comparison of myopic outcomes after PRK and LASIK

Several studies have compared PRK and LASIK outcomes at least one year after surgery (el Danasoury et al. 1999, El-Maghraby et al. 1999, Helmy et al. 1996, Wang et al. 1997). In low-to-moderate attempted corrections (≤6. 00 D) efficacy and safety were similar, yet stability was reported to be better after LASIK than after PRK. In corrections over 6.00 D efficacy, safety and stability were superior in LASIK. In a recent editorial Waring GO (Waring 2008) compared the long-term results of PRK and LASIK (Waring 2008) closer to today’s criteria (≤ than 6.00 and 10.00 D for PRK and LASIK respectively) and concluded that PRK showed more regression and loss of lines of BCVA than LASIK.
Table 2 Postoperative outcomes of myopic long-term LASIK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (Eyes)</th>
<th>Male/Female N</th>
<th>Mean Age (Range) (Y)</th>
<th>Follow-up Period (Y)</th>
<th>Range of Pre-operative MRSE (D)</th>
<th>UCVA ≥20/50 (%)</th>
<th>MRSE Within ±1.0 D (%)</th>
<th>Loss of 2 or more Lines of BCVA (%)</th>
<th>Mean Myopic Regression (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Doherty et al. 2006</td>
<td>90</td>
<td>26/23</td>
<td>39 (NR)</td>
<td>5</td>
<td>1.5–13.0</td>
<td>89</td>
<td>83</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Alio et al. 2008c</td>
<td>196</td>
<td>52/66</td>
<td>32.9 (18 -58)</td>
<td>10</td>
<td>10 - 24</td>
<td>40</td>
<td>42</td>
<td>5</td>
<td>1.61</td>
</tr>
<tr>
<td>Alio et al. 2008d</td>
<td>97</td>
<td>33/36</td>
<td>33.2 (17 - 57)</td>
<td>10</td>
<td>&lt; 10</td>
<td>90</td>
<td>73</td>
<td>3</td>
<td>0.91</td>
</tr>
<tr>
<td>Kato et al. 2008</td>
<td>779</td>
<td>221/181</td>
<td>34.6 (NR)</td>
<td>5</td>
<td>0.7-14.5</td>
<td>NR</td>
<td>90</td>
<td>1.3</td>
<td>NR</td>
</tr>
<tr>
<td>Sekundo et al. 2003</td>
<td>33</td>
<td>NR</td>
<td>39.9 (28 - 59)</td>
<td>6</td>
<td>5.3 - 17.5</td>
<td>33</td>
<td>46</td>
<td>15</td>
<td>0.6</td>
</tr>
<tr>
<td>Kymionis et al. 2007</td>
<td>11</td>
<td>2/5</td>
<td>41.7 (34 - 50)</td>
<td>11</td>
<td>10.0 -19.0</td>
<td>46</td>
<td>55</td>
<td>27</td>
<td>NR</td>
</tr>
<tr>
<td>Liu et al. 2008</td>
<td>104</td>
<td>60/44</td>
<td>NR (22 – 41)</td>
<td>7</td>
<td>3.3-15.2</td>
<td>100</td>
<td>90</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- NR: Not reported
2.7 PRK AND LASIK COMPLICATIONS


Under and overcorrections and regression

The most common complications after laser refractive surgery are under- and overcorrections, with different prevalence among published studies (Alio et al. 2008a, Alio et al. 2008b, Alio et al. 2008c, Alio et al. 2008d, Bricola et al. 2009, Honda et al. 2004, Kato et al. 2008, Kim et al. 1997, Koshimizu et al. 2010, Kymionis et al. 2007, Liu et al. 2008, O'Doherty et al. 2006, Pietila et al. 2004, Rajan et al. 2004, Sekundo et al. 2003, Shojaei et al. 2009, Stephenson et al. 1998). In general after PRK, eyes tend to be slightly overcorrected soon after the operation, but the refraction stabilizes three to six months after surgery. Regression after PRK has been attributed to the differential changes in corneal thickness related to epithelial hyperplasia (Gauthier et al. 1996) and stromal remodelling (Moller-Pedersen et al. 2000) and may even continue up to five to ten years after PRK (Alio et al. 2008a, Alio et al. 2008b, Kim et al. 1997). Resynthesis of ECM by activated fibroblasts and altered keratocytes (Moller-Pedersen et al. 2000) appears to compensate the photoablated tissue at the anterior stroma leading to corneal re-steepening. Regression after LASIK seems to be secondary to an increase in the central epithelial hyperplasia leading to an increase in central thickness of the cornea (Chayet et al. 1998, Moilanen et al. 2008). A faster regression in the first two years followed by a slower rate of regression even ten years after LASIK has been reported (Alio et al. 2008d, Liu et al. 2008, O'Doherty et al. 2006). Various preoperative ocular factors, such as refraction, keratometric values, size of optic zone and age have been associated with LASIK regression (Chen et al. 2007).
**Glare, halos, and contrast sensitivity**
Many studies have reported glare, halos, and impaired contrast sensitivity after laser refractive surgery, especially for correction of high myopia (Ambrosio et al. 1994, Holladay et al. 1999, Mutyala et al. 2000, Vetrugno et al. 2000). These complaints have been associated with large pupils and small ablation zones with abrupt transition areas. Increase of ablation zones and transition edges zones have alleviated most of the complaints, but not in all cases. Visual effect of glare, halos and reduction in contrast sensitivity may also arise from changes in the shape and corneal aberration structure induced by the laser (Holladay et al. 1999). Postoperatively the cornea becomes oblate (flat in the centre with steepening at the periphery) increasing the incidence of postoperative HOA (Endl et al. 2001, Holladay et al. 1999, Martinez et al. 1998, Oshika et al. 2006, Perez-Santonja et al. 1998).

**Decentration**
Although current active eye-tracking systems have reduced the incidence of decentration misalignment of the laser over the patient’s entrance pupil or eye movement may result in decentration. According to earlier reports (Cavanaugh et al. 1993, Wilson et al. 1991), ablations centred on the entrance pupil centre are more accurate than those centred on the corneal vertex. Eccentric ablation may induce irregular astigmatism, glare, monocular diplopia, decreased contrast sensitivity, or even impaired visual acuity.

**Central islands**
Central islands can occur after either PRK or LASIK. Central islands are characterized by circular or oval area of greater topographic power within an area of reduced corneal power, usually localized centrally. Compared to LASIK, PRK is more prone to this complication (Krueger et al. 1996), but most of them tend to resolve spontaneously within 6 months (McGhee and Bryce 1996). LASIK, by contrast shows a small incidence of central island, however at 6 months may persist in a relatively high percentage of cases (Kang et al. 2000). The hypothesis about the nature of central islands includes different levels of corneal hydration in the centre and the periphery of the ablated zone (Dougherty et al. 1994, Oshika et al. 1998), or blockage of the laser beam by the ejected vortex plume and particulate debris generated during surgery (Noack et al. 1997). Nowadays, with the development of technology, the incidence of central islands is low.

**Pain**
Pain has been one of the major complaints post-PRK, and also one of the greatest advantages of LASIK over PRK. Pain usually intensifies in the first 24 hours after PRK followed by less intense discomfort abating as re-epitelization progresses, yet it may persist for weeks or months after surgery (McCarty et al. 1996b, Stein et al. 1994). Gallar et al. (Gallar et al. 2007) showed that post-PRK pain may be attributable to the direct injury of the nerve and the subsequent enhanced spontaneous activity developed by injured nerve fibres. Less importantly, the release of endogenous mediators may contribute to the maintenance of ongoing activity at the cut nerve fibres of the injured area.
**Dry eye**

Dry eye is one of the most common complications after refractive surgery (Hong and Kim 1997, Sugar et al. 2002), being more often reported after LASIK than after PRK (De Paiva et al. 2006). Impairment in the ocular surface-lacrimal gland unit seems to be the origin. It is believed that transection of corneal nerves by the microkeratome is the main cause, besides the nerve damage caused by the excimer laser. Other possible causes have been attributed to alterations in the distribution of the tear film secondary to changes in the corneal shape and the relation with the ocular surface to the upper lid. In addition, it seems that post-LASIK dry eye represents a neurotrophic neuropathy most probably secondary to aberrantly regenerated corneal nerves rather than a real dry eye syndrome (De Paiva et al. 2006).

**Scarring**

Postoperative superficial stromal opacification (haze) is a common finding after PRK. Haze appears to be the effect of an enhanced cellular reflection by activated keratocytes (Moller-Pedersen et al. 2000) and the subsequent synthesis of ECM (Moller-Pedersen et al. 1998).

Haze after PRK begins during the first month postoperatively, peaks between the second and third months (Corbett et al. 1996), and decreases by six months to one year. Long-term follow-up studies have shown that induced haze may continue to disappear even after the first postoperative year (Rajan et al. 2004, Stephenson et al. 1998). Haze after LASIK is uncommon, and seems to be confined to the flap edges.

**Flap striae and interface debris**

Flap striae are classified into macro- and microstriae. Macrostriae are easily detected by retroillumination as parallel straight lines and are the results of flap dislocation. Microfolds are more common (Vesaluoma et al. 2000a), and seem to be related to the flap setting. The impact of microstriae on visual performance appears to be minimal, especially when they lie outside the pupil axis. Nevertheless, if they lie over the pupil or macrostriae coexist, they may induce higher-order aberrations (Pallikaris et al. 2002). In this case lifting the flap as soon as possible is indicated (Ambrosio and Wilson 2001, Linna et al. 2000b, Sugar et al. 2002). The presence of particles in the interface after LASIK is common, even with aggressive irrigation. An in vivo confocal microscope study revealed interface debrides in 100% of eyes 3 days after LASIK, which then decrease over time (Vesaluoma et al. 2000a). The particles presumably include cells, cell fragments (apoptotic bodies), debris, salt and metallic and plastic particles (Ivarsen et al. 2004, Perez-Gomez and Efron 2003). Strangely enough, the use of FS has not decreased the incidence of interface debris after flap creation (Ramirez et al. 2007).

**Button hole**

Button hole, free caps, or incomplete flaps may be the result of either inadequate suction, excessively steep cornea (K>47 D), or a damaged blade. Other possible aetiologies include small eyes and deep eye sockets. A buttonhole occurs when the microkeratome blade runs more superficial than intended (Davis et al. 2000, Melki and Azar 2001). The
formation of an epithelial defect allows epithelial–stromal interaction and facilitates scar formation (Li and Tseng 1995, Wilson 2001). As a result, these corneas show a variable degree of subepithelial haze and irregular astigmatism.

**Epithelial ingrowth**

Epithelial cells may grow in the flap interface after LASIK. Usually the cells are located at the periphery, at the flap edge, and do not progress toward the centre of the cornea (Davis et al. 2000, Melki and Azar 2001). The condition may also lead to flap melt (Alio et al. 2000, Holland et al. 2000, Vesaluoma et al. 2000b), when the cells block the diffusion of aqueous humour and compromise flap nutrition. The areas involved in epithelial ingrowths show keratocyte activation, which is probably associated with the expression of proteolytic enzyme cascades (Ambrosio and Wilson 2001) which may also contribute to the melting of the flap. The epithelial tissue under the flap needs to be removed if the melt progresses (Ambrosio and Wilson 2001, Holland et al. 2000, Sugar et al. 2002).

**Corneal infections and inflammation**

Incidence of microbial keratitis has been reported only after LASIK and occurred in 0-0.16% of eyes (Lin and Maloney 1999). The pathogen in post-LASIK keratitis was most often *staphylococcus aureus* (Quiros et al. 1999, Rubinfeld and Negvesky 2001, Solomon et al. 2007). Other bacterial pathogens and fungal species have, however, been reported (Hamam et al. 2006, Moshirfar et al. 2007, Pache et al. 2003). The presence of bacterial ulcer on the LASIK flap is also rare (Chung et al. 2000, Lindbohm et al. 2005, Quiros et al. 1999, Rubinfeld and Negvesky 2001). The usual approach includes treatment with topical antibiotics and, if necessary, by lifting the flap and cleaning and rinsing the wound surfaces, or occasionally, in case of serious melt, by removal of the flap. DLK is a syndrome characterized by the appearance of diffuse white opacities at the LASIK flap interface in an inflamed cornea in the first week after refractive correction (Smith and Maloney 1998). The presence of a fine granular infiltrate in the interface periphery that looks like dust is the initial presentation. In 2000, Linebarger (Linebarger et al. 2000) proposed a classification based on the density and location of the corneal infiltrate. It can vary in severity from a mild self-limiting condition to severe inflammation. The aetiology of DLK is likely to be multifactorial (Johnson et al. 2001), being higher after flap creation by a FS than after flap creation with a mechanical microkeratome (Moshirfar et. al 2010).
3 AIMS OF THE STUDY

The general purpose of this study was to investigate the long-term safety, efficacy, and stability of excimer laser refractive surgery performed for myopia and/or astigmatism. To achieve this aim, we divided our study into five parts:

1. The aim of Study I was to investigate the long-term results of PRK. Differences between the two most common laser delivery systems used in excimer laser were also evaluated.

2. In Study II, we investigated the long-term results, subjective parameters, and late sequels of LASIK.

3. Study III aimed to reveal possible differences and complications when moderate-to-high astigmatism was corrected with PRK or LASIK.

4. The purpose of Study IV was to demonstrate the presence of irregular astigmatism, which may depend exclusively upon the corneal epithelium.

5. The aim of Study V was to evaluate the role of corneal nerve recovery in corneal wound healing in eyes previously treated by LASIK and enhanced by PRK.
4 PATIENTS AND METHODS

4.1 PATIENTS

The studies were carried out according to the tenets of the Helsinki Declaration and approved by the Ethical Review Committee of the Helsinki University Eye Hospital. Studies I, III, IV, V were retrospective studies, patients included in Study II attended a postoperative control seven to eight years after surgery. All patients and controls gave informed consent to their information being used in clinical studies. The patient demographics included in studies I–V is given in Table 3.

Table 3 Preoperative demographic of patients enrolled in Studies I-V

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients n</th>
<th>Eyes n</th>
<th>Female/ Male Eyes n</th>
<th>Patients age (mean ± SD)</th>
<th>Laser procedure</th>
<th>Mean MRSE</th>
<th>Follow-up (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>46</td>
<td>61</td>
<td>24/37</td>
<td>28.5 ± 6.5</td>
<td>PRK</td>
<td>-4.3 ± 1.5</td>
<td>8.3 -12.2 y</td>
</tr>
<tr>
<td>Study II</td>
<td>21</td>
<td>38</td>
<td>20/18</td>
<td>30 ± 6.8</td>
<td>LASIK</td>
<td>-6.8 ± 1.7</td>
<td>6.7 – 8.2 y</td>
</tr>
<tr>
<td>Study III</td>
<td>60</td>
<td>74</td>
<td>51/23</td>
<td>34.8 ± 9.7</td>
<td>PRK/ LASIK</td>
<td>-5.4 ± 2.4</td>
<td>1 y</td>
</tr>
<tr>
<td>Study IV</td>
<td>9</td>
<td>11</td>
<td>5/6</td>
<td>47.2 ± 8.9</td>
<td>PTK/PRK</td>
<td>-1.9 ± 1.9</td>
<td>15 -1704 d</td>
</tr>
<tr>
<td>Study V</td>
<td>7</td>
<td>7</td>
<td>6/1</td>
<td>35 ± 10</td>
<td>PRK</td>
<td>-6.5 ± 3.2</td>
<td>7 -29 m</td>
</tr>
</tbody>
</table>

- d: Day; m: Month; y: Year
4.2 PROTOCOLS

The patients included in study I, II and III were recruited from a private clinic, Silmäkeskus Laser, in Helsinki, Finland. The patients included in Study IV and V belonged to a group of patients referred to Helsinki University Eye Hospital by other hospitals throughout the country or by private ophthalmologists.

All patients were examined preoperatively and at the follow-up time stipulated in each study. UCVA, BCVA (logMAR scale), manifest refraction, corneal pachymetry, and VK were performed before excimer laser treatment. Exclusion criteria were immunocompromised patients, patients with uncontrolled uveitis, blepharitis, or any condition apart from their corneal pathology that could affect corneal healing. Postoperative control in all the studies included biomicroscopy, UCVA, BCVA, and manifest refraction. Study II additionally included a questionnaire to measure patient satisfaction after LASIK and a wavefront analysis. Study III included non-vector and vector analysis as described by Eydelman et al. (Eydelman et al. 2006) at each visit. In Study IV we studied pre- and postoperative VK.

4.3 METHODS

4.3.1 PRK/LASIK preoperative therapy

The pre-postoperative medical therapy included either Ofloxacin (Exocin®, Allergan, Irvine, CA, USA) or Levofloxacin (Oftaquix®, Santen, Tampere, Finland) ophthalmic drops started the night before excimer laser and continued for a week 4 times a day. A drop of ketorolac tromethamine ophthalmic solution (Acular®, Allergan, Irvine, CA, USA) or alternatively diclofenac sodium 0.1% (Voltaren® Ophtha, Novartis, Basel, Switzerland) was used before the procedure. All patients received 25 mgs of oral diclofenac sodium (Voltaren®, Novartis, Basel, Switzerland) 30 minutes before the operation. Oral diazepam (5–10 mg; Diapan®, Orion, Helsinki, Finland) was prescribed for the first postoperative night. Prior to surgery the eyes were anaesthetized with topical 0.4% oxibuprocaine hydrochloride (Oftan Obucain®; Santen, Tampere, Finland).

4.3.2 PTK procedure

After scraping of the whole corneal epithelium except 0.5 – 1.0 mm from the limbus, PTK was performed on the debridement area. The PTK procedure was performed with a 6 mm central ring, 2 µm depth and 3 mm overlapping peripheral rings (6 – 8) covering the whole cornea. No masking agents were used.
4.3.3 PRK procedure

Laser ablation diameter was between 5.0 and 6.5 mm. The laser delivery system and software are described in detail in each study. Mechanical debridment of the epithelium with a Beaver eye blade (Becton Dickinson, Franklin Lakes, NJ, USA) was performed on the eyes included in Studies I, III and IV. Transepithelial ablation was performed on all eyes included in Study IV. Epithelial ablation was performed with a 6-mm central ring, 2-µm depth, and 3-mm overlapping peripheral rings (six to eight) covering the whole cornea with the same laser used for the PRK treatment.

4.3.4 LASIK procedure

The flap was created using a Hansatome microkeratome (Bausch and Lomb Surgical, Inc., San Dimas, CA). A superior hinge technique without suture was used (intended parameters were: thickness 160 µm, diameter 8.5 or 9.5 mm). Laser ablations data are given in each study. A balanced salt solution (BSS, Alcon Laboratories Inc., Fort Worth, TX, USA) was used to irrigate the cornea before and after the flap formation and after photoablation.

4.3.5 PTK/PRK postoperative therapy

Immediately after the procedure a soft contact lens (CL) was placed over the cornea for three days. After removal of the CL, chloramphenicol ointment (Oftan Chlora®, Santen, Tampere, Finland) was applied three times daily for three days and, subsequently, for three nights. Fluoromethalone 0.1% drops (Liquifilm-FML®, 1 mg/ml. Allergan Inc., Irvine, CA) starting on the fourth postoperative day, three times a day for the first two weeks, reduced to twice daily for the next two months and the tapered off by the third month. Carbomer eye gel (Viscotears®, Novartis, Bagel, Switzerland) for at least one month was also used. Diclofenac sodium (25 mg) 2 – 3 times a day for the first days was used to alleviate postoperative pain. Mitomycin C was not used.

4.3.6 LASIK postoperative therapy

After the operation a soft CL was placed over the cornea for the first night and topical Ofloxacin (Exocin®, Allergan, Irvine, CA, USA) twice a day was initiated. Fluoromethalone 0.1% drops twice a day (Liquifilm-FML®, 1 mg/ml. Allergan Inc., Irvine, CA) were initiated once the CL was removed and continued for one week. In addition artificial tears (Oculac®, povidone) were used for three months.
4.3.7 Study subjects

4.3.7.1 Study I. Longer-term PRK results

The study included 61 PRK patients undergoing myopic or myopic astigmatism correction. Inclusion criteria for this study were preoperative myopic spherical refractive correction between -1.25 and -7.00 diopter (D) and myopic astigmatism lower than -2.50 D. UCVA, BCVA, and manifest refraction at preoperative and at three months and at least eight years were collected. Twenty-seven excimer laser ablations were done with a broad beam laser (VISX (VISX Star VISX; Santa Ana, CA, USA) equipped with 2.5 software) and 34 eyes with a scanning-slit laser (Nidek (NIDEK EC-5000, Nidek Technologies, Gamagory, Japan)). To ensure that the sample size was enough to detect significant differences between both delivery systems a retrospective power analysis was performed.

4.3.7.2 Study II. Longer-term LASIK results

The charts of 101 patients who underwent LASIK between 1999 and 2000 in a private clinic were located. These patients were invited to a free-of-charge ophthalmological examination seven to eight years after the surgery. Twenty-one patients (38 eyes) attended the follow-up. Laser ablations were done with the excimer laser (VISX Star (36 eyes) and Star2 (2 eyes), VISX; Santa Ana, CA, USA) equipped with 2.5 or 3.1 software. Preoperative examination included ophthalmological examination, UCVA, BSCVA, manifest refraction, US and VK. At each control UCVA, BCVA, and manifest refraction were assessed. At the last follow-up an additional questionnaire was administered and WF analysis (version 2.0 software; iTrace Technologies, Houston, Tex, USA) was performed.

4.3.7.3 Study III. Correction of regular astigmatism

A retrospective study that included 44 eyes treated with PRK and 30 eyes with LASIK. The inclusion criterion for this study was astigmatism >2.0 D. PRK treatments were performed with NIDEK EC-5000 (18 eyes), Visx 20/20 (5 eyes), Visx Star (4 eyes), Visx Star S2 (14 eyes) and Visx Star S4 (3 eyes). LASIK treatments were performed with Visx 20/20 (1), Star (1), Star S2 (22) and Star S4 (6). Follow-up included a visit at six and twelve months. Non-vector and vector analyses were performed at each visit. Vector analysis estimates the surgically induced refraction correction (SIRC), the error vector (EV), the axis shift (AS), the normalized error vector (NEV), the error ratio (ER), the correction ratio (CR), the error of magnitude (EM), the error of angle (EA) and the treatment error vector (TEV). Briefly, the SIRC vector is the vector difference between the pre- and postoperative astigmatism correction vectors, and corresponds to the correction
achieved. The EV is the vector difference between the intended refraction correction (IRC) and the SIRC. NEV is equal to EV, in magnitude, but it is rotated to allow easy visualization in the graphs. AS corresponds to the angular difference between the post- and preoperative manifest cylinder axes. ER is the proportion of the intended correction that was unsuccessfully treated. CR is the ratio of the correction magnitude achieved to the required correction. EM corresponds to the arithmetical difference in the magnitudes between SIRC and IRC, zero being the ideal result. EA measures whether the treatment was applied at the correct axis and TEV represents the magnitude of EM and the angle of EA containing both aspects of treatment error.

4.3.7.4 Study IV. Correction of irregular astigmatism

In Study IV, 11 eyes of 9 patients referred to the Helsinki Eye Hospital with diagnose of map-dot-fingerprint dystrophy and irregular astigmatism that did not respond to medical therapy were included. Our goal in this study was to call attention to the presence of irregular astigmatism, which may depend exclusively upon the corneal epithelium. Pre- and postoperative examination included ophthalmological examination, UCVA, BSCVA, manifest refraction and VK. Irregular astigmatism was assessed by VK according to the classification of Bogan et al. (Bogan et al. 1990) Irregular astigmatism was classified into two groups based on the possibility to define steep or flattened areas in the central and peripheral zones of the VK. The central zone was defined as an area of 3 mm. Group 1 had a VK with easily identifiable steep or flat areas and was divided into five basic types: Central elevation, central flat area, eccentric elevation, eccentric flat area and mixed. Group 2 had irregular astigmatism without pattern.

4.3.7.5 Study V. PRK enhancement

Seven eyes of seven patients who had had previous LASIK for myopia were retreated at least 2 years later by PRK. Inclusion criteria for PRK were flap-related complications during initial LASIK or strong adherences of the flap that prevented flap-lift retreatment. All eyes received transepithelial PTK/PRK using the Visx S4 excimer laser (Visx Co, Sunnyvale CA, USA). PRK treatment was limited to the flap thickness in order to preserve the residual stroma. On follow-up visits complete eye examination was performed. The postoperative corneal haze was graded subjectively during slit-lamp examination using the clinical grading scale (0+ to 4+) by Fantes (Fantes et al. 1990).

4.3.8 Statistical methods

In Studies I and III statistical analysis of paired outcomes was performed with the Mann-Whitney test for nonparametric comparison and one-way analysis of variance for repeated measures with the Bonferroni multiple comparison adjustment. The Kruskal-Wallis test
with the post hoc Dunn multiple comparison was used to test for equality between the broad-beam group and the scanning-slit group (GraphPad Prism, version 4.03 for Windows, GraphPad Software). In Study II, statistical calculations were performed with Statview (version 5.0.1; SAS Institute Inc, Cary, NC) using analysis of variance with Bonferroni adjustment for repeated measures and non-paired t test.

In Study IV, pre- and postoperative levels of BSCVA were compared with Wilcoxon signed rank t test (SPSS version 6.0; SPSS, Chicago, Ill). A P value less than 0.05 was considered statistically significant.
5 RESULTS

5.1 STUDY I AND II (PRK and LASIK long-term follow-up)

Studies I and II measured the long-term postoperative results after PRK and LASIK. Details on patients demographics are given in Table 4.

Table 4 Patients’ preoperative characteristic before PRK and LASIK

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PRK VISX</th>
<th>PRK Nidek</th>
<th>LASIK VISX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>27</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>10.3±0.7</td>
<td>9.8±0.4</td>
<td>7.5 ± 0.4</td>
</tr>
<tr>
<td>Mean age (y ± SD)</td>
<td>28±5</td>
<td>28 ± 9</td>
<td>30 ± 6.8</td>
</tr>
<tr>
<td>Men/Women</td>
<td>12/15</td>
<td>12/22</td>
<td>20/18</td>
</tr>
<tr>
<td>Right/left eye</td>
<td>14/13</td>
<td>18/16</td>
<td>20/18</td>
</tr>
<tr>
<td>Sphere (D ± SD)</td>
<td>-4.3 ± 1.7</td>
<td>-3.9 ± 1.5</td>
<td>-6.5 ± 1.7</td>
</tr>
<tr>
<td>Range of myopic Sphere(D)</td>
<td>1.25 - 7</td>
<td>1.25 - 7</td>
<td>3.25 - 11</td>
</tr>
<tr>
<td>Cyl (D ± SD)</td>
<td>-0.4 ± 0.4</td>
<td>-0.5 ± 0.6</td>
<td>-0.63 ± 0.5</td>
</tr>
<tr>
<td>Range of myopic cylinder</td>
<td>0 - 1.5</td>
<td>0 - 2.5</td>
<td>0 - 2.3</td>
</tr>
<tr>
<td>MRSE (D ± SD)</td>
<td>-4.5±1.6</td>
<td>-4.2±1.6</td>
<td>-6.8 ± 1.7</td>
</tr>
<tr>
<td>UCVA (mean ± SD)</td>
<td>2.8 ± 0.6</td>
<td>2.7 ± 0.7</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>BCVA (mean ± SD)</td>
<td>-0.1±0.1</td>
<td>0.0±0.0</td>
<td>0.0 ± 0.1</td>
</tr>
</tbody>
</table>

Efficacy:

PRK

UCVA ≤0.0 was achieved postoperatively in 74% and 62% of the eyes at three months, and at last follow-up these values were 55% and 65% after VISX and Nidek, respectively. UCVA ≤0.5 was achieved postoperatively in 100% of the eyes at three months and at last follow-up in both PRK groups. MRSE within ±0.5 D was found in 85% and 59% at three months after VISX and Nidek, respectively. At the last follow-up MRSE within ±0.5 D was found in 48% of the VISX treated eyes and 73% of the Nidek treated eyes. Ninety-three percent of VISX eyes and 85% of the Nidek eyes were within ±1.0 D of MRSE at three months and 85% (both groups) were within ±1.0 D at last follow-up.
LASIK

UCVA \leq 0.0 was achieved postoperatively in 55% of the eyes at two months, 54% at two years, and 29% at the last follow-up (seven to eight years). UCVA \leq 0.5 was achieved postoperatively in 100% of the eyes at two months, 97% at two years, and 87% at the last follow-up. This decrease in UCVA was statistically significant. At two months 75% of the eyes were within ±0.5 D and 83% of the eyes were within ±1.0 D of the MRSE. After two years these values were 63% and 83% respectively. At seven to eight years 34% of the eyes were within ±0.5 D and 42% were within ±1.0 D of the MRSE.

PRK VISX vs. LASIK VISX

Intended correction was significantly higher in LASIK eyes that in PRK eyes (p<0.001). Postoperatively UCVA was significantly better after PRK than after LASIK (p<0.05), and a higher percentage of eyes achieved an UCVA \leq 0.0 and \leq 0.5 after PRK than after LASIK. This difference could be explained by the higher correction after LASIK. However, in terms of MRSE at follow-up no significant differences were found between PRK and LASIK. The efficacy of refractive treatments is given in Table 5.

Table 5 Efficacy postoperative values after PRK (VISX and Nidek) and LASIK (VISX)

<table>
<thead>
<tr>
<th></th>
<th>PRK VISX</th>
<th>PRK Nidek</th>
<th>LASIK VISX</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCVA \leq 0.0</td>
<td>55%</td>
<td>65%</td>
<td>29%</td>
</tr>
<tr>
<td>UCVA \leq 0.5</td>
<td>100%</td>
<td>100%</td>
<td>87%</td>
</tr>
<tr>
<td>MRSE ±0.50 D</td>
<td>48%</td>
<td>73%</td>
<td>34%</td>
</tr>
<tr>
<td>MRSE ±1.00 D</td>
<td>85%</td>
<td>85%</td>
<td>42%</td>
</tr>
</tbody>
</table>
Safety

PRK

In terms of loss/gain of visual acuity, 59% of the eyes in the VISX group at three months maintained the preoperative BCVA, 30% gained one line, and 11% lost one line. At the last follow-up 56% showed no changes in lines of BCVA and 22% showed increase of one line and four % two lines; 19% lost one line. In the Nidek group, 68% of the eyes at three months maintained the preoperative BCVA, 24% gained one line, six % gained two lines, and three % lost one line. At the last follow-up 71% showed no changes in BCVA and 15% showed an increase of one line and three % two lines; 12% lost one line. There was no difference between groups in terms of gain or loss of BCVA.

At the last follow-up, the mean BCVA was 0.0±0.1 (range 0.0 – -0.2) for both VISX and Nidek groups. Compared to preoperative BCVA, no significant differences were found at three months or at last follow-up in either group or between groups (p>0.05). Postoperatively, in the VISX group BCVA ≤0.0 was obtained in 96%, and 100% of the eyes at three months and at last follow-up respectively. In the Nidek group BCVA ≤0.0 was obtained in 100% at three months and in 97% of the eyes at last follow-up.

LASIK

After two years 57% showed no changes in pre-LASIK BCVA and 32% showed an increase of one to two lines. Six % lost one line and six % lost to two lines. At last follow-up 42% of the eyes preserved the pre-LASIK BCVA, 34% gained one line and 18% lost one line and five % lost two lines. Postoperatively, at two years the mean BCVA was 0.0 ± 0.0 (range 0.0 - -0.2), and at the last follow-up was 0.0 ± 0.0 (range -0.1 - 0.2).

PRK VISX vs. LASIK VISX

BCVA ≤0.0 was obtained in 89% of the eyes after LASIK and in 100% of the eyes after PRK at the last follow-up. No significant differences were found between LASIK and PRK (p>0.05). Safety results at last follow-up after PRK and LASIK are given in Table 6.
Table 6 Safety postoperative values after PRK (VISX and Nidek) and LASIK (VISX)

<table>
<thead>
<tr>
<th></th>
<th>PRK VISX</th>
<th>PRK Nidek</th>
<th>LASIK VISX</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA ≤0.0</td>
<td>100%</td>
<td>97%</td>
<td>89%</td>
</tr>
<tr>
<td>loss of 2 or more</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>lines of BCVA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stability

PRK

Three months after PRK mean MRSE was +0.1 D for VISX and +0.5 for Nidek. At last follow-up it changed to -0.7 D after VISX and -0.4 D after Nidek. Similar myopic regression was observed for both VISX and Nidek. In order to study the rate of regression we used the mean MRSE achieved at three months and compared that to mean MRSE achieved at last visit. We found that MRSE regressed by -0.09 D per year.

LASIK

In LASIK patients at first follow-up visit (2 months after procedure) mean MRSE was -0.41 D, then at two years -0.57 D, and at seven to eight years continued to decrease to -1.38 D. Change in MRSE was not statistically significant up to two years, whereas at last follow-up MRSE was significantly smaller compared to MRSE at two months (p<0.01). In order to study the rate of regression we used the mean MRSE achieved at two months and compared that to the mean MRSE achieved at two years and seven to eight years. We found that SE regressed -0.13 D per year in the first two years. When we analysed the regression at last follow-up, it regressed -0.16 D per year.
VISX PRK VS. VISX LASIK

Postoperative stability seems to be slightly better after PRK than after LASIK. Although, preoperative Spherical Equivalent (SphEq) and Intended SphEq correction were statistically higher in eyes treated by LASIK than in eyes treated by PRK.

Figure 1 Stability values after PRK and LASIK

Patient satisfaction after LASIK

A questionnaire that included 8 questions related to postoperative satisfaction was distributed at last follow-up visit in the LASIK study. Patients were instructed to answer “yes” or “no” to the questionnaire. Response rate to the questionnaire was 86%. All respondent reported that they would have LASIK surgery again and that they considered that LASIK surgery had improved their quality of life substantially. Eighty-nine % were very satisfied with the surgery but only 55% were currently happy with their refractive status. Eleven % complained of visual performance in daylight and 39% complained of problems in dim light. Thirty-three % reported experiencing “tired eyes” in the past last month and 33% reported dry eye. Fifty-seven % did not wear corrective spectacles, 16% wore them occasionally, and 27% used spectacles for distance vision every day.
5.2 STUDIES III AND IV. Regular and irregular astigmatism

5.2.1 Regular astigmatism

In study III we evaluated the postoperative outcomes of moderate-to-high astigmatism in eyes treated by PRK and LASIK by non-vector and vector analyses.

Table 7 Patients’ preoperative characteristics before PRK and LASIK

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PRK</th>
<th>LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>6 and 12</td>
<td>6 and 12</td>
</tr>
<tr>
<td>Mean age (y ± SD)</td>
<td>36±10</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>Men/Women</td>
<td>13/23</td>
<td>6/18</td>
</tr>
<tr>
<td>Right/left eye</td>
<td>25/19</td>
<td>14/16</td>
</tr>
<tr>
<td>Sphere (D ± SD)</td>
<td>-3.6 ± 2.3</td>
<td>-5.2 ± 2.4</td>
</tr>
<tr>
<td>Range of myopic Sphere (D)</td>
<td>0.25 - 8.25</td>
<td>0 - 10</td>
</tr>
<tr>
<td>Cylinder (D ± SD)</td>
<td>-2.4 ± 0.5</td>
<td>-2.4 ± 0.4</td>
</tr>
<tr>
<td>Range of myopic Cylinder (D)</td>
<td>0 - 1.5</td>
<td>2.0 – 3.5</td>
</tr>
<tr>
<td>MRSE (D ± SD)</td>
<td>-4.9 ± 2.3</td>
<td>-6.5 ± 1.4</td>
</tr>
<tr>
<td>UCVA (mean ± SD)</td>
<td>1.8 ± 0.7</td>
<td>2 ± 0.6</td>
</tr>
<tr>
<td>BCVA (mean ± SD)</td>
<td>0.0±0.1</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

5.2.1.1 Non-vector results

PRK vs. LASIK

Efficacy

Postoperatively, UCVA was significantly better at twelve months for LASIK compared to PRK eyes ($p=0.03$). Comparison of postoperative outcomes of MRSE between PRK and LASIK at six and twelve months was not statistically significant ($p>0.05$). The percentages values of UCVA and MRSE after moderate-to-high astigmatism correction at last follow-up are given in Table 8.
Table 8 Efficacy postoperative values after PRK (VISX and Nidek) and LASIK (VISX)

<table>
<thead>
<tr>
<th></th>
<th>PRK</th>
<th>LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCVA ≤0.0</td>
<td>29%</td>
<td>57%</td>
</tr>
<tr>
<td>UCVA ≤0.5</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>MRSE ±0.50 D</td>
<td>57%</td>
<td>80%</td>
</tr>
<tr>
<td>MRSE ±1.00 D</td>
<td>80%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Safety

In terms of loss of lines of BCVA at the end of the follow-up nine and three % of the eyes after PRK and LASIK respectively lost two or more lines of BCVA. Comparative analysis at 12 months showed a higher incidence of eyes that gained one or more lines of BCVA after LASIK (66%) than after PRK (23%). Twenty-three and 10% of eyes lost one or more lines of BCVA after PRK and LASIK respectively. Comparison of postoperative outcomes of MRSE between PRK and LASIK at six and twelve months was not statistically significant (p>0.05). No eye in either group showed an increase in astigmatism >2.0 D compared to preoperative values.

Table 9 Safety non-vector postoperative values after PRK and LASIK for correction of moderate-to-high astigmatism

<table>
<thead>
<tr>
<th></th>
<th>PRK VISX</th>
<th>LASIK VISX</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA ≤0.0</td>
<td>81%</td>
<td>89%</td>
</tr>
<tr>
<td>loss of 2 or more lines of BCVA</td>
<td>11%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Stability

PRK

Mean MRSE at six months after PRK, was 0.2 ± 1.1 D (range 3.0 — -5.0) and at twelve months it was 0.1 ± 1.4 D (range 3.0 — -6.0). Stability analysis showed that between six and twelve months, 14% of eyes showed no changes in MRSE after PRK. A change less than 0.5 D was found in 66% of eyes, and a change >1.0 D was found in 14% of eyes after PRK.

LASIK

After LASIK, mean MRSE at six months was -0.3 ± 0.8 D (range 1.25 — -2.5) and at twelve months MRSE was -0.5 ± 0.8 D (range 1 — -2.5). Stability analysis showed that between six and twelve months, 13% of eyes showed no changes in MRSE after LASIK. A change less than 0.5 D was found in 83% of eyes after LASIK, all eyes were less than 1.0 D of change after LASIK.

PRK vs. LASIK

Comparison of postoperative outcomes of MRSE and defocus between PRK and LASIK at six and twelve months were not statistically significant (p>0.05).

5.2.1.2 Vector analysis

Vector analysis was performed at the corneal plane. The mean intended refractive correction (IRC) was 2.4±0.5 and 2.4±0.4 D for PRK and LASIK respectively (Fig. 2).
EV showed no significant differences between PRK and LASIK (Fig. 3).

Yet, NEV graph showed that LASIK outcomes were more accurate than those for PRK (Fig. 4).
TEV showed that PRK had more under- and overcorrection than LASIK (Fig. 5).

At 12 months, SIRC was 2.2±0.6 D for PRK and 2.3±0.5 D for LASIK, with a success index of astigmatism correction of 76% and 81% for PRK and LASIK respectively. In line with this result a small difference in correction ratio was found between PRK and LASIK. ER showed no significant differences between PRK and LASIK. EM at 12 months follow-up after PRK was 0.1±0.05 and after LASIK was 0.02±0.5. Statistically we found no differences between these parameters.
Table 10  Vector stability of cylinder at 6 and 12 months follow-up

<table>
<thead>
<tr>
<th>Magnitude of vector change in cylinder</th>
<th>PRK 6 months to 12 months</th>
<th>LASIK 6 months to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with ≤ 1.00 D of vector change</td>
<td>n/N % % CI</td>
<td>n/N % % CI</td>
</tr>
<tr>
<td>Eyes with ≤ 0.5 D of vector change</td>
<td>n/N % % CI</td>
<td>n/N % % CI</td>
</tr>
<tr>
<td>Mean magnitude ± SD of vector change</td>
<td>n/N % % CI</td>
<td>n/N % % CI</td>
</tr>
</tbody>
</table>

No significant differences were found in angle stability of the cylinder axis after PRK and LASIK, yet PRK showed a higher incidence of eyes within ≤ 15º of stability at 6 and 12 months. Analysis of vector cylinder stability, SIRC, EM, EV, CR, ER between PRK and LASIK at 6 and 12 months showed no statistically significant differences (p>0.05). The values of vector stability of cylinder at 6 and 12 months are given in Table 10.

5.2.2 Irregular astigmatism

In Study IV we evaluated the postoperative outcomes in eyes with irregular astigmatism secondary to recurrent corneal erosion due to map-dot-fingerprint dystrophy treated by PTK.

Efficacy

UCVA ≤0.0 was achieved postoperatively in four (4/11) eyes at last follow-up, the same number of eyes achieved UCVA ≤0.5 at last follow-up. MRSE within ±0.50 D was found in four eyes, and five eyes were within ±1.00 D of MRSE at last follow-up.
Safety

Nine eyes out of eleven gained lines of BCVA (one eye gained two lines, three eyes gained three lines, two eyes gained four lines and three eyes gained more than five lines). Two eyes showed no changes. The mean preoperative BCVA in the eye to be operated on was -0.18 ± 0.14 on a logarithm of the minimal angle of resolution (log MAR) scale. The mean postoperative BCVA was 0.04 ± 0.04 (log MAR). This increase in BCVA was statistically significant.

Irregular astigmatism and VK

All preoperative VK showed irregular astigmatism. However, postoperatively, all eyes showed a regular pattern. No correlation was found between the pre- and postoperative VK patterns.

5.3 STUDY V. PRK after LASIK

In study V, the mean time interval between the primary LASIK and the PRK enhancement was 45±13 months (range 27 to 61 months), and the mean follow-up time after PRK was 14±10 months (range 7 to 29 months). Prior to LASIK the mean preoperative BCVA in log MAR scale was 0.0±0.0. The initial mean preoperative MRSE of the refractive error was -6.5±3.2 diopters (D, range -2 to -9.25).

Efficacy

UCVA ≤0.0 was achieved postoperatively in three (3/7) eyes at last follow-up, seven (7/7) eyes achieved UCVA ≤0.5 at last follow-up. MRSE within ±0.50 D was found in five eyes, and six eyes were within ±1.00 D of MRSE at last follow-up.

Safety

No eye lost lines of BCVA. One eye gained three lines, one eye gained two lines, four eyes gained one line, and one eye showed no change. The mean preoperative BCVA in the eye to be operated on was -0.18 ± 0.14 on a log MAR scale. The mean postoperative BCVA was 0.04 ± 0.04 (log MAR). This increase in BCVA was statistically significant.
6 DISCUSSION

No other medical subspeciality has advanced as much as excimer laser in such a short period of time refractive surgery. Despite the large number of excimer laser refractive procedures performed around the world long-term follow-up studies have been scarce. Until 2007, the time when this project was started, just only three studies with a follow-up over 10 years had been published (Kymionis et al. 2007, O’Connor et al. 2006, Rajan et al. 2004). The lack of uniform parameters between studies made it difficult to compare results or detect the possible changes in efficacy, safety, or stability after excimer laser surgery. Furthermore, the claims made in the marketing of new methods and equipment/instruments lack strong back-up. The rapid technological progress during the course of this study might actually be a drawback since most of the lasers used in this study have undergone evolution, and new ablation profiles and nomograms are now available.

STUDIES I AND II. PRK/LASIK follow-up

PRK

Follow-up studies after PRK include 12-year (Rajan et al. 2004) and 14-year (Bricola et al. 2009) follow-up, both of them performed using the Summit UV200 excimer laser, a BB system. These studies reported PRK to be a safe procedure with stability achieved between three months to one year after the procedure and maintained in follow-up. Two others studies (Alio et al. 2008a, Shojaei et al. 2009) have reported at least eight-year long–term postoperative outcomes after PRK with the same laser delivery systems as in our report, yet neither of the studies compared different excimer laser systems.

In terms of efficacy, we found a better result in postoperative UCVA at last follow-up compared to earlier long-term studies with the same laser delivery system (Alio et al. 2008a, Shojaei et al. 2009). Our postoperative BCVA results were slightly better than other long-term results (Alio et al. 2008a, Bricola et al. 2009, O’Connor et al. 2006, Rajan et al. 2004) These results in UCVA and BCVA were independent of the delivery system used.

Compared to earlier studies, after eight years of follow-up after treatment (Shojaei et al. 2009) in a subgroup of moderate correction (≤6.0 D) 69% of eyes with a SS laser were within ±0.5 D, and 83% were within ±1.0 D of emmetropia at last follow-up. After 10 years of follow-up after treatment with a BB laser (Alio et al. 2008a) eyes with myopia <6.0 D showed that 55% of eyes were within ±0.5 D, and 75% were within ±1.0 D of emmetropia. In our series, at last follow-up the number of eyes within ±0.50 D was greater in the SS group compared to the BB group (73% vs. 48%), yet 85% of eyes were within
±1.00 D of the intended correction in both groups. No significant differences were found postoperatively between groups.

Similar results were found in lines of BCVA gained or lost when we compared delivery systems, given good safety in long-term follow-up.

Long-term studies (Alio et al. 2008a, Shojaei et al. 2009) reported that MRSE after SS (Shojaei et al. 2009) stabilized at 2 years, yet after BB (Alio et al. 2008a) seems to stabilize after five years. We found a similar myopic regression for both lasers procedures and the amount of regression in our study was similar to that in other long-term studies (Honda et al. 2004, Rajan et al. 2004).

LASIK

Although LASIK is the most common laser refractive surgery currently performed in the world (Sandoval et al. 2005) there are only four studies reporting follow-up longer than five years at the time when this study was conducted (Condon et al. 2007, Kymionis et al. 2007, O'Doherty et al. 2006, Sekundo et al. 2003) and three of them focused on results after high myopic corrections (Condon et al. 2007, Kymionis et al. 2007, Sekundo et al. 2003) and just one of them (O'Doherty et al. 2006) included all levels of myopia with an intended correction close to emmetropia. Two other studies (Alio et al. 2008c, Alio et al. 2008d) with ten-year follow-up were published after our results were published, and one of them (Alio et al. 2008c) focused on high myopia results.

The maximum FDA approved limit of correction for treating eyes by LASIK varies from one laser to another, but it is close to -12 D. We included MRSE between -3.9 and -11.5 D (mean -6.9 D); in our study, 74% of eyes were within ±0.5 D and 83% within ±1.0 D at two years. At last follow-up seven to eight years postoperatively, however, 34% of eyes were within ±0.5 D and 42% were within ±1.0 D. These results show that although refractive results after LASIK are relatively good short-term; they tend to decline over time. Compared to earlier studies (Alio et al. 2008d, O'Doherty et al. 2006) our results showed a smaller percentage of eyes within ±0.5 D or ±1.0 D at last follow-up. This finding was also evident in the percentage of eyes achieving UCVA ≥0.0 at last follow-up. Congruent with these results, myopic regression of the MRSE was noticed in our study. At two months an undercorrection of -0.41 D was found; the follow-up study showed a minimal myopic regression to -0.6 D at two years, which continued to regress to -1.4 D by the last visit. This trend toward myopic regression was noted in all eyes, but was more pronounced in eyes with preoperative MRSE >6.0 D, and also in subjects <30 years old. The incidence of myopic regression after LASIK has been attributed to both corneal and non-corneal causes. (Chayet et al. 1998, Chayet et al. 1998, Ditzen et al. 1999, Lyle and Jin 2000) It seems that eyes with greater levels of myopia tend to develop more myopia over time, probably secondary to myopia progression and/or adult-onset myopia (Jorge et al. 2007, Kinge and Midelfart 1999). Long-term follow-up studies should consider that regression may be related to changes in the axial dimensions or corneal parameters of the eye.
In terms of safety, at two years every third eye gained lines of visual acuity whereas ~one in ten eyes lost lines. Compared to two years post-operatively, the number of eyes that gained one or more lines of visual acuity slightly increased at last follow-up visit, yet the number of eyes losing lines of visual acuity doubled from two years to seven to eight years. This may be related to subclinical opacities in the lens or secondary to higher order aberrations. As in other studies (Kymionis et al. 2007, O'Doherty et al. 2006) patient satisfaction was extremely high with 100% stating that they would have LASIK surgery again.

PRK VISX vs. LASIK VISX in moderate myopia

The advantages of LASIK over PRK are faster visual recovery and less pain. However, PRK entails lower risk of operative and post-operative complications. The long-term outcomes of moderate myopic correction treated by PRK or LASIK with the VISX laser used in our studies showed no significant differences in terms of efficacy, predictability or stability. A recent study (Alio et al. 2009) compared postoperative outcomes after PRK and LASIK using the VISX 20/20 and showed that both procedures were safe with slightly better efficacy and predictability after LASIK than after PRK, yet the range of correction –6 to -10 D included in that report exceeded the accepted ranges of correction nowadays used in PRK. In light of our results we suggest that the range of correction of myopic eyes should not exceed 6.0 D with PRK.

STUDIES III AND IV. Regular and irregular astigmatism

Regular astigmatism

Earlier reports have found that PRK and LASIK results in a similar proportion of eyes postoperative with UCVA ≤ 0.3, yet a greater proportion of eyes with UCVA ≤ 0.0 has been reported found after LASIK than after PRK (El-Maghraby et al. 1999, Steinert and Hersh 1998, Van Gelder et al. 2002). Our findings showed that compared to PRK LASIK yielded not only better results in UCVA ≤ 0.0 but also in terms of UCVA ≤ 0.3 at six and twelve months postoperatively when high astigmatism corrections were compared. LASIK was found to be superior to PRK in terms of BCVA and also gained more lines of BCVA compared to PRK. Loss of two or more lines of BCVA was reported more frequently in PRK than in LASIK. This difference may result from the more aggressive wound healing and haze development after PRK.

Earlier studies have reported almost identical results in MRSE after PRK and LASIK (el Danasourey et al. 1999, El-Maghraby et al. 1999, Steinert and Hersh 1998). Neither did we observe any significant differences between PRK and LASIK in terms of MRSE. The efficacy in correcting astigmatism was slightly superior in the LASIK group. PRK showed
a tendency to overcorrection in MRSE compared to LASIK. PRK typically showed a regression between 0.5 and 3.0 D in MRSE at one to twelve months. (Hersh et al. 1997, Kim et al. 1997) It appears that the PRK nomogram is planned to induce overcorrection to compensate this regression. A spherical overcorrection has been reported with the Nidek EC 5000 (SS) (Huang et al. 1999) after elliptical ablation for astigmatism, yet no differences were found here between BB and SS excimer lasers. Vector analysis in our study found no significant differences between PRK and LASIK.

Analysis of the stability of the cylinder by either non-vector or vector analysis revealed no difference between PRK and LASIK. This may reflect the accuracy of the nomogram, which was the same in both procedures. Both procedures showed undercorrection of intended astigmatism correction regardless of the technique. Furthermore, no differences were found secondary to misalignment, and accordingly it seems that the forces created by the suction ring, or the flap creation in LASIK do not interfere with the treatment. Our results are comparable to those of other studies (el Danasoury et al. 1999, Fraunfelder and Wilson 2001, Helmy et al. 1996, Hersh et al. 1998, Pop and Payette 2000) reporting accuracy and efficacy of astigmatic correction using various types of excimer laser (Stojanovic and Nitter 2001) or even wave front based nomograms (Partal and Manche 2006).

**Irregular astigmatism**

A variable epithelial thickness may contribute to or generate a morphologically irregular anterior corneal surface that may be result in irregular corneal astigmatism (Rosenberg et al. 2000). This is the case of anterior basement membrane dystrophy, such as Recurrent Corneal Erosion Syndrome (RCES) Map-dot-fingerprint (MDF). This corneal dystrophy has been suggested to arise from abnormal adhesion between the epithelium and the basement membrane-Bowman's layer complex (Brown and Bron 1976, Werblin et al. 1981) generating a morphologically unstable irregular anterior corneal surface. MDF may be present in as many as 15% of general population (Cavanaugh et al. 1999, Werblin et al. 1981) although it may not be associated with biomicroscopically observable changes at the time of examination (Rosenberg et al. 2000).

In general refractive surgery has been used to correct spherical and cylindrical components of refractive defects. The standard preoperative examinations performed before laser refractive procedures cannot show the anatomical location of the tissue in the optical system of the eye that generates the optical irregularity. Preoperative assessment included the use of VK, and in cases of irregular astigmatism also WF technology enabling customized corneal photoablations in patients. (Arbelaez 2001, Doane and Slade 2003, Waheed and Krueger 2003) Unfortunately, these methods do not distinguish in which corneal layer(s) the elevation prevails. In our study we showed the presence of irregular astigmatism that depends exclusively upon the corneal epithelium. The main clinical finding of this study is that if we assume that the astigmatism is due to epithelial irregularity and a PRK/LASIK customed correction is performed based on WF measures
taken from an intact cornea, irregular astigmatism may be caused rather than treated by WF excimer laser.

**STUDY V. PRK enhancement**

Several studies have focused on using PRK enhancements after prior LASIK surgery. Yet the development of haze has been the most frequent limitation (Astudillo and Ortiz 1999, Carones et al. 2001, Gimbel and Stoll 2001, Jain et al. 2002, Muller et al. 2005, Shaikh et al. 2005). CM (Moilanen et al. 2003, Tervo and Moilanen 2003) and histopathological studies (Dawson et al. 2005) have shown differences between corneal wound healing after PRK and LASIK, the direct innervation of individual keratocytes by nerve bundles at the central stroma (Muller et al. 1996, Muller et al. 2003), and the changes in density of corneal subbasal nerve after photoablation procedures (Erie et al. 2005, Lee et al. 2002, Tervo and Moilanen 2003). This nerve density after PRK improves significantly even after one year, and reaches near normal mean values at two years. Nerve density after LASIK, however, recovers more slowly and normal nerve density is not reached until five years postoperatively (Erie et al. 2005). CM studies have shown that two years after LASIK the subbasal nerves density reach ~ 60% of the preoperative values (Erie et al. 2005, Moilanen et al. 2008). Similar values have been reported to be reached one year after PRK (Erie et al. 2005). Accordingly, it is feasible to suggest that LASIK enhancements after PRK are probably safe one year after the primary operation, whereas PRK enhancements after primary LASIK should be performed over two years after the primary operation.

One previous report (Carones et al. 2001) advised against PRK after LASIK reporting severe haze three to ten months after the enhancement. In that study the re-treatments were performed between six and 15 months after LASIK when the active stage of corneal wound healing was supposed to be finished but the recovery of corneal sensory nerve innervation was still below 50% (Erie et al. 2005, Moilanen et al. 2003, Tervo and Moilanen 2003). Earlier studies (Muller et al. 2005, Weisenthal et al. 2003) have alternatively used prophylactic mitomycin C after transepithelial PTK/PRK to prevent haze formation in eyes with flap complications. In those studies the enhancements were performed between two weeks and five years after the flap complication. Shaikh et al. (Shaikh et al. 2005) reported good results after performing PRK enhancement in eyes with flap complications and/or previous LASIK treatment and stressed the importance of time interval between refractive procedures to minimize the keratocyte activity.
7 SUMMARY AND CONCLUSIONS

The present study evaluated the postoperative outcomes of excimer laser refractive surgery in myopic and myopic astigmatism correction. We also compared the results of moderate-to-high astigmatism correction by PRK and LASIK. Furthermore, we demonstrated the presence of irregular astigmatism that depends exclusively on the corneal epithelial cells, and suggest that corneal sensory nerve recovery may have a substantial effect on corneal wound healing. Our results demonstrate the following:

1. The long-term follow-up after PRK/LASIK demonstrated that outcomes of moderate myopic correction are safe and efficient.
2. In the long-term the laser delivery system does not seem to play a major role in the safety and efficiency after PRK.
3. We found an amount of regression after PRK similar to that reported in other long-term studies. Yet, when delivery systems were compared, we found that myopic regression favored the initial overcorrection achieved by the SS type laser.
4. LASIK refractive outcomes are relatively good in the short terms, but tend to decline over time. The incidence of myopic regression was more pronounced when the intended correction was >6.0 D and in patients aged <30 years.
5. Patient satisfaction after LASIK was high and most of the patients would reportedly have LASIK surgery again.
6. The long-term outcomes of moderate myopic correction treated by PRK or LASIK with the BB showed no significant differences. The results did not reveal any undesirable long-term complications with either technique or laser. Moreover, the similarity of PRK and LASIK results might challenge the current discussion on the superiority of "flap makers", i.e. femtosecond lasers vs. microkeratomes.
7. Correction of moderate to high myopic astigmatism was not as precise as non-astigmatic myopic corrections.
8. Postoperative outcomes after moderate to high astigmatism were better after LASIK than after PRK.
9. LASIK and PRK in moderate to high astigmatism corrections showed a tendency for under correction.
10. Correction of myopic astigmatism >2.0 D was associated with a greater risk of decrease in BCVA after PRK.
11. Irregular astigmatism was proven to depend exclusively on the corneal epithelium.
12. The standard preoperative examinations performed before laser refractive surgery cannot detect the anatomical location of the defect in the eye’s optical system that causes optical irregularity.
13. Corneal sensory nerve recovery may have an important role in the modulation of corneal wound healing and post-operative anterior stromal scarring. PRK enhancement may be an option in eyes with previous LASIK after a sufficient time interval of at least two years.
14. Our results strengthen the importance of intact corneal subbasal nerve plexus to maintain corneal transparency and also highlight their importance in corneal wound healing.
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