A systematic review of the safety and efficacy of elective photorefractive surgery for the correction of refractive error

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The Health Services Research Unit (HSRU) is a multidisciplinary research group of about 50 people based in the University of Aberdeen. The Unit is core-funded by the Chief Scientist Office of the Scottish Executive Health Department, and has responsibility for the following general remit:

1. To study or evaluate clinical activities with a view to improving effectiveness and efficiency in health care;
2. To work for the implementation of proven changes in clinical activities;
3. To encourage and support similar work thoughout Scotland;
4. To train NHS staff in Scotland, and others, in the principles and practice of health services research in general, and health care evaluation in particular.

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Contributions of authors

Alison Murray commented on the scope, screened the LASIK search results, assessed full text LASIK papers for inclusion, undertook data abstraction and quality assessment of LASIK studies, drafted the methods and LASIK sections of the review, and contributed to the writing of the rest of the review. Lisa Jones screened the PRK search results, assessed full text PRK papers for inclusion, undertook data abstraction and quality

assessment of PRK studies, drafted the PRK section of the review, and contributed to the writing of the rest of the review. Anne Milne screened LASEK search results, assessed full text LASEK papers for inclusion, undertook data abstraction and quality assessment of the LASEK studies, drafted the LASEK sections of the review, and contributed to the writing of the rest of the review. Cynthia Fraser developed and ran the literature search strategies, obtained papers and formatted the references. Tania Lourenco contributed to writing the background, unpublished data, quality assessment and appendices. Jennifer Burr wrote the scope for the review and the conclusions, contributed to writing the background, discussion, unpublished data and executive summary, commented on the rest of the review and provided a clinical oversight.

Conflict of interest

None

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EXECUTIVE SUMMARY

Background

Refractive error includes myopia, hyperopia, astigmatism and presbyopia; these are usually corrected by wearing spectacles or contact lenses. Modifying the shape of the cornea can reduce myopia, hyperopia and astigmatism. Corneal reshaping is achieved in photorefractive surgery using excimer laser ablation and is indicated in the range of refractive error from +6 dioptres (D) of hyperopia to –10 D of myopia, with up to 4 cylinders of astigmatism. This surgery is widely available in the private sector but is not performed as an NHS procedure unless indicated for therapeutic reasons. Excimer laser refractive surgery techniques in current use include photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK) and laser in-situ keratomileusis (LASIK). PRK involves the removal of the corneal epithelium and ablation of the corneal stromal bed. LASEK is a modification of PRK but instead of completely removing the epithelium, dilute alcohol is used to loosen the epithelium, which is lifted from the treatment zone as a hinged sheet and is swept back into place at the end of surgery. In LASIK, a flap is created with a microkeratome, this is lifted, the underlying corneal stromal bed is ablated, and the flap is repositioned. LASIK has been performed in the UK since 1995. Initially it was used to treat higher levels of myopia not suitable for PRK but now it has become the dominant technique for correction of refractive error.

Ectasia due to weakening of the cornea is the most serious complication of refractive surgery. Risk factors are high myopia, keratoconus, and a residual cornea\thickness after ablation of less than 250 µm. Assessment for suitability for the procedure requires an appropriate medical, ophthalmological and occupational history followed by a comprehensive ophthalmological examination; in particular to assess the front and back surface of the cornea (corneal topography) and measure of corneal thickness.

Other important potential adverse effects of photorefractive surgery include reduced best spectacle corrected visual acuity, infection and problems related to overall visual performance such as glare, halos and difficulties in low light conditions.

Objective

To systematically review the evidence for safety and efficacy of PRK, LASEK and LASIK for the correction of myopia, hyeropia and astigmatism.

Number and quality of included studies

Only papers published from 2000 onwards were included in the review. From the initial 3036 reports identified by the search strategy, 40 case series were included in the review of PRK, 26 case series published in 40 reports in the review of LASEK, and 64 case series published in 73 reports in the review of LASIK. For studies with multiple publications only the most up-to-date report was considered. In addition, 11 randomised controlled trials (RCTs) comparing PRK and LASEK, three RCTs comparing LASEK and LASIK, and two RCTs comparing PRK and LASIK, were included in the review.

More evidence was available for LASIK than for PRK and LASEK (total number of eyes in case series were 293,278, 15,785 and 5,091, respectively). Nine of the LASEK case series were only published as abstracts. Some of the studies had high drop-out rates and this raises questions about the reliability of the results. Direct comparisons between techniques could be made using evidence from the RCTs. However, the RCTs were too small to reliably identify differences in rare adverse events.

Summary of evidence of safety

Comparisons between the PRK, LASEK and LASIK case series must be made with care as sample sizes, participant populations, length of follow-up, surgeon experience and technologies differ. The median event rates were presented due to the high degree of heterogeneity.

Incidence of ectasia was only reported in five LASIK studies, median rate 0.2% (range 0% to 0.87%). However, on review, six of the 40 eyes with ectasia had preoperative topography suspicious of keratoconus, which is a contraindication to LASIK. The majority of remaining eyes (28 out of 34 eyes) had a residual layer of cornea below 250 µm. After exclusion of these cases, the median rate was 0%. Microbial keratitis was also only reported in LASIK studies and occurred in 0% to 0.16% of eyes.

The median rate of loss of two or more lines of best spectacle corrected visual acuity (BSCVA) was 0.5%, 0% and 0.6% of myopic and myopic astigmatic eyes treated with PRK, LASEK and LASIK respectively. Eyes treated for high myopia were more likely to lose two or more lines of BSCVA than eyes treated for low to moderate myopia. The overall median rate of 7.0% of hyperopic eyes treated with hyperopic-PRK (H-PRK), and

3.5% treated with LASIK, were reported to lose two or more lines BSCVA. H-PRK for hyperopia of > +3.50 D was more likely to result in loss of lines of BSCVA than treatment for lower levels of hyperopia. Only one study (an RCT) included eyes with hyperopia treated by LASEK; this reported no eyes losing more than two lines BSCVA.

Flap complications may occur in LASIK and LASEK; these may result in postponement of ablation (LASIK), conversion to PRK, or occasionally loss of BSCVA. Buttonhole flaps and incomplete flaps were reported in 0.1% and 0.3% of LASIK eyes and free caps (where the hinge is cut) in 0.1%. Epithelial ingrowth was reported in 1.3% of LASIK eyes. Diffuse lamellar keratitis occurred in 1.4% of eyes receiving LASIK. Outcome after diffuse lamellar keratitis was unclear because this was rarely reported; when it was reported eyes rarely lost vision after resolution of diffuse lamellar keratitis. Approximately 2% (range 0% to 19%) of LASEK treatments were converted to PRK due to flap complications.

Severe early post-operative pain was reported for PRK (range 1.3% to 3.8%) and LASEK (range 0% to 19%) in case series. Conflicting results were reported in RCTs comparing pain following PRK and LASEK and meta-analysis suggested no significant difference between the two treatments. Occurrence of significant corneal haze was reported following all three procedures; in 0% to 31% of PRK eyes, 0% to 25% of LASEK eyes, and 0% to 2.0% of LASIK eyes, although definition of haze varied between studies, particularly for LASIK. Less corneal haze was reported following LASEK than PRK in RCTs. Reports of subjective visual outcomes following refractive surgery varied. Glare and night vision were worse after PRK in 55% and 32% of participants respectively. Glare and night driving difficulty were less common after LASIK, although dry eye and fluctuations of vision were more common. There was no significant difference between PRK and LASIK in change in glare or halo symptoms following treatment in one RCT.

Intraocular pressure was not found to be persistently raised following photorefractive surgery and none of the included studies reported cases of glaucoma after PRK, LASEK or LASIK. The incidence of retinal detachment was below the reported incidence for people with similar levels of myopia who have not undergone refractive surgery.

Summary of evidence of efficacy

Overall, for the three treatments, correction of myopia and myopic astigmatism, the median rates were between 68% to 75% of eyes achieving within 0.5 D of their intended spherical equivalent correction and around 86% to 92% of eyes achieved within 1.0 D. Eyes with low to moderate myopia treated by PRK or LASIK appeared more likely to achieve their intended correction than eyes with high myopia. There were insufficient data to determine the effect of different levels of myopia on the accuracy of LASEK. There were no significant differences in accuracy between the three procedures for myopia or myopic astigmatism in any of the RCTs.

The accuracy of photorefractive surgery was lower for hyperopic correction; a rate of around 61% of eyes achieved within 0.5 D of intended correction after PRK and LASIK. Seventy-nine and 88% for PRK and LASIK respectively were within 1.0 D. Eyes with hyperopia of <+3.50 D were more likely to achieve the intended correction after PRK than eyes with higher hyperopia. One RCT found LASEK to be significantly more accurate than PRK for eyes with hyperopia.

Retreatment rates depend on the criteria for retreatment. Between 0.7% and 25.8% of PRK or PARK and 0% and 6% of LASEK eyes were reported to be retreated. Retreatment for under or over-correction was common after LASIK; 11% of myopic eyes and 12% of hyperopic eyes were retreated. More eyes with high myopia (23%) than low to moderate myopia (3%) were retreated after LASIK.

Uncorrected visual acuity (UCVA) of 20/20 or better was achieved at last follow-up in 70%, 62% and 64% respectively of myopic eyes treated with PRK, LASEK and LASIK, and 20/40 or better in 92%, 92% and 94%, respectively. Highly myopic eyes achieved 20/20 UCVA in 14% and 44% compared with 76% and 81% for low to moderately myopic eyes treated with PRK and LASIK respectively. There were insufficient data to identify trends in the efficacy of LASEK at different levels of myopia. Overall, 59% of H-PRK treated hyperopic eyes and 52% of LASIK treated hyperopic eyes achieved an UCVA or 20/20 or better with 86% to 96% achieving 20/40 or better. No RCT reported any significant difference between PRK, LASEK or LASIK in UCVA at six months.

Conclusions

The safety and efficacy of photorefractive surgery should be considered against the alternative methods of correction: spectacles and contact lenses. Also, the surgical technologies are changing rapidly and some lasers and microkeratomes used in studies reviewed have been superseded.

The review of efficacy found broadly similar performance for PRK, LASEK and LASIK. Participants with a milder degree of myopia were more likely to achieve the intended refractive correction. Treatment of hyperopia was less successful than treatment of myopia.

Most adverse events were statistically rare. It was unclear what effect refractive surgery had on commonly reported subjective visual symptoms, such as dry eye and night driving difficulty. The safety profiles of PRK, LASEK and LASIK reflected their technical differences: corneal haze was more common after PRK; flap problems followed LASEK and LASIK. The most serious problem, ectasia, was only reported after LASIK. Review of the cases of ectasia confirmed the importance of appropriate patient selection and treatment: the majority were found to have a contraindication to LASIK or to have received inappropriate treatment.

LIST OF ABBREVIATIONS

BSCVA	Best spectacle corrected visual acuity
D	Dioptres
FDA	Food and drug administration, USA
H-PRK	Hyperopic photorefractive keratectomy
IOL	Intraocular lens
IOP	Intraocular pressure
LASEK	Laser epithelial keratomileusis
LASIK	Laser in-situ keratomileusis
PARK	Photoastigmatic refractive keratectomy
PRK	Photorefractive keratectomy
SD	Standard deviation
RCT	Randomised controlled trial
RST	Residual stromal thickness
UCVA	Uncorrected visual acuity

GLOSSARY

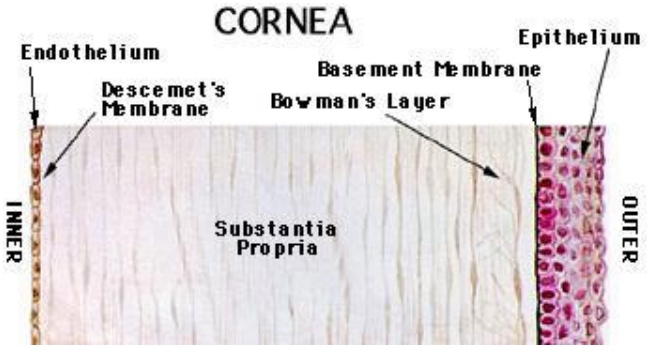
Aberration – A deficiency of the optical system in which light rays are scattered thereby degrading the optical image

- **Lower order aberration –** Collective term for refractive errors; myopia, hyperopia and astigmatism

- **Higher order aberration –** Collective term for a series of imperfections in the eye's optical system that may lead to vision problems, particularly low light vision difficulties

Broad Beam – A laser with a relatively large (6-8mm) diameter beam for ablation

Cornea – The transparent, avascular convex front surface of the eye. The cornea is made up of five layers, and the average corneal thickness is approximately 550 μm.



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(substantia propria is commonly known as the stroma)

Closed-loop – A constant connection between eye tracking device and the laser system to influence the placement of the beam

Customised ablation – The use of a wavefront sensing system and a flying spot excimer laser to treat the lower and higher order aberrations

Decentration – A complication of refractive surgery. In perfect centration the centre of the corneal ablation exactly coincides with the centre of the visual axis, and or pupil.

Decentration can cause symptoms such as edge glare or monocular double vision (diplopia)

Diffuse Lamellar Keratitis – An inflammation under the LASIK flap of the cornea, believed to be in response to the presence of sterile infiltrates in the flap interface.

Dioptre – Unit of measurement for the power of a lens or of refractive error

Epithelial Ingrowth – A LASIK complication wherein epithelial cells proliferate underneath the corneal flap

Ectasia – Refractive instability associated with a corresponding progressive structural corneal deformation

Enhancement - A re-treatment procedure to further reduce the refractive error

Eye tracker – A system for tracking involuntary movements during refractive surgery to ensure accurate beam placement

Flying spot laser – The latest generation excimer laser that uses a small (1mm-2mm) diameter treatment beam to precisely sculpt the cornea

Gaussian beam – A type of small-spot laser beam with a unique round shape for smooth ablation

Glare – Points of light look brighter and indistinct

Haloes – A point of light appears to have rings of light around it

Haze – The cornea is not clear, and is graded on a four-point scale 0-4, > grade 2 is clinically significant and can reduce vision

Keratoconus – A disease of the cornea leading to a cone shape protrusion of the cornea

Microkeratome – A surgical device for creating a flap of corneal tissue, this can be mechanical or a laser. The mechanical microkeratome uses a sharp thin metal blade. The Femtosecond laser uses amplified light energy to create and incision.

Open loop – The opposite of a closed loop, referring to an absent connection between the eye tracking device and the laser system.

Pachymetry – Measurement of corneal thickness. Methods of measurement are based on wave reflection of optical light or ultrasonic energy through the corneal tissue.

Regression – Loss or refractive surgical effect in time following treatment

Starbursts – Flares of light seen around a lighted object that may appear like a star

Visual acuity – Visual acuity is the minimal angle (or size) that a letter projected at a given distance must have for the retina to be able to discriminate the letter. A visual acuity of 20/20 (6/6) means that if you and a person with "normal" eyesight both stand 20 feet away from an object, you would see the same thing. If you have a visual acuity of 20/40 (6/12), then if you stood 20 feet (6 metres) away from an object and the "normal" person stood 40 feet away, you would both see the same thing: this suggests that you have worse eyesight than normal. It is possible to have vision superior to 20/20: the maximum acuity of the human eye) is generally thought to be around 20/15 (6/4.5).

Wavefront sensing – A computerised technology that analyses all the eye's higher order aberrations as well as myopia, hyperopia and astigmatism

1 OBJECTIVE OF THE REVIEW

To systematically review the evidence for safety and efficacy of surface based photorefractive surgery and laser in-situ keratomileusis (LASIK) for the correction of myopia, hyperopia and astigmatism.

2 BACKGROUND

2.1 Description of the underlying condition

2.1.1 Refractive errors

Clear vision depends, in part, on the ability of the eye to focus light on the retina. Refraction by the cornea and lens and the length of the eye determine the precision of focus. Refractive errors include myopia (short-sightedness), hyperopia (long-sightedness), astigmatism and presbyopia.

Myopia

Myopia occurs when light is focused in front of the retina, either because the refractive power of the cornea or the lens is too strong or the eye is too long. Myopia results in blurred distance vision. This condition commonly develops in childhood or adolescence. Myopia is not only a disabling refractive error[1] requiring correction but may also have other serious visual problems. In advanced cases of myopia (greater than -6.00 dioptres [D]) the eye is more susceptible to a range of major ocular pathologies including an increased incidence of retinal detachment[2] and an increased risk of developing cataract.[3] The incidence of idiopathic retinal detachment in persons older than 50 years is approximately 30/10,000 per year.[4] The risk of retinal detachment increases with increasing myopia, a four fold increase in people with myopia of –1 to –3 dioptres (D) and ten fold in people with myopia more than -3 D compared with people who are not myopic.[2]

Hyperopia

Hyperopia occurs when light is focused behind the retina because the refractive power of the cornea and lens is too weak or the eye is too short. With this condition, the eye makes a compensating effort to re-focus by accommodation. Accommodation is achieved by involuntary contraction of the ciliary muscle, relaxing the support for the natural lens allowing it to change shape and increasing focusing power. Young people may not always require correction for hyperopia because of their ability to accommodate. Hyperopia is associated with an increased risk of primary angle-closure glaucoma in later life.[5]

Astigmatism

Astigmatism, or irregular focusing power, occurs if there is a difference in refractive power between the two principle meridians (vertical and horizontal axes) of the cornea, if uncorrected it results in blurred near and distance vision. The shape of the cornea is often described in lay terms as being more rugby ball shaped than football shaped.

Presbyopia

Presbyopia is the gradual deterioration of near focus with increasing age. This results from thickening and loss of elasticity of the lens and results in a loss of ability for precise near tasks, particularly reading. Most people will require a near correction by about 45 years of age, in addition to any required distance vision correction.

Epidemiology

Refractive errors are common, but current information on the epidemiology and prevalence of myopia, hyperopia and astigmatism is lacking for England and Wales. Data from other countries in Europe, including Spain,[6] Norway,[7] and Denmark[8] indicates that the prevalence of myopia is highest in young adults, with between 30% and 35% having this error. The prevalence of hyperopia was shown to increase with age in two of the European data sets, from 13.2% in young adults to 17.4% in middle age in the Norwegian population[7] and from 31.1% to 39.9% in an equivalent Spanish population.[6]

Data from the 1994 General Household Survey[9] indicated that around 65% of adults in the UK wore glasses or contact lens, with around a third of younger adults aged 16 to 34 years (36%) wearing glasses or contact lenses.

2.1.2 Current management and alternative procedures

Refractive errors are routinely corrected by the wearing of spectacles (glasses) or contact lenses. Concave lens (-) are used to correct myopia and convex lenses (+) for hyperopia. Astigmatism is corrected with lenses with different powers in each of two perpendicular meridians. Astigmatic error can be corrected by spectacles or rigid contact lenses, however rigid lenses can be uncomfortable and poorly tolerated. Soft contact lenses mould to the shape of the cornea and are generally better tolerated than rigid contact lenses; to correct astigmatism, soft contact lens wearers require specially designed

"toric" lenses. For the correction of presbyopia people with myopia require a reduced correction for reading and depending on their level of myopia may read unaided. People with emmetropia (no refractive error for distance) will require a + lens for reading and people with hyperopia require an additional + lens to the normal distance correction. Presbyopic correction is usually by reading, bifocal or varifocal spectacles; occasionally people may opt for monovision (blended vision), achieved by wearing a contact lens one eye such that one eye is corrected for near vision (usually the non-dominant eye) and the other eye is corrected for distance vision.

Spectacle wear

Spectacles are the safest and most common method of correcting a refractive error. However, visual function in spectacles can be compromised; aberrations, reduced field of vision, peripheral distortion, and minified images increase with increasing lens power, and fogging during exercise or in rainy conditions may limit work-related and sporting activities.

Contact lenses

Contact lenses are used to correct refractive errors by modifying the curvature of the cornea and hence the refractive power of the eye. Rigid gas-permeable lenses and soft hydrogel lenses are most commonly used. Daily disposable soft lenses are popular and more recently silicone hydrogel lenses have been advocated as safe for 'extended' wear use. People who do not wish to wear spectacles frequently opt to wear contact lenses. Many patients who use contact lenses note a better field of vision, greater comfort, and/or an improved quality of vision compared with spectacle wear.[10]

Complications of contact lens wear

Most people who choose to wear contact lens experience safe and effective correction; however contact lens wear is associated with an increased risk of ocular surface problems, in particular corneal infection (microbial keratitis). Contact lens associated microbial keratitis is the most serious complication of contact lens wear and leads to serious loss of vision in approximately 5% of cases.[11,12] The risk of microbial keratitis is estimated as 1.1 per 10,000 (95% CI 0.6-1.7) for users of daily-wear rigid gas permeable lenses, 3.5 per 10,000 (95% CI 2.7-4.5) for users of daily wear soft lenses, and rises to 20.0 per 10,000 (95% CI 10.3-35.0) when lenses are worn overnight (extended wear soft lenses). [11] Acanthamoeba keratitis (AK) is a particularly severe form of microbial

keratitis causing prolonged morbidity and significant loss of visual acuity for up to 15% of affected patients. A study of the incidence of AK in England and Wales found that 88% of those diagnosed between 1997 and 1999 were contact lenses wearers, with and estimated annual incidence of 2/100,000 adult contact lens wearers.[13] Risk factors for acanthamoeba keratitis include swimming whilst wearing lenses, irregular or absent disinfection regimen, and poor basic contact lenses storage case hygiene.

2.2 The interventional procedures under review

Modifying the shape of the cornea can be used to reduce refractive error. Myopia can be corrected by reducing the curvature (flattening) of the anterior corneal surface, thus reducing the power. Correction for hyperopia requires an increase in power, achieved by increasing the curvature (steepening) of the anterior corneal surface; this is achieved by removing a paracentral portion of corneal tissue. Variations in these target shape changes can be used to correct astigmatism. The photorefractive surgery techniques in current use are photorefractive keratectomy (PRK), Laser Epithelial Keratomileusis (LASEK), and Laser In Situ Keratomileusis (LASIK) and recently Epi-LASIK. Alternatives such as radial keratotomy and intracorneal ring implantation are now virtually obsolete although the latter is used to treat keratoconus. Photorefractive surgery can be used in the approximate range of refractive error from + 6 Dioptres (D) of hyperopia to –10 D of myopia, with up to 4 cylinders of astigmatism. For high levels of myopia, intra-ocular surgical techniques such as phakic intra-ocular lens implantation and clear lens extraction are considered.

2.2.1 Candidate assessment

The preoperative evaluation of a potential refractive surgery patient comprises a complete medical, ophthalmological and occupational history as well as a comprehensive ophthalmological examination. In addition to standard ophthalmological examination including refraction, corneal topography and measurement of corneal thickness are required.

Corneal topography

Corneal topography measures the shape of the front and back surface of the cornea. Detailed assessment of the topography of the cornea pre-operatively is required to detect abnormalities that are major risk factors for the development of ectasia such as

keratoconus and sub-clinical 'forme- fruste' keratoconus, and if correctly identified preclude LASIK surgery. Keratoconus, a condition where the cornea becomes progressively ectatic and irregular, is an absolute contraindication to corneal refractive surgery.

Corneal pachymetry (thickness)

For any refractive procedure, but particularly LASIK, the residual layer of cornea, called the residual stromal thickness (RST), must be at least 250 µm.[14] A RST of less than this is a risk factor for the development of ectasia.[15,16] Ectasia is a biomechanical weakening of the cornea leading to long-term progressive shape instability and is the most serious complication of refractive surgery. Corneal thickness can be measured using computerised topography, commonly the Orbscan, and by ultrasound pachymetry.

2.2.2 The Laser

Corneal reshaping is achieved using an excimer (excited dimer) laser. It is a gas laser (argon and fluorine) producing ultraviolet light of a wavelength of 193 nm. The photon energy at this wavelength is high enough to break the biological molecular bonds directly and ablate corneal tissue. The ablation results in submicron tissue removal per laser pulse with minimal or no damage to surrounding tissue. There have been many technological advances in refractive surgery techniques, including new generation excimer lasers, scanning laser eye tracking systems, and customised ablation profiles using wave front guided technology.

Customised ablation

A wavefront device allows the surgeon to detect aberrations of the structural components of the eye and to customize the laser vision correction procedure. Aberrations can cause light rays to focus incorrectly and reduce the overall quality of vision.[17] The wavefront device creates a 3D focusing map of the eyes, representing the patient's unique visual distortions, including both lower and higher order aberrations. Various wavefront measuring technologies exist. Information from the wavefront device together with the required refractive correction is programmed into the wavefront guided excimer laser, and treatment is delivered to correct the refractive error and higher order aberrations that may cause vision problems. Wavefront guided treatments are purported to reduce surgically induced higher order aberrations; these aberrations are associated with light scatter symptoms and night vision difficulties.[18]

2.2.3 *Photorefractive keratectomy (PRK)*

In PRK a speculum is placed in the eye to hold the lids open, the eye is anaesthetised with local anaesthetic eye drops, the corneal epithelium is removed either by laser, chemically with dilute alcohol, or manually. The excimer laser is then applied to the corneal stromal bed, to flatten and remodel the anterior corneal surface. Modifications of PRK are Photoastigmatic refractive keratectomy (PARK) to treat astigmatism and hyperopic PRK (H-PRK) for the correction of hyperopia. These techniques use different ablation patterns in order to correct the intended amount of refractive error.

After the procedure, medications which might include topical antibiotics, topical cycloplegics and/or non-steroidal anti-inflammatory drugs (NSAIDs) are applied and an eye pad. The use of bandage contact lenses after PRK is popular in the USA but their use is been limited in the UK. There is evidence of an association between sterile corneal infiltrates and the use of NSAIDs with bandage contact lenses following PRK.[19] Post-operative topical steroids may also be used to control pain and inflammation but can increase the intraocular pressure (IOP). This increase is usually transient and is treatable, but can potentially lead to glaucoma if not recognised and managed appropriately.

Re-epithelialisation generally occurs within three to four days after PRK depending on the size of the initial epithelial defect. Patients may experience severe post-operative pain after PRK, and moderate analgesia, with or without a concomitant NSAID preparation, is usually administered for the first 24 to 36 hours. Epithelial problems related to irregular removal of the epithelium during the procedure have largely been eliminated by the introduction of new lasers with eye tracking facilities, flying spot delivery, and autocentration. The main risk factor for an irregular ablation is uneven hydration in the ablation area and with appropriate training this is easy to achieve. An epithelial defect has an associated risk of infection, microbial keratitis, a rare but potentially serious and sight threatening complication. Refractive complications include under correction, over correction, induced astigmatism and haze. Long-term loss of best-corrected visual acuity can occur due to corneal haze and irregular astigmatism.

Suitable candidates and putative impact of the procedure

PRK, using current excimer lasers, can correct low to moderate myopia (less than –6.0 D), astigmatism (up to 4.0 D) and hyperopia (up to +4.0 D). Although eyes with greater refractive errors may be treated, there are safety concerns about using PRK, and the proportion of successful outcomes falls with the increasing degree of initial refractive error.[19] PRK is particularly indicated for patients unsuitable for LASIK (see below), for example people with thin corneas, and people with professions or lifestyles predisposing them to flap trauma such as people in the armed forces.

2.2.4 Laser Epithelial Keratomileusis (LASEK)

LASEK is a relatively new procedure which has only been available in the UK since 1999. LASEK is a modification of PRK. Like PRK, LASEK is a surface corneal ablation technique, but unlike PRK, instead of completely removing the epithelium, dilute alcohol is used to loosen the epithelial adhesion to the corneal stroma. The epithelium is then lifted from the treatment zone as a hinged sheet and subsequently swept back into place to cover the ablated area at the end of surgery. The rationale for the development of LASEK was to avoid the flap-related complications associated with LASIK (see below) and to theoretically provide a faster recovery time, reduced post-operative pain and lower risk of corneal haze than PRK.

Many surgeons perform LASEK using Camellin's technique,[20] in which alcohol is used to loosen the epithelium rather than remove it. The 20% alcohol is then instilled into the holding well on the corneal surface for about 30 seconds. The surface is rinsed with balanced salt solution before detaching the epithelium with a spatula and folding it at the 12 o'clock position, it is returned after ablation with another spatula. Other surgeons mark the epithelium and apply 18% alcohol using a semi-sharp circular well before the epithelium is cut (Azar's method,[21] following ablation the epithelium is then carefully re-aligned with the previous marks. Vinciguerra's butterfly method[22] involves abrading a thin paracentral line with a specially designed spatula. Following alcohol contact the epithelium is separated from the Bowman's layer proceeding from the centre to the periphery on both sides using a special retractor to hold the two sheets in place. The epithelial flaps are replaced with the margins overlapping.

Suitable candidates and putative impact of the procedure

Although current literature is not presecriptive as to who should receive LASEK, it has been suggested that LASEK surgery (like PRK) is particularly indicated in patients with thin corneas, or wide pupils and for patients with professions or lifestyles that predispose them to flap trauma.

Like PRK, the major complication of LASEK is postoperative corneal haze. Corneal haze resolves over a few months in most cases, but may reduce visual quality, decrease the predictability of the correction or refraction and increase regression from corrected refraction.[23] Lin et al[23] proposed that clinically significant haze during the first six months is much more likely in patients with an ablation depth ≥ 100 μm. Most surgeons therefore try to avoid the use of LASEK in higher myopes.[24]

Lee at al[25] do not recommend LASEK in patients over 40 years of age, as it appears to produce contact lens intolerance in some older people. It has also been suggested that prolonged topical alcohol exposure may be required to loosen the epithelium in young men, post-menopausal women, and long time contact lens wearers.[26] The period of healing is both longer for LASEK than for LASIK, and more unpredictable, which may be unacceptable to some patients.

2.2.5 *Laser in-situ Keratomileusis (LASIK)*

LASIK evolved from a surgical technique to reshape the cornea called keratomileusis.[15] This technique was subsequently refined to a technique, automated lamellar keratoplasty, where the surgeon creates a flap using a microkeratome and the microkeratome is then used to remove a disc of tissue from the exposed surface. The flap is then replaced without suturing. After the ophthalmic excimer laser was developed, the technique has been further refined such that the exposed layer of cornea is reshaped by an excimer laser. In LASIK the flap is created with a microkeratome, although a femtosecond laser can be an alternative. Flap cutting requires the placement of a suction ring, raising the intraocular pressure to around 65 mm Hg, a corneal flap commonly around 9.5 mm in diameter and approximately 160 μm thick is then cut. An excimer laser is used to ablate the underlying corneal stromal bed; the required size of the optical zone and the depth and profile of the laser ablation are determined according to the pupil size and refractive correction required.[27] The flap is repositioned over the stromal area and no sutures are required.

LASIK corrects myopia by removing tissue in the centre of the cornea, thereby flattening the cornea. In hyperopia, a ring of tissue is removed around the centre of the cornea causing the cornea to become steeper. In order to correct for astigmatism, the curve has to be evened out by removing more tissue from the steeper side of the cornea.[17,27]

Additional equipment and devices required

Microkeratome

A microkeratome is a precision surgical instrument with an oscillating blade designed for creating the corneal flap in LASIK surgery. A suitable microkeratome should have a low level of flap complications, consistent flap thickness, good visibility, fixed depth plate, loss of suction indicators and should fit into small eyes.[28] The most commonly used microkeratome in the United Kingdom is the Hansatome (Bausch & Lomb) and, to a lesser extent, the Moria M_2.[29] The calculation of the predicted residual stromal thickness relies on the accuracy of measurements of corneal thickness, flap thickness and ablation depth. Flap thickness depends on the type of microkeratome used, and also varies according to other factors at time of surgery e.g. atmospheric conditions, hydration of corneal surface and IOP (Reinstein, personal communication).

Femtosecond laser

Alternatively the flap can be created using a femtosecond laser (IntraLase or Femtec) instead of a microkeratome and this is now used in approximately 5% of procedures worldwide.[30]

Suitable candidates and putative impact of the procedure

LASIK is generally considered suitable for adults with up to –10.0 D of myopia, astigmatism up to 4 cylinders and for adults with up to +6.0 D of hyperopia, who desire to reduce or eliminate their dependence on glasses or contact lenses. They should have a stable prescription, healthy eyes and good general health.[17] The usual minimum age for LASIK adopted by major groups is 21 years.

Mild postoperative discomfort is expected for a few hours after surgery and antibiotic and corticosteroid eye drops are usually prescribed for at least a week. A bandage contact lens is only required if the surface epithelium is scratched during the procedure. Return to work or usual activities can be expected within two to three days after the

LASIK. Recovery of useful vision should occur within one to two days, with stability and visual outcome by one month.[17]

2.3 Personnel involved (e.g. surgeons, anaesthetists, nurses) and skill/experience required

There is currently no regulation of surgeons undertaking laser refractive surgery. A recent government enquiry (All Party Parliamentary Panel of Enquiry into the Safety of Eye Laser surgery in the UK) into the safety of eye laser surgery reported that over 60% of surgeons practicing laser eye surgery in the UK do not belong to the General Medical Council specialist register.[31] In the light of public concern about patient safety, the Royal College of Ophthalmologists, have issued revised standards for laser refractive surgery and recommend that all surgeons carrying out the procedure should be registered with the General Medical Council, have undergone specific training in refractive surgery, and must provide appropriate follow up care; a surgeon without inpatient admitting rights should have an arrangements with an appropriate consultant ophthalmologist should the need arise.[32]

2.4 Current use in the UK (including existing guidance)

Photorefractive surgery is widely available in the private sector but is not performed as an NHS procedure unless it is indicated for therapeutic reasons, e.g. to correct refractive error following cataract or corneal graft surgery.

LASIK has been performed in the UK since 1995. Initially it was used to treat higher levels of myopia not suitable for PRK but now it has become the dominant technique for refractive errors in the range +4.0 to –10.0 D.

The Optician's annual survey of laser eye surgery practice in the UK, in September-October 2004, identified 92 clinics undertaking laser refractive surgery. 67 clinics (73%) responded to the survey and of these, 97% offer LASIK treatment, 94% offer LASEK and 49% offer treatment with PRK. Optimax, the largest UK group, expected to carry-out around 14,000 LASEK and 17,000 LASIK treatments in 2004. Almost all clinics offer monovision correction for presbyopes.[29] The most common types of laser used in the UK in 2004, as reported by the Optician's survey, were Bausch & Lomb's Technolas 217,

followed by Nidek EC5000 and Alcon's LadarVision 4000.[29] The most common wavefront system was the Bausch & Lomb's Zyoptix; others include Alcon's LadarWave system, VISX S4, and OPD Nidek.[29] All the major groups of clinics offered wavefront-guided procedures with 92% of clinics having wavefront technology. However, there was a wide variation in the proportion of treatments carried out using this technology.[29]

3 METHODS FOR REVIEWING EVIDENCE ON SAFETY AND EFFICACY

3.1 Search strategy

Initial database and website searches were undertaken to identify relevant systematic reviews and other evidence-based reports. Full details of the main sources consulted are listed in Appendix 1.

Electronic searches were conducted to identify both published and unpublished reports of studies evaluating the safety and efficacy of PRK, LASEK and LASIK for refractive errors. Searches were restricted to the years 2000 onwards and to papers published in the English language. Reports published only as abstracts were excluded for LASIK and PRK but included for LASEK due to the paucity of evidence published in full papers. The following databases were searched and full details of the searches are documented in Appendix 1:

MEDLINE
MEDLINE Extra
EMBASE
BIOSIS
Science Citation Index
Cochrane Controlled Trials Register
National Research Register
Clinical Trials
Current Controlled Trials
FDA Premarket Approval (PMA) Database

In addition, to identify potentially relevant abstracts for LASEK, the following additional databases were searched electronically:

Web of Science Proceedings
Conference Papers Index
Zetoc
Association for Research inVision and Ophthalmology (ARVO) Abstracts Database

American Society of Cataract and Refractive Surgery-American Society of Ophthalmic Administrators (ASCRS-ASOA) Abstracts Database

The proceedings of the European Society for Cataract and Refractive Surgery (ESCRS) were not available electronically and so were handsearched. The reference lists of all included studies were scanned to identify additional potentially relevant reports. Authors of included studies were contacted where necessary to provide clarification on aspects of their studies.

The results of the searches are presented in Table 1. Databases were searched independently for each technique. The number of hits presented for the searches in Biosis, SCI and CENTRAL are after de-duplication against the results from the Medline/Embase multifile search.

Table 1 Searching results

Database	PRK	LASEK	LASIK
Medline/Embase/Medline extra multifile search (after deduplication in Ovid)	668	81	1516
Biosis	35	3	64
SCI	29	9	426
CENTRAL	4	0	0
NRR	1	2	12
CCT	0	0	1
Clinical Trials	0	0	0
FDA	1	0	11
Conference abstracts	-	183	-
Total screened	**738**	**278**	**2020**
Total selected for full text assessment	**163**	**85**	**505**
Excluded after full text assessment	107	28	409
Retained for background information	0	2	19
Included	**49**	**55**	**77**

3.2 Inclusion and exclusion criteria

3.2.1 Types of studies

In accordance with the methods agreed by NICE for the reviews conducted by the Review Body for Interventional Procedures, we aimed to limit numbers of included

studies for each procedure to 40 studies. This review primarily assessed the risk of rare adverse events associated with photorefractive surgery. Large case series were considered likely to be the best source of evidence to assess such safety issues. Only studies published from 2000 onwards were included as technological advances in excimer laser systems have occurred and the most recent reports are likely to be the most relevant.

Prospective studies with at least 300 eyes receiving the intervention were included in the review. Retrospective studies are more prone to bias, therefore larger retrospective case series with at least 500 eyes receiving the intervention were included in the review. However, where less than 40 studies met these inclusion criteria the number of eyes required was reduced until at least 40 studies were included. Abstracts were only considered where there were insufficient full-text studies.

Randomised controlled trials (RCTs) comparing LASIK and PRK, LASIK and LASEK, and PRK and LASEK in addition to case series were also included in the review. The RCTs were not limited by number of eyes or participants.

Case reports and non-English language reports were excluded.

3.2.2 Types of participants

Adults undergoing photorefractive surgery for correction of myopia, hyperopia or astigmatism.

Studies of photorefractive surgery for therapeutic reasons, such as to correct refractive error following cataract or corneal graft surgery, were excluded.

3.2.3 Types of intervention

Studies of primary treatment with any type of excimer laser used to perform PRK and its derivatives (PARK, H-PRK, H-PARK), LASEK, and LASIK for refractive correction of myopia, hyperopia or astigmatism.

Studies of other refractive surgery techniques for management of refractive error, i.e. radial keratotomy, intracorneal ring implantation, phakic intraocular lens and clear lens extraction, were excluded.

3.2.4 Types of outcomes

Safety

Two categories of adverse events were considered for the assessment of safety. Adverse events in each of these categories included, but were not limited to:

a) Potentially serious complications (though not necessarily sight threatening with appropriate care)

- Corneal ectasia
- Microbial keratitis
- Epithelial ingrowth
- Retinal detachment
- Intraoperative flap complications (buttonhole flap, thick flaps, incomplete flaps)
- Need for corneal graft
- Optic neuropathy
- Loss of an eye

b) Undesired consequences

- Dislodge flaps, flap folds, thin flaps
- Patient reported outcomes (e.g. Glare, dry eyes, difficulty with night driving)
- Measurement error for diagnostic measurement in glaucoma
- Measurement error for intraocular lens calculation for subsequent cataract surgery

Efficacy

Efficacy was assessed in terms of achievement of the intended visual outcome, uncorrected visual acuity, stability of visual result and need for further refractive surgery.

3.3 Quality assessment strategy

The methodological quality of all included full-text reports was assessed using one of two quality assessment checklists depending on study design. These checklists were developed in conjunction with the Review Body for Interventional Procedures for use in

interventional procedure reviews. An additional question was added to each checklist to assess whether the paired nature of eyes was taken into account in the analysis. The 18-question checklist used to assess the quality of the case series studies (Appendix 2) was adapted from the NHS Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews[33] and from Downs and Black.[34] Five of these questions were not considered relevant to this review. The 14-question checklist used to assess randomised controlled trials is a modified version of the Delphi List, a criteria list developed using Delphi consensus methods by Verhagen and colleagues[35] to assess the quality of randomised controlled trials (Appendix 3). The methodological quality of the included abstracts was not assessed as not enough information was provided.

3.4 Data extraction strategy

One reviewer for each of the three techniques screened the titles (and abstracts where available) of all papers identified by the search strategy. Full text copies of all reports deemed to be potentially relevant were obtained and the same reviewer assessed them for inclusion. Any areas of uncertainty were resolved by consultation with a second reviewer. A data extraction form was specifically developed to record details of the design of included studies, characteristics of participants, technical aspects of the procedure, and outcome measures. Data were extracted by the same reviewer. Where possible, for each reported outcome, data were sought on every eye treated. The reviewer was not blinded to the names of study authors, institutions, and publications.

3.5 Data analysis

Data from case series studies were tabulated and presented, where possible, for short-term and long-term follow-up and according to type and level of refractive error. A pooled estimate across the case series were provided if the case series were sufficiently homogenous otherwise summary values were restricted to presentation of the median and range. Patient reported outcomes were presented as a comparison between baseline and follow-up. For randomised controlled studies, data were tabulated and between-group comparisons were presented for last follow-up.

3.6 Unpublished data

Manufacturers of the excimer lasers, and hospital-based and corporate laser centres in the UK providing photorefractive surgery were contacted with a request for published or unpublished data for inclusion in the review.

3.7 Included studies

The numbers of studies and papers included in each review are shown in Table 2. Safety and efficacy results based on the case series are presented separately for each intervention, and where available for each case series. Direct comparisons between PRK, LASEK and LASIK from the RCTs are presented at the end of this section. An overall summary value for each intervention is presented by providing the median and range over the individual studies.

Table 2 Numbers of studies and papers included

Study design	**PRK**		**LASEK**		**LASIK**	
	Studies	**Papers**	**Studies**	**Papers**	**Studies**	**Papers**
Case series	40	40	26	40	64	73
RCT PRK vs LASEK	*7*	*7*	*11*	*13*	-	-
PRK vs LASIK	*2*	*2*	-	-	*2*	*2*
LASEK vs LASIK	-	-	*3*	*3*	*2*	*2*
Total RCTs	9	9	14	16	4	4
Total	**49**	**49**	**40**	**56**	**68**	**77**

4 PRK RESULTS

4.1 Type and quantity of available evidence

A total of 738 papers were identified from the literature searches and screened for inclusion in the review of PRK. Of the titles and abstracts screened for inclusion, 163 were ordered as full papers and assessed in detail.

4.2 Number and type of included studies

A total of 40 case series were identified that met the criteria for inclusion in the review of PRK (Appendix 5). Full text prospective studies with more than 50 eyes, and full text retrospective studies with more than 100 eyes were eligible for inclusion. In addition, two of the RCTs [36,37] which met the criteria for the review included a sufficient number of eyes for inclusion in this section. Data on PRK was extracted and treated as a single arm case series. Full details and characteristics of these studies are reported in Chapter 7. The main characteristics of the included case series are shown in Table 4.

4.2.1 Myopia

Thirty studies[38-67] examined patients with myopia and myopic astigmatism treated with conventional PRK. The total number of eyes in all studies was approximately 15,785. The number of eyes analysed in the included studies ranged from 51 to 5936 and length of follow-up ranged from a minimum of one month to a maximum of 12 years. Mean age ranged from 22 to 46 years and the mean spherical equivalent ranged from -2.10 D to -11.43 D. The most frequently used excimer laser system was the Nidek EC-5000 (6 studies) followed by the Summit SVS Apex, VISX 20/20B and VISX STAR S2 systems (5 studies each, respectively).

Eight studies[44,45,47,48,50,51,60,63] did not report treatment dates. The earliest study was initiated in 1990 and two studies[42,62] carried out treatments after January 2000.

Six studies were set in the USA;[43-45,54,64,67] three in the UK,[52,58,60], Canada[39,50,51] Spain,[55-57] Hungary,[46-48] and Italy,[40,65,66] two in Taiwan,[41,59] and one each in South Africa,[38] Iran,[42] Finland,[49] India,[53] Norway,[61] Japan[62] and Australia.[63]

The source of funding was unclear in 19 included studies. Of these, 11 studies[47,49-51,55-59,61,63] reported that the authors had no proprietary and/or financial interest in the product under investigation.

Funding or support from a variety of sources was reported in 11 studies.[39,43-46,48,52,54,60,64,67] Of these, nine studies received government funding,[39,43-46,48,54,64,67] one study[60] was supported by the manufacturer (VISX Inc) and one study[52] was partly funded though a charitable foundation (Iris Fund for the Prevention of Blindness). Six[43-45,54,64,67] of the 11 studies reported that support was received from Research to Prevent Blindness Inc.

In terms of post-operative care, bandage contact lenses were applied after treatment in 16 studies.[38,41,42,44,45,48,50,51,54,59,61,62,64-67] Six studies[40,46,49,53,58,63] reported that bandage contact were not used and/or a pressure patch applied. Where reported, 20 studies[38,41,42,44-51,53,54,61-66] prescribed corticosteriods after re-epithelisation had occurred. The most frequently prescribed corticosteriod was fluorometholone, other corticosteriods used were prednisolone,[44,45] betamethsone,[53] and dexamethasone.[61,66] Duration of corticosteriod therapy ranged from under one month[50,51,63,64] to 12 months.[62] However, the majority of studies administered therapy for three to four months. One study[40] stated that steriods were not administered, and in another study,[58] steriods were only prescribed if there was signifcant haze or regression.

4.2.2 Hyperopia

Six studies[68-73] examined patients treated with H-PRK for hyperopia. The total number of eyes was approximately 1,599. The number of eye analysed ranged from 52 to 800 and follow-up ranged from six to 36 months. Mean age ranged from 35.4 to 51.8 years and the mean spherical equivalent ranged from +2.48 D to +5.64 D.

The excimer laser systems used in the included studies were the Aesculap Meditec MEL 60 and MEL 70, and the VISX STAR. Three studies did not report treatment dates.[68,70,73] Where reported the earliest treatments dated back to 1994 and the latest treatment date was August 1999.

Three studies[69-71] were set in Hungary and one each was set in Canada,[68] the USA,[72] and the UK.[73]

The source of funding was unclear in two of included studies, of which, one study,[68] reported that the authors had no proprietary and/or financial interest in the product under investigation. Funding or support from a variety of sources was reported in four studies.[69-72] Of these, three studies by Nagy et al.[69-71] received government funding and one study[72] was supported by the manufacturer (VISX Inc).

In terms of post-operative care, where reported, bandage contact lenses were used in two studies[70,73] and not used (a pressure patch was applied) in two studies.[69,71] Corticosteroids (fluorometholone) were administered in five studies.[68-71,73] Duration of treatment ranged from three to four months, with the exception of the study by Williams et al.[73] in which duration of therapy was one week.

4.2.3 Astigmatism

Six studies[58,59,74-77] examined the use of PARK in patients with myopic astigmatism. The total number of eyes was approximately 7,009. The number of eyes analysed ranged from 70 to 6097 and follow-up ranged from three to 24 months. Mean age ranged from 32 to 43 years and the mean spherical equivalent ranged from -4.63 D to -7.18 D.

The excimer laser systems used were the Summit Apex Plus and the Nidek EC-5000. Where reported, treatment dates ranged from 1994 to 1999. Four studies did not report dates of treatment.[74-77]

Four studies[74-77] were set in the USA and one study each was set in the UK[58] and Taiwan.[59]

The source of funding was unclear in five of the six included studies. Of these, four studies[58,59,74,76] reported that the authors had no proprietary and/or financial interest in the product under investigation. The study by MacRae et al.[77] was partly funded though a number of sources including a charitable foundation and Research to Prevent Blindness Inc.

In terms of post-operative care, bandage contact lenses were used in five studies[59,74-77] and not used in one study.[58] The studies by Haw et al.[74-76] were the only studies that routinely prescribed corticosteroids. Treatment lasted for two months. Two studies[58,77]

reported that corticosteroids were only prescribed if there was excessive haze or regression.

4.3 Number and type of excluded studies

A total of 101 studies were excluded from the review of PRK. The majority were excluded because they did not include sufficient numbers of eyes undergoing treatment with PRK (45.5%) or did not report relevant outcomes related to the safety and efficacy of the procedure (29.7%).

4.4 Quality of available evidence

Case series

The results for the quality assessment of the included PRK case series are summarised in Table 3 (detailed results are shown in Appendix 6). Inclusion and/or exclusion criteria were clearly described in the majority of the included studies, however, there were 13 studies[38,44,49-54,58,60,62,64,67] where this was not the case. All studies selected a sample from a relevant population. Data collection was undertaken prospectively in 21 of the studies[38,39,42,43,47,49,52,58,60,62,63,65,66,70-77] and was retrospective[40,44,45,50,51,53-57,59,61,64,67,68] or unclear[41,46,48,69] in the remaining 19 studies. In most of the included studies, it was unclear whether the selection of patients was consecutive; 15 studies[39,51,52,55-58,60-63,65,66,68,76] reported that the selection of patients had been undertaken consecutively.

The intervention was clearly described in the majority of the included studies, except in the study by Yang et al,[67] where details were reported in a linked publication.[64] Only one study[42] reported that the surgeon undertaking the procedure was experienced in PRK; in all other studies it was unclear. One study[77] reported that all surgeons undertaking the procedure received training prior to administering the intervention, but the level of experience was unclear.

The majority of the included studies presented a range of safety and efficacy outcomes, which were objective and reliable. However, the study by Cennamo et al.[40] presented limited safety outcomes and two studies[39,43] solely reported patient reported outcomes. Follow-up exceeded three months in all but one study.[62] Eleven studies[40,41,51,63-66,72,74-76] provided information on drop-outs and patients lost to follow-up but only three studies

discussed this issue in detail.[40,63,64] It was, therefore, unclear in the majority of studies whether patients lost to follow-up were likely to introduce bias. Very few studies described the statistical methods they had used to analyse data, so it was unclear whether the paired nature of the eyes had been taken into account in a number (68%) of the included studies.

Table 3 Summary of the quality assessment of PRK, H-PRK and PARK case series

Criteria		Yes	No	Unclear
1.	Were participants a representative sample selected from a relevant population?	40	0	0
2.	Are the inclusion/exclusion criteria of the participants in the study clearly described?	27	13	0
4.	Was selection of participants consecutive?	15	1	24
5.	Was data collection undertaken prospectively?	22	14	4
7.	Was the intervention (and comparison) clearly defined?	39	1	0
8.	Was the intervention undertaken by someone experienced in the procedure?	1	0	39
9.	Were the staff, place, and facilities where the participants were treated appropriate for performing the procedure?	40	0	0
10.	Were all important outcomes considered?	39	1	0
11.	Were objective (valid and reliable) outcome measures used?	38	2	0
13.	Was the follow-up long enough to detect important effects on outcomes of interest?	39	0	1
14.	Was information provided on non-respondents and dropouts?	11	29	0
15.	Were participants lost to follow up likely to introduce bias?	1	6	33
17.	Were all important prognostic factors identified?	34	2	4
19.	Was the paired nature of eyes taken into account in the analyses?	11	2	27

Note: questions 3, 6, 12, 16 and 18 were not relevant to either case series or this intervention

Table 4 Included studies – PRK case series

Study id	Number of participants	Number of eyes	Mean age (years)	Follow-up (months)	Pre-opoerative spherical Equivalent (D)			Laser	Treatment dates
					mean	SD	range		
Myopia									
Amoils 2000[38]	250	500	NR	mean 9.32	-	-	-	Nidek EC-5000	Initiated in Jul 1996
Brunette 2000[39]	690	NR	38	4 to 30	-5.32	2.85	-0.38, -27.75	VISX 20/20; Technolas 116; Nidek EC-5000	May 1994 - May 1997
Cennamo 2003[40]	554	582	NR	24	-	-	-7.00, -17.00[a]	Aesculap Meditec	Oct 1991 – Sep 1998
Chen 2000[41]	80	A: 24	30.4	6	-4.72[b]	1.15	-	Omnimed, Apex Plus	Mar 1994 – Jan 1998
		B: 20	35.7		-4.75[b]	1.07	-		
		C: 43	32.9		-4.85[b]	0.91	-		
		D: 25	30		-7.25[b]	0.66	-		
		E: 42	34.1		-7.47[b]	1.04	-		
		F: 46	34		-8.05[b]	1.23	-		
Hashemi 2004[42]	28	54	29.3	6	-7.08	1.11	-5.00, -9.88	Technolas 217-C	Apr - Oct 2002
Hovanesian 2001[43]	231	241	NR	≥6	-	-	-	Summit SVS Apex	Mar 1996 - Jun 1998
Kapadia 2000a[44]	347	559	38	12	-	-	-	Summit SVS Apex	Not reported
Kapadia 2000b[45]	NR	453	38.8	12	-4.3	2.0	-1.0, -13.1	Summit SVS Apex	Not reported
Nagy 2001b[46]	69	130	30	12	-	-	-	Aesculap Meditec MEL 70	Sep - Nov 1998
Nagy 2002a[47]	38	A: 38	NR	12	-3.40[b]	-	-1.00, -6.00	Aesculap Meditec MEL 60	Not reported
	38	B: 38	NR		-3.38[b]	-	-1.50, -6.00		
Nagy 2002c[48]	104	150	33.4	6	-4.04	1.04	-1.50, -6.50	Aesculap Meditec MEL 70	Not reported
Pietila 2004[49]	55	A: 69	31.8	8 years	-4.07	1.26	-	Aesculap Meditec MEL 60	Initiated in Oct 1991
		B: 16			-7.78	0.85	-		
		C: 7			-11.43	1.04	-		
Pop 2000a[50]	418	836	35	12	-5.61	2.86	-18.5, -1.00	Nidek EC-5000	Not reported
Pop 2000b[51]	91	107	40	12	-6.03	2.19	-	Nidek EC-5000	Not reported
Rajan 2004[52]	68	68	46	12 years	-4.06	1.73	-	Summit Omnimed UV 200	Initiated in 1990
Rao 2000a[54]	35	A: 43	NR	12	-4.95	2.26	-	VISX STAR S2	Feb 1993 - Jul 1998
	56	B: 72			-5.57	2.43	-		
	47	C: 69			-5.19	2.61	-		
	59	D: 73			-5.95	2.79	-		
Rao 2000b[53]	133	A: 133	26.6	mean 16.5	-8.2	3.5	-2.5, -18.5	Summit Omnimed UV 200	Feb 1994 – Dec 1996
		B: 133			-7.9	3.7	-2.3, -20.3		
Ruiz-Moreno 2000a[56]; 2000b[55]	NR	5936	30.5	mean 38.5	-4.71	2.86	-1, -14	VISX 20/20	Apr 1992 - Apr 1998
Ruiz-Moreno 2003[57]	NR	5936	30.5	mean 68.5	-4.71	2.86	-1, -14	VISX 20/20	Apr 1992 - Dec 2000
Shah 2002[58]	NR	3004	35.2	mean 20	-3.74	1.61	-	Nidek EC-5000	1994 – 1996

Study id	Number of participants	Number of eyes	Mean age (years)	Follow-up (months)	Mean Spherical Equivalent (D) mean	SD	range	Laser	Treatment dates
Shen 2002[59]	46	70	35	6	-6.06	1.82	-2.88, -10.38	Summit Apex Plus	May 1997 - Jul 1999
Stevens 2002[60]	117	200	NR	12	-3.50	-	-	VISX Star S2	Not reported
Stojanovic 2003[61]	212	A: 404	31.2	mean 23.2	-4.66	2.11	-1.25, -11.50	Lasersight	Feb 1996 - Jan 2000
	152	B: 266	30.6	mean 22.5	-4.38	2.44	-1.25, -12.50		
Tanabe 2004[62]	27	51	NR	1	-	-	-	VISX Star S2	Sep 2000 - Oct 2002
Tole 2001[63]	392	A: 119	34.7	6	-2.10	0.58	-0.50, -3.00	Nidek EC-5000	Not reported
		B: 129	37.5		-4.10	0.75	-3.12, -6.00		
Van Gelder 2002[64]	161	161	34.2	3	-3.95[c]	1.94	-	VISX 20/20B or STAR S2; Summit SVS Apex	Mar 1996 - Mar 1998
Vetrugno 2000[65]	52	A: 44	21.9	12	-2.65[c]	1.20	-	Laserscan 2000	Jan 1998 - Feb 1998
		B: 60	22.2		-2.89[c]	1.59	-		
Vetrugno 2001[66]	40	A: 40	24.8	12	-4.65[c]	1.20	-	Laserscan 2000	Apr - Jun 1998
	40	B: 40	25.2		-4.89[c]	1.59	-		
Yang 2002[67]	104	104	35.7	3	-4.13[c]	-	-	VISX 20/20B or STAR S2; Summit SVS Apex	Mar 1996 - Mar 1998
Hyperopia (H-PRK)									
FDA 2000[72]	172	276	51.3	12	-	-	+0.50, +6.00	VISX STAR S2	Aug 1998 - Aug 1999
Munger 2001[68]	111	191	51.8	24	+3.30	1.56	-	VISX STAR	Not reported
Nagy 2001a[69]	NR	A: 482	43.1	12 to 36	+2.88	1.34	+1.50, +3.50	Aesculap Meditec MEL 60	Jan 1994 - Jan 1998
	NR	B: 318	35.4		+5.64	2.96	+3.75, +9.00		
Nagy 2002b[71]	NR	A: 62	NR	12	+2.48[b]	0.82	-	Aesculap Meditec MEL 70	Sep - Dec 1998
		B: 44			+2.61[c]	0.32	-		
		C: 56			+4.88[b]	2.18	-		
		D: 38			+4.88[c]	1.89	-		
Nagy 2002d[70]	20	A: 40	37.2	6	+3.10	0.80	+1.00, +4.00	Aesculap Meditec MEL 60	Not reported
	20	B: 40	38.4	6	+2.90	0.80	+1.50, +4.00		
Williams 2000[73]	52	52	51	12	+3.03	-	-	VISX STAR	Not reported
Astigmatism (PARK)									
Haw 2000a[75]; 2000b[74]; 2000c[76]	56	93	41.4	24	-4.98	1.80	-1.75, -8.50	Summit Apex Plus	Not reported
MacRae 2000[77]	486	749	43.0	12	-4.90	1.74	-1.00, -8.50	Nidek EC-5000	Not reported
Shah 2002[58]	NR	6097	35.2	mean 20	-4.63	1.95	-0.75, -13.00	Nidek EC-5000	1994 - 1996
Shen 2002[59]	46	70	32	6	-7.18	1.91	-2.38, -10.50	Summit Apex Plus	May 1997 - Jul 1999

[a] Range of myopic error
[b] Mean spherical power where cylinder power approximated 0.
[c] Calculated from mean spherical power (D) + one half mean cylinder power (D).

4.5 Overview of safety findings

This next section describes the safety findings for the three main clinical groups; myopia, hyperopia and astigmatism. The data available for each are first described followed by a summary table of case study findings.

4.5.1 Myopia

An overview of complications of PRK for treatment of myopia is presented in Table 8.

Potentially serious complications

Ectasia

No studies reported incidence of ectasia.

Other potentially serious complications

Van Gelder at al[64] reported a single case (0.6%) of epithelial ingrowth and a single case (0.6%) of subepithelial infiltrate in 161 myopic eyes. Vetrugno et al.[66] reported two cases of corneal infiltrates in their series of 80 eyes (2.5%). Hashemi et al[42] reported that no complications such as eccentric ablation, delayed re-epithelisation, persistent epithelial defect, or microbial keratitis occurred during follow-up.

Ruiz-Moreno et al.[56] analysed the incidence of retinal detachment in a series of 5936 consecutive myopic eyes that had undergone PRK. The incidence of retinal detachment was 0.08% (5/5936 eyes) after a mean follow-up of 38.5 (±17.4) months. After a mean follow-up of 68.5 (±32.4) months,[57] the incidence of retinal detachment was 0.15% (9/5936 eyes). Ruiz-Moreno et al. also examined the incidence of choroidal neovascularization. There was a single case of choroidal neovascularization at 26 months (0.019%).[55]

Undesired complications

Delayed re-epithelisation

Across the two studies that reported this outcome,[38,65] 3.8% of eyes experienced delayed re-epithelisation. It usually takes three to four days for the epithelium to heal after PRK and all reported cases took an additional one to two days to heal.

Refractive complications

Across the studies reporting BSCVA, 4.5% of eyes (range, 0.7% to 15.3%) lost one line of BSCVA and 0.5% (range, 0 to 20.5%) lost two or more lines (Table 5).

Where possible, the data were grouped according to the reported level of pre-operative myopia. In eyes with low to moderate myopia, 10.4% (range, 0.7% to 15.5%) lost one line of BSCVA and 0.5% (range, 0% to 1.1%) lost two or more lines. In the high myopia sub-group, 17.0% (range, 17% to 17%) lost one line, and 11.9% (range, 2.4% to 22.2%) of eyes lost two or more lines of BSCVA.

Two studies used newer generation lasers (MEL 70). Overall, 0.7% of eyes treated with wavefront-guided technology lost one line of BSCVA.[48] In eyes with low to moderate myopia, 1.1% of eyes lost two or more lines of BSCVA and 7.5% of eyes with high myopia lost two or more lines.[46]

Table 5 PRK case series (myopia): Reduced BSCVA

Study id		Follow-up (months)	Lost Snellen lines of BSCVA 1		≥2	
			n	%	n	%
Amoils 2000[38]		18	5/95	5.2	0/95	0
Autrata 2003a[37]		24	4/89	4.5	0/89	0
Cennamo 2003[40]		24	-	-	53/258	20.5
Kapadia 2000a[44]	-1.0 to -3.0 D	12	11/71	15.5	0/71	0
	3.1 to -6.0 D	12	18/123	15	0/123	0
	>-6.1 D	12	7/42	17	1/42	2.4
Nagy 2001b[46]	-1.5 to 6.0 D	12	-	-	1/90	1.1
	-6.1 to –9.0 D	12	-	-	1/31	3.2
	-9.1 to –14.0 D	12	-	-	2/9	22.2
Nagy 2002c[48]		6	1/135	0.7	-	-
Pietila 2004[49]		8 years	-	-	1/92*	1.1
Pop 2000a[50]		12	-	-	1/647	0.2
Pop 2000b[51]		12	1/82	1.2	0/82	0
Rajan 2004[52]		12 years	3/68	4	1/68	1.4
Shen 2002[59]		6	2/61	3.3	0/61	0
Stevens 2002[60]		12	17/198	8.6	1/198	0.5
Tole 2001[63]		6	12/209	5.7	2/209	1.0

*Due to irregular astigmatism induced by decentration

Haze

Studies reporting haze are shown in Table 6. Nine studies[38,46,48-52,65,66] graded haze according to Hanna's scale (zero to four point scale). The median rate for the percentage of eyes with clinically significant haze graded two or more was 0% (range, 0% to 31.4%). Excluding the study with one month follow-up,[62] reduced the range to 0% to 16.3%. It

was unclear why the rate of clinically significant haze was higher in the two studies by Vertugno et al.[38,46,48-52,65,66] In two studies[49,52] with the longest follow-up (eight and 12 years, respectively) no eyes had grade two or more haze. In two studies[46,48] that used newer generation lasers (MEL 70), 0.8% of eyes showed evidence of clinically significant haze.

Table 6 PRK case series (myopia): Haze at last follow-up

Study ID	Follow-up (Month)	Haze score (Hanna's scale)							
		Clear (0)		Trace (0.5)		1		≥2	
		Rate	%	Rate	%	Rate	%	Rate	%
Amoils 2000[38]	18	89/95	93.8	49/95	5.2	10/95	1.0	0/95	0
Nagy 2001b[46]	12	107/130	82.3	-	-	-	-	1/130	0.8
Nagy 2002c[48]	6	-	-	-	-	1/150[a]	0.7	-	-
Pietila 2004[49]	8 years	80/92	87.0	12/92	13.0	0/92	0	0/92	0
Pop 2000a[50]	12	-	-	14/646	2.2	1/646	0.2	0/646	0
Pop 2000b[51]	12	-	-	-	-	0/107	0	0/107	0
Rajan 2004[52]	12 years	64/68	94.1	3/68	4.4	1/68	1.5	0/68	0
Shen 2002[59]	6	-	-	-	-	-	-	0/70	0
Tanabe 2004[62]	1	4/51	7.8	7	13.7	24/51	47.1	16/51	31.4
Vetrugno 2000[65]	12	-	-	58/104[b]	55.8	40/104	38.5	6/104	5.8
Vetrugno 2001[66]	12	5/80	6.3	21/80	26.3	41/80	51.3	13/80	16.3

[a] Patient lost 1 Snellen line of BSCVA
[b] graded 0 to 0.5

Raised intraocular pressure (IOP)

This outcome was reported in five studies.[46,48,52,61,65] A median rate of 1.9% of eyes experienced an increase in their IOP. Two studies[48,52] reported that no eyes had experienced a raise in IOP during follow-up (six months and 12 years follow-up, respectively).

Participant reported outcomes

Haloes and glare

In the study by Amoils et al.[38] six participants (12 eyes) reported symptoms of haloes. Overall in two studies by Pop et al.,[50,51] mild haloes were reported by 23.0% (153/664 eyes) and 17.0% (124/728 eyes) at three and 12 months, respectively. Moderate or 'high' haloes were reported by 7.1% (47/664 eyes) and 3.3% (24/728 eyes) at three and 12 months, respectively. One study.[46] using the MEL 70 laser reported that 23.8% (31/130 eyes) of participants reported glare and haloes. These symptoms were reported more frequently in participants with myopia greater than -6.0 D (35.0% versus 18.8%). Vetrugno et al.[65] reported that 2.9% (3/104 eyes) of eyes experienced symptoms of glare but that no patient reported symptoms of haloes. Glare or light sensitivity on sunny

days was reported by 66.4% of participants in the study by Brunette et al.[39] 55% of participants reported that daytime glare sensitivity was "more bothersome" than before surgery.

Problems with night driving and/or night vision

Amoils et al.[38] reported that eight participants (3.2%; 16 eyes) reported mild problems with night driving at short term follow-up (three to six months). Five participants (2.0%; ten eyes) reported moderate problems with night driving. Vetrugno et al.[65] reported "driving unfitness" at one week; 57.7% of participants reported this outcome. Brunette et al.[39] reported that quality of night vision was rated as poor or very poor in 20.2% of participants, and 31.7% of participants reported that it was worse or much worse than before surgery. The most frequently reported night vision complaint was haloes, fog or haze around street lights (52.4%). Rajan et al.[52] reported that 12 years after surgery, 12% of participants experienced problems with night vision (haloes during night driving or round streetlights at dusk). However, all participants reported a subjective improvement in their night vision over the 12-year period.

Pain

Two studies by Vetrugno et al.[65,66] reported pain scores after complete re-epithelisation had occurred four to five days after surgery (Table 7). Participants were asked to complete a modified McGill Pain questionnaire. Overall, 25.0% of participants (33/132) reported that the pain was distressing, 1.5% of participants (2/132) found the pain "horrible" and 0.8% (1/132) were in "excruciating" pain.

Table 7 PRK case series (myopia): Present Pain Intensity (PPI) scores

PPI Score	Vetrugno 2000[65]		Vetrugno 2001[66]		TOTAL	
	Rate	%	Rate	%	Rate	%
1 (mild)	20/52	38.5	16/80	20.0	36/132	27.3
2 (discomforting)	16/52	30.8	39/80	48.8	55/132	41.7
3 (distressing)	14/52	26.9	19/80	23.8	33/132	25.0
4 (horrible)	1/52	1.9	1/80	1.3	2/132	1.5
5 (excruciating)	1/52	1.9	0/80	0	1/132	0.8

Ocular symptoms

Vetrugno et al.[65] reported subjective ocular symptoms at one week; 44.2% of participants reported epiphora (excessive tearing), 38.5% reported itching and 38.5% reported foreign body sensation. Photophobia at one week was reported by 36.5% of participants in the

study by Vetrugno et al.[65] Rajan et al.[52] reported that 12 years after treatment, 5.9% of participants reported an occasional foreign body sensation.

Table 8 PRK case series (myopia): Overview of complications

Complications	Reference	Rate	%	Follow-up (months)
Potentially serious				
Keratitis/Infection	Hashemi 2004[42]	0/54	0.0	6
Persistent epithelial defect	Hashemi 2004[42]	0/54	0.0	6
Retinal detachment	Ruiz-Moreno 2003[57]	9/5936	0.15	mean 68.5
Choroidal neovascularization	Ruiz-Moreno 2000b[55]	1/5936	0.019	26
Epithelial ingrowth	Van Gelder 2002[64]	1/161	0.62	NR
Undesired complications				
Infiltrates	Van Gelder 2002[64]	1/161[a]	0.62	NR
	Vetrugno 2001[66]	2/80[b]	2.5	NR
Delayed re-epithelisation	Amoils 2000[38]	21/500	4.1	NR
	Vetrugno 2001[66]	1/80[c]	1.3	NR
Regression	Nagy 2001b[46]	27/130	20.8	12
	Pop 2000a[50]	25/646	3.9	12
Over correction	Autrata 2003a[37]	3/92	3.2	12
	Rao 2000a[54]	17/257	6.8	12
	Stevens 2002[60]	16/200	8.0	12
Under correction	Rao 2000a[54]	25/257	9.9	12
	Stevens 2002[60]	8/200	4.0	12
Raised intraocular pressure	Nagy 2001b[46]	10/130	7.6	NR[d]
	Nagy 2002c[48]	0/150	0	6
	Rajan 2004[52]	0/68	0	12 years
	Stojanovic 2003[61]	14/529	2.6	3
	Vetrugno 2000[65]	2/104	1.9	1
Re-treatment	Amoils 2000[38]	6/500	1.2	18
	Stevens 2002[60]	3/200	1.5	12
	Tole 2001[63]	11/308	3.6	6
Participant reported outcomes				
Haloes and/or glare	Amoils 2000[38]	12/500	2.4	18
	Pop 2000a[50]	136/646	21.0	12
	Pop 2000b[51]	12/82	14.6	12
	Nagy 2001b[46]	31/130	23.8	12
	Vetrugno 2000[65]	3/104[e]	2.9	6
Problems with night driving	Amoils 2000[38]	26/500	5.2	6
	Brunette 2000[39]	201/645	31.1	NR
	Vetrugno 2000[65]	60/104	57.7	<1 week
Night vision problems	Rajan 2004[52]	8/68[f]	12.0	12 years
Epiphora	Vetrugno 2000[65]	46/104	44.2	<1 week
Photophobia	Vetrugno 2000[65]	38/104	36.5	<1 week
Foreign body sensation	Vetrugno 2000[65]	40/104	38.5	<1 week
	Rajan 2004[52]	4/68	5.9	12 years
Itching	Vetrugno 2000[65]	40/104	38.5	<1 week
Dryness	Hovanesian 2001[43]	99/241	41.1	6
Soreness	Hovanesian 2001[43]	65/241	27.0	6
Eyelid sticking	Hovanesian 2001[43]	37/241	15.4	6
Sharp pains	Hovanesian 2001[43]	49/241	20.3	6

[a] Subepithelial
[b] Corneal
[c] >5 days to re-epithelisation
[d] Follow-up not reported; IOP normalised within 1 month after termination of fluorometholone treatment
[e] Glare only; no symptoms of haloes reported
[f] All participants reported subjective improvement in symptoms over 12 years of follow-up

4.5.2 Hyperopia

An overview of complications of H-PRK is presented in Table 11.

Potentially serious complications

Ectasia

No studies reported incidence of ectasia.

Other potentially serious complications

In the FDA report,[72] there was one eye (0.4%) with corneal oedema at one month, one eye (0.4%) with recurrent corneal erosion at three months, and three eyes (1.1%) with corneal infiltrates at one month. Williams et al.[73] reported that there were no cases of corneal infiltrates, decentred ablations, or infections.

Undesired complications

Delayed re-epithelisation

Williams et al. reported that one eye (1.9%), took seven days to completely heal. In the FDA report, 12 eyes (4.3%) took more than seven days to completely heal. Eight cases (15.4%) of superficial punctate keratitis were reported in the series by Williams et al.[73]

Refractive complications

A median rate of 16.3% (range, 5.5% to 27.0%) of participants lost one line of BSCVA and 7.0% (range, 0% to 13.5%) lost two or more lines (Table 9).

Three studies included participants with mild to moderate hyperopia. Across these studies, 14.9% (range, 3.8% to 16.3%) lost one line of BSCVA and 4.7% (range, 2.1% to 11.3%) lost two or more lines. Two studies included participants with high hyperopia (> +3.50 D), 19.8% (range, 7.4% to 32.1%) lost one line of BSCVA and 20.2% (range, 9.6% to 30.8%) lost two or more lines.

In eyes treated with newer generation lasers,[70,71] overall 8.5% (range, 5.5% to 16.3%) of eyes lost one line of BSCVA and 8.2% (range, 7.0% to 11.3%) lost two or more lines of BSCVA. In 40 eyes treated with wavefront-guided technology,[70,71] 17.5% and 12.5% lost one and two or more lines of BSCVA, respectively.

Table 9 H-PRK case series (hyperopia): Reduced BSCVA

Study ID		Follow-up (months)	Lost Snellen lines of BSCVA 1 line		≥2 lines	
			Rate	%	Rate	%
Autrata 2003b[36]		24	13/108	12	0	0
FDA 2000[72]		12	64/237	27.0	1/237	0.4
Nagy 2001a[69]	< +3.50	NR	72/482	14.9	10/482	2.1
	> +3.50	NR	102/318	32.1	98/318	30.8
Nagy 2002b[71]	< +3.50	12	4/106	3.8	5/106	4.7
	> +3.50		7/94	7.4	9/94	9.6
Nagy 2002d[70]		6	13/80	16.3	9/80	11.3

Haze

Two studies[69,71] reported average haze grade at 12 months according to Hanna's scale (Table 10). Williams et al.[73] reported that at 12 months, 79% (15/19 eyes) of eyes were clear of haze, 5% (1/19 eyes) had trace haze and that 16% (3/19 eyes) had haze graded one or more.

Table 10 H-PRK case series (hyperopia): Average haze grade at 12 months

Study ID	Group	Average haze at 12 months*
Nagy 2001a[69]	< +3.50 D	0.22 ±0.10
	> +3.50 D	0.34 ±0.21
Nagy 2002b[71]	≤ +3.50 D (astigmatism <1.00 D)	0.16 ±0.10
	≤ +3.50 D (astigmatism ≥1.00 D)	0.18 ±0.10
	≥ +3.50 D (astigmatism <1.00 D)	0.24 ±0.20
	≥ +3.50 D (astigmatism ≥1.00 D)	0.30 ±0.20

*according to Hanna's scale

In addition, the authors report that four eyes (0.5%) showed a central "bumplike" corneal opacity at two to three months, which decreased BSCVA.

Raised intraocular pressure (IOP)

Two studies by Nagy et al.[69,71] reported that, overall, 8.6% (range, 8.5% to 8.6%) of eyes experienced an increase in their IOP greater than 21 mm Hg. Follow-up was not reported but the authors stated that the problem resolved after discontinuation of corticosteroid therapy.

Participant reported outcomes

Haloes and glare

Four out of 52 eyes (7.7%) experienced haloes and shadowing at one week in the study by Williams et al.[73] All cases had resolved at one month. Glare and ghost images during

the daytime were reported in 13.9% of eyes (111/800 eyes) in a study by Nagy et al.[69] Participants with hyperopia > +3.50 D reported this symptom more frequently than those with hyperopia <+3.50 (21.6% versus 10.5%). In another study by Nagy et al.,[71] glare symptoms were reported in 15% of eyes (30/200 eyes). In a third study by Nagy et al.,[70] daytime glare and haloes were reported in 10% (8/80 eyes). Glare symptoms were reported less frequently in participants who had received wavefront-guided customised ablation (5% versus conventional H-PRK 15%).

Problems with night driving

Problems with night driving, including problems with glare effect from oncoming headlights, were reported in the three studies by Nagy et al.[69-71] a median rate of 24.8% (range, 15.0% to 26.8%) of participants reported problems with night driving. In 280 eyes treated with a newer generation laser (MEL 70),[70,71] a median of 18.0% of participants reported problems. Of these 40 eyes were treated with wavefront-guided technology, with 7.5% of participants reporting problems. In the FDA report,[72] 12 months after treatment, 3.4% (6/180) of participants reported that night driving was worse than before surgery.

Ocular symptoms

Photophobia at one week was reported by 7.7% of participants in the study by Williams et al.[73] There was one eye with foreign body sensation at the three, six and 12 months follow-up, respectively, reported in the FDA report.[72]

Table 11 H-PRK case series (hyperopia): Overview of complications

Complications	Reference	Rate	%	Follow-up (months)
Potentially serious				
Keratitis/Infection	Nagy 2002b[71]	0/200	0.0	12
Corneal oedema	FDA 2000[72]	1/275	0.4	1
Recurrent corneal erosion	FDA 2000[72]	1/272	0.4	3
	Nagy 2002b[71]	0/200	0.0	12
Undesired complications				
Superficial punctuate keratitis	Williams 2000[73]	8/52	2.5	NR
Infiltrates	FDA 2000[72]	3/275	1.1	1
	Nagy 2002b[71]	0/200	0.0	12
	Williams 2000[73]	0/52	0.0	12
Delayed re-epithelisation	FDA 2000[72]	12/276[a]	4.3	NR
	Vetrugno 2000[65]	2/104	1.9	NR
	Williams 2000[73]	1/52	1.9	NR
Regression of UCVA	Nagy 2001a[69]	457/800	57.0	12
Over correction	FDA 2000[72]	4/217	1.8	12
	Nagy 2002b[71]	2/200	1.0	12
Under correction	FDA 2000[72]	47/217	21.7	12
Raised intraocular pressure	Nagy 2001a[69]	69/800	8.6	NR[b]
	Nagy 2002b[71]	17/200	8.5	NR[b]
Re-treatment	FDA 2000[72]	2/276	0.7	12
Participant reported outcomes				
Haloes and glare	Nagy 2001a[69]	111/800	13.9	12
	Nagy 2002b[71]	30/200	15.0	12
	Nagy 2002d[70]	8/80	10.0	6
	Williams 2000[73]	4/52[c]	7.7	1 week
Problems with night driving	FDA 2000[72]	6/180	3.4	12
	Nagy 2001a[69]	214/800	26.8	12
	Nagy 2002b[71]	42/200	21.0	12
	Nagy 2002d[70]	12/80	15.0	6
Photophobia	Williams 2000[73]	4/52	7.7	1 week
Foreign body sensation	FDA 2000[72]	1/237	0.4	12

[a] >7 days to re-epithelisation
[b] Follow-up not reported but IOP normalised within 1 month after termination of fluorometholone treatment
[c] All cases had resolved at 1 month

4.5.3 Astigmatism

An overview of complications of PARK is presented in Table 13.

Potentially serious complications

Ectasia

No studies reported incidence of ectasia.

Other potentially serious complications

MacRae et al.[77] reported on a series of 749 eyes that had undergone PARK for myopic astigmatism. One eye developed persistent corneal epithelial defect and viral keratitis at four days resulting in stromal scarring. Another eye developed significant stromal

infiltrates a few days after treatment. The authors reported that each of these cases resolved and did not lead to persistent or significant lost of visual acuity. Corneal oedema was reported in 0.4% of eyes within the first month. There was one case of retinal detachment and one case of vitreous haemorrhage at six months, both considered to be unrelated to treatment. In addition, there was one case of anterior ischaemic optic neuropathy, which occurred at 18 months.

Undesired complications

Refractive complications

Three studies reported the number of lines of BSCVA lost following treatment with PARK; 7.1% lost one line of BSCVA and 0.6% (range 0% to 1.6%) lost two or more lines (Table 12).

Table 12 PARK case series (astigmatism): Reduced BSCVA

Study id	Follow-up (months)	Lost Snellen lines of BSCVA 1		≥2	
		Rate	%	Rate	%
Haw 2000a[75]	24	-	-	1/63	1.6
MacRae 2000[77]	12	-	-	6/473	0.6
Shen 2002[59]	6	4/56	7.1	0/56	0

Haze

Haw et al.[75] reported that at two years, 13.5% of eyes (8/59 eyes) have trace or mild corneal haze and no eyes had moderate or severe haze (0 to 5 scale). MacRae et al.[77] reported haze scores at six months: 0.6% (4/634 eyes) of eyes showed mild (2+) haze, 0.3% (2/634 eyes) had moderate (3+) haze. There were no reports of 'marked' (4+) haze in any eye. Shen et al.[59] reported that no eye had greater than grade two haze (graded according to Hanna's scale) at any time during follow-up.

Raised intraocular pressure (IOP)

MacRae et al.[77] reported that five eyes (0.6%) had IOP readings >25 mmHg at three months.

Participant reported outcomes

Haw et al.[76] reported that at 12 months, 37.3% of eyes had an increase in halo score compared to baseline. Median halo score increased from 0 prior to PRK to 1 at 12 months. At two years,[75] mean halo score was statistically significantly increased

compared to the preoperative level. Haw et al.[76] also reported that 27.1% of eyes experienced an increase in glare score from baseline at 12 months. At two years,[75] the mean glare score showed a non-significant increase compared to the preoperative score. There were no other participant reported outcomes presented in any of the included studies.

Table 13 PARK case series (astigmatism): Overview of complications

Complications	Reference	Rate	%	Follow-up (months)
Potentially serious				
Keratitis/Infection	MacRae 2000[77]	1/749[a]	0.13	4 days
Persistent epithelial defect	MacRae 2000[77]	1/749	0.13	4 days
Infiltrates	MacRae 2000[77]	1/749	0.1	4 days
Retinal detachment	MacRae 2000[77]	1/749[b]	0.13	6
Optic neuropathy	MacRae 2000[77]	1/749	0.13	18
Corneal oedema	MacRae 2000[77]	3/749	0.4	1
Vitreous haemorrhage	MacRae 2000[77]	1/749[b]	0.13	6
Undesired complications				
Over correction	Haw 2000a[75]	3/59	5.1	24
Under correction	Haw 2000a[75]	8/59	13.6	24
Raised IOP	MacRae 2000[77]	5/749	0.6	3
Re-treatment	Haw 2000a[75]	24/93	25.8	24
Participant reported outcomes				
Haloes	Haw 2000c[76]	NR	37.3	12
Glare	Haw 2000c[76]	NR	27.1	12

[a] Viral keratitis
[b] Considered unrelated to treatment

4.6 Overview of efficacy findings

4.6.1 Myopia

Accuracy

Three to six months after treatment with PRK, a median rate of 75.9% (range, 53.9% to 92.3%) of eyes treated for myopia and myopic astigmatism were within 0.5 D of their intended correction and 93.0% (range, 48.0% to 97.8%) were within 1.0 D (Table 14).

Table 14 PRK case series (myopia): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (3 – 6 months follow-up)

Study id		Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
			Rate	%	Rate	%
Amoils 2000[38]		6	354/405	87.3	400/405	97.8
Cennamo 2003[40]		6	-	-	217/452	48.0
Hashemi 2004[42]		3	33/48	68.7	43/48	89.6
Pop 2000a[50]		3	442/578	76.5	539/578	93.3
Pop 2000b[51]		3	64/86	74.4	80/86	93.0
Rao 2000a[54]		3	138/257	53.9	215/257	83.7
Shen 2002[59]		6	-	-	52/61	85.2
Tole 2001[63]	≤ 3.00 D	3	100/119	84.0	115/119	96.6
	>3.00 to ≤ 6.00 D	3	97/129	75.2	122/129	94.6
Vetrugno 2000[65]		4	96/104	92.3	-	-

After 12 or more months of follow-up, a median rate of 68.0% (range, 56.5% to 87.4%) of eyes were within 0.5 D of their intended correction and 86.0% (range, 39.1% to 95.8%) were within 1.0 D (Table 15).

For eyes with low to moderate myopia, after 12 months or more follow-up, a median rate of 71.6% (range, 65% to 88.7%) and 90.4% (range, 78.3% to 98.8%) were within 0.5 D and 1.0 D of their intended correction, respectively. In highly myopic eyes, 44.4% (range, 25.0% to 61.2%) were within 0.5 D of their intended correction and 61.9% (range, 33.3% to 83.8%) were within 1.0 D, these findings were largely dominated by the large study by Cennamo et al.[40] including eyes with particularly high myopia between -7.0 and -17.0 D.

One study included participants treated with newer generation lasers.[46] In participants with low to moderate myopia 73.3% and 98.8% of eyes were within 0.5 D and 1.0 D of their intended correction, respectively. In eyes with high myopia, 57.5% and 80.0% achieved within 0.5 D and 1.0 D respectively.

Rao et al.[54] reported that, at three months, 9.1% (23/257 eyes) of eyes had an overcorrection of 1.0 D or more and that 4.3% (11/257 eyes) had an under correction of 1.0 D or more. Across three studies,[37,54,60] 6.6% (range, 3.2% to 8%) of eyes were overcorrected of 1.0 D or more at 12 months. Across two studies,[54,60] 7.2% (range, 4% to 9.9%) of participants were undercorrected ≥1.0 D at 12 months.

Table 15 PRK case series (myopia): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (last follow-up)

Study id		Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
			Rate	%	Rate	%
Amoils 2000[38]		18	83/95	87.4	91/95	95.8
Autrata 2003a[37]		24	52/91	57.0	84/91	91.0
Cennamo 2003[40]		12	-	-	134/343	39.1
Kapadia 2000a[44]	-1.0 to -3.0 D	12	63/71	88.7	70/71	98.6
	-3.1 to -6.0 D	12	86/123	69.9	112/123	91.0
	> -6.1 D	12	24/42	57.1	34/42	81.0
Nagy 2001b[46]	-1.5 to -6.0 D	NR	66/90	73.3	89/90	98.8
	-6.1 to –9.0 D	NR	19/31	61.2	26/31	83.8
	-9.1 to –14.0 D	NR	4/9	44.4	6/9	66.6
Pietila 2004[49]	≤ -6.0 D	96	45/69	65.2	54/69	78.3
	-6.1 to –10.0 D	96	4/16	25.0	11/16	68.8
	> -10.0 D	96	3/7	42.9	4/7	57.1
Pop 2000a[50]		12	539/646	83.5	617/646	95.5
Pop 2000b[51]		12	68/82	82.9	77/82	93.9
Rajan 2004[52]		12 years	-	-	33/69	47.8
Rao 2000a[54]		12	146/257	56.9	188/257	73.6
Rao 2000b[53]	<-6.0 D	NR	-	-	78/87	89.7
	-6 to -9.9 D	NR	-	-	54/98	55.1
	> -10 D	NR	-	-	27/81	33.3
Stevens 2002[60]		12	116/200	58	171/200	86.0
Vetrugno 2001[66]		NR	54/80	67.5	64/80	80.0

NR not reported

Uncorrected visual acuity (UCVA)

Three to six months after treatment with PRK, a median rate of 66.7% (range, 54.9% to 69.9%) had a UCVA of 20/20 or better and 93.0% (range, 48.9% to 98.6%) had a UCVA of 20/40 or better (Table 16). The study by Cennamo et al.[40] included highly myopic eyes (-7.0 D to -17.0 D), 48.9% of participants achieved a UCVA of 20/40 or better.

Table 16 PRK case series (myopia): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (3 – 6 months follow-up)

Study id		Follow-up (months)	20/20 or better		20/40 or better	
			Rate	%	Rate	%
Amoils 2000[38]		6	283/405	69.9	400/405	98.6
Cennamo 2003[40]		6	-	-	221/452	48.9
Hashemi 2004[42]		3	32/48	66.7	47/48	97.7
Pop 2000b[51]		3	60/86	69.8	81/86	94.2
Rao 2000a[54]		3	141/257	54.9	227/257	88.2
Shen 2002[59]		6	-	-	56/61	91.8
Tole 2001[63]	≤ -3.0 D	3	77/120*	64*	-	-
	>-3.0 to -6.0 D	3	69/130	53	-	-

*Approximated from bar chart

After at least 12 months of follow-up, a median rate of 70.4% (range, 0.4% to 87.0%) and 92.3% (range, 37.6% to 98.8%) of participants had a UCVA of 20/20 and 20/40, respectively (Table 17).

In eyes with low to moderate myopia, 76.4% (range, 50.7% to 82%) and 96.3% (range, 78.2% to 97%) had a UCVA of 20/20 and 20/40, respectively, after 12 months or more. In eyes with high myopia, 14.3% (range, 0% to 45%) had a UCVA of 20/20 or better and 68.4% (range, 22.2% to 100%) had a UCVA of 20/40 or better.

Two studies[46,48] treated participants using newer generation lasers (MEL 70) and, in eyes with low to moderate myopia 79.2% and 95.5% of eyes had an UCVA of 20/20 and 20/40 or better respectively. In eyes with high myopia, 20.0% had an UCVA of 20/20 or better and 62.5% of eyes had an UCVA of 20/40 or better. In 150 eyes treated using wavefront-guided technology,[48] 80.7% of patients achieved an UCVA of 20/20 or better.

Table 17 PRK case series (myopia): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (last follow-up)

Study id		Follow-up (months)	20/20 or better		20/40 or better	
			Rate	%	Rate	%
Amoils 2000[38]		18	66/95	69.5	94/95	98.8
Cennamo 2003[40]		24	-	-	97/258	37.6
Kapadia 2000a[44]	-1.0 to -3.0 D	12	53/71	75	69/71	97
	-3.1 to -6.0 D	12	78/123	63	119/123	97
	>-6.1 D	12	19/42	45	39/42	93
Nagy 2002c[48]		NS	121/150	80.7	-	-
Nagy 2001b[46]	-1.5 to 6.0 D	12	70/90	77.7	86/90	95.5
	-6.1 to –9.0 D	12	8/31	25.8	23/31	74.2
	-9.1 to –14.0 D	12	0/9	0	2/9	22.2
Pietila 2004[49]	≤-6.0 D	8 years	35/69[a]	50.7	54/69	78.2
	-6.1 to –10.0 D	8 years	0/16[a]	0	10/16	62.5
	>-10.0 D	8 years	1/7[a]	14.3	7/7	100
Pop 2000a[50]		12	560/646	87	633/646	98
Pop 2000b[51]		12	70/82	85.4	80/82	97.6
Rao 2000a[54]		12	143/257	55.6	216/257	84.0
Stevens 2002[60]		12	163/199	82	-	-
Vetrugno 2000[65]		12	74/104	71.2	96/104	92.3

[a] Participants achieving 20/20

Myopic astigmatism

Three studies[50,51,67] reported the percentage of participants achieving their intended astigmatic correction (Table 18). Overall in two studies by Pop et al.,[50,51] 84.5% of eyes (range, 83% to 86%) were within 0.5 D and 95.5% (range, 93% to 98%) were within 1.0 D, of their intended correction. Yang et al.[67] reported that 42.3% (44/104 eyes) were within 0.25 D. In the same study it was reported that 33.7% of eyes (35/104 eyes) experienced

an increase of more than 0.25 D of astigmatism and 24.0% of eyes (25/104 eyes) experienced a decrease more than 0.25 D of astigmatism.

Table 18 PRK case series (myopia): Refractions within ±0.5 D and ±1.0 D of intended cylinder correction

Study id	Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
		Rate	%	Rate	%
Pop 2000a[50]	12	556/646	86	633/646	98
Pop 2000b[51]	12	68/82	83	76/82	93

Stability of corrected vision

Stevens et al.[60] reported that 40% (70/175 eyes) of eyes changed by more than 1.0 D between one to 12 months. Change in refraction between two and eight years was reported by Pietila et al.[49] 68.6% (48/70 eyes) of eyes had a change of 0.5 D or more and no eye had a change of more than -2.0 D. Rajan et al.[52] reported that there was no significant change in refractive stability in their study between one and 12 years. Two studies reported regression rates at 12 months. Nagy et al.[46] reported that 20.8% of eyes (27/130 eyes) had 'slight' regression towards to their pre-operative error. Regression was more frequent in participants with myopia more than -6.00 D (30% versus 16.7%). Pop[50] reported that at 12 months 3.9% eyes had regression of their corrected vision more than 1.0 D.

Re-treatment

Tole et al.[63] reported that 3.6% (11/308 eyes) of eyes required re-treatment. Re-treatments were performed in six eyes (1.2%) in the study by Amoils et al.[38]

4.6.2 Hyperopia

Accuracy

After six months, 67.4% (range, 63.3% to 76.3%) of participants were within 0.5 D of their intended correction and 88.4 % (range, 86.7% to 91.3%) were within 1.0 D (Table 19).

One study[70] included eyes treated with a newer generation laser, including 40 eyes treated with wavefront-guided technology. Overall, 76.3% and 91.3% of eyes were within 0.5 D and 1.0 D of their intended correction. In the 40 eyes treated using wavefront, 85% were within 0.5 D and 100% were within 1.0 D.

Table 19 H-PRK case series (hyperopia): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (3 - 6 months follow-up)

Study id	Follow-up (months)	Achieving ≤±0.5 D		Achieving ≤±1.0 D	
		Rate	%	Rate	%
FDA 2000[72]	3	157/248	63.3	215/248	86.7
Nagy 2002d[70]	6	61/80	76.3	73/80	91.3
Williams 2000[73]	6	29/43	67.4	38/43	88.4

Twelve months or more after treatment, 60.8% (range, 53.8% to 79.0%) and 78.9% (range, 69.6% to 86.0%) of participants were within 0.5 D and 1.0 D of their intended correction, respectively (Table 20).

In participants with hyperopia less than +3.50 D, 75.4% (range, 74.4% to 76.4%) were within 0.5 D and 86.8% (range, 84.8% to 88.7%) were within 1.0 D, of their intended correction. In participants with hyperopia more than +3.50 D, 42.6% (range, 22.3% to 62.8%) and 62.8% (range, 46.8% to 78.7%) of eyes were within 0.5 D and 1.0 D of their intended correction, respectively.

One study[71] included patients treated with a newer generation laser (MEL 70). In eyes with hyperopia less than +3.50 D, 76.4% and 88.7% were within 0.5 D and 1.0 D of their intended correction, respectively. In eyes with hyperopia more than +3.50, 62.8% were within 0.5 D and 78.7% were within 1.0 D.

Table 20 H-PRK case series (hyperopia): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (last follow-up)

Study id		Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
			Rate	%	Rate	%
Autrata 2003b[36]		24	62/109	56.9	93/109	86.0
FDA 2000[72]		12	132/217	60.8	166/217	76.5
Nagy 2001a[69]	< +3.50 D	NS	359/482	74.4	408/482	84.8
	> +3.50 D	NS	71/318	22.3	149/318	46.8
Nagy 2002b[71]	≤ +3.50 D	12	81/106	76.4	94/106	88.7
	≥ +3.50 D	12	59/94	62.8	74/94	78.7
Williams 2000[73]		12	15/19	79.0	15/19	78.9

One study[71] that used the MEL 70 laser reported 4% of eyes were overcorrected at three months falling to 1% at 12 months. In the FDA report,[72] 1.8% (4/217 eyes) of eyes were overcorrected less than -1.0 D and 21.7% (47/217 eyes) of eyes were under corrected by more than 1.0 D, at 12 months.

Uncorrected visual acuity (UCVA)

Three to six months after H-PRK, 39.0% (range, 37.8% to 72.5%) and 85.4% (range, 85.0% to 89.1%) of participants achieved 20/20 or better and 20/40 or better UCVA, respectively. Results are shown in Table 21. In the study that treated eyes with the MEL 70 laser,[70] 72.5% and 85.0% of eyes had an UCVA of 20/20 and 20/40 or better, respectively. In 40 eyes treated using wavefront technology, 70% had an UCVA of 20/20 or better and 75%, 20/40 or better.

Table 21 H-PRK case series (hyperopia): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (3-6 months follow-up)

Study id	Follow-up (months)	20/20 or better		20/40 or better	
		Rate	%	Rate	%
FDA 2000[72]	3	87/230	37.8	205/230	89.1
Nagy 2002d[70]	6	58/80	72.5	68/80	85.0
Williams 2000[73]	3	16/41	39.0	35/41	85.4

After more than 12 months following PRK treatment, 59.0% (range, 48.8% to 84.0%) of participants had an UCVA of 20/20 or better and 85.5% (range, 72.1% to 95.1%) had UCVA 20/40 or better.

For participants with low/moderate hyperopia (< +3.50 D), 79.9% (range, 75.7% to 84.0%) and 89.5% (range, 88.4% to 90.6%) had 20/20 or better and 20/40 or better UCVA, respectively, after 12 or more months of follow-up. For participants with hyperopia greater than +3.50, 52.8% (range, 34.2% to 71.3%) had a UCVA of 20/20 or better and 63.7% (range, 47.5% to 79.8%) had an UCVA of 20/40 or better. Results are shown in Table 22.

In one study using the newer generation MEL 70 laser,[71] 84.0% and 90.6% of eyes with low to moderate myopia, had an UCVA of 20/20 and 20/40 or better, respectively. In eyes with high myopia, 71.3% and 79.8% of eyes had an UCVA of 20/20 or 20/40 or better, respectively.

Table 22 H-PRK case series (hyperopia): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (last follow-up)

Study id		Follow-up (months)	20/20 or better		20/40 or better	
			Rate	%	Rate	%
Autrata 2003b[36]		24	79/108	73.1	87/108	80.5
FDA 2000[72]		12	100/205	48.8	195/205	95.1
Nagy 2001a[69]	< +3.50 D	NS	365/482	75.7	426/482	88.4
	> +3.50 D	NS	109/318	34.2	151/318	47.5
Nagy 2002b[71]	≤ +3.50 D	NS	89/106	84.0	96/106	90.6
	≥ +3.50 D	NS	67/94	71.3	75/94	79.8
Williams 2000[73]		12	10/19	52.3	17/19	89.5

Stability of corrected vision

In the FDA report,[72] 95.7% of eyes changed ≤1.00 D of manifest refractive spherical equivalent between nine and 12 months. Nagy et al.[71] reported that UCVA was stable in 76.0% of eyes (152/200 eyes). Nagy et al.[69] also reported that overall, regression of UCVA occurred in 57% (457/800) of eyes during follow-up. Regression occurred more frequently in participants with hyperopia > +3.50 D (> +3.50 84% versus < +3.50 39.4%).

Re-treatment

In the FDA report,[72] two eyes (0.7%) underwent re-treatment.

4.6.3 Astigmatism (PARK)

Accuracy

At six months follow-up, 58.7% (range, 55% to 62.3%) and 75.0% (range, 62.5% to 86.1%) were within 0.5 D and 1.0 D of their intended correction, respectively (Table 23).

Table 23 PARK case series (astigmatism): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (3 – 6 months follow-up)

Study id	Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
		Rate	%	Rate	%
Haw 2000a[75]	6	47/86	55	64/86	75
MacRae 2000[77]	6	394/632	62.3	544/632	86.1
Shen 2002[59]	6	-	-	35/56	62.5

After at least 12 months of follow-up, 55.3% (range, 40.7% to 69.8%) of participants had post-operative refraction within 0.5 D of their intended correction and 83.8% (range, 81.3% to 87.9%) were within 1.0 D (Table 24).

Table 24 PARK case series (astigmatism): Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction (last follow-up)

Study id	Follow-up (months)	Achieving ≤± 0.5 D		Achieving ≤± 1.0 D	
		Rate	%	Rate	%
MacRae 2000[77]	12	-	-	397/474	83.8
Haw 2000a[75]	24	24/59	40.7	48/59	81.3
Shah 2002[58]	NS	4256/6097	69.8	5359/6097	87.9

Haw et al.[75] reported that 25.9% (22/85 eyes) and 13.6% (8/59 eyes) of eyes were undercorrected by more than 1.0 D, at six months and last follow-up, respectively. No eyes were overcorrected at six months and 5.1% (3/59 eyes) of eyes were overcorrected by more than 1.0 D at last-follow up.

Uncorrected visual acuity (UCVA)

At six months, following treatment with PARK, 60.2% (range, 56% to 64.3%) of participants had achieved a UCVA of 20/20 or better and 83.9% (82% to 93.5%) had a UCVA of 20/40 or better (Table 25).

Table 25 PARK case series (astigmatism): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (3 - 6 months follow-up)

Study id	Follow-up (months)	20/20 or better		20/40 or better	
		Rate	%	Rate	%
Haw 2000a[75]	6	48/86	56	70/86	82
MacRae 2000[77]	6	406/631	64.3	590/631	93.5
Shen 2002[59]	6	-	-	47/56	83.9

After 12 or more months of follow-up, 62.6% (range, 58% to 67.1%) had a UCVA of 20/20 or better and 93.5% (range, 91.2% to 95%) had a UCVA of 20/40 or better (Table 26).

Table 26 PARK case series (astigmatism): Eyes achieving Snellen acuity 20/20 or better and 20/40 or better (last follow-up)

Study id	Follow-up (months)	20/20 or better		20/40 or better	
		Rate	%	Rate	%
Haw 2000b[74]	24	34/59	58	56/59	95
MacRae 2000[77]	12	320/477	67.1	446/477	93.5
Shah 2002[58]	12	-	-	5561/6097	91.2

Astigmatism

MacRae et al.[77] reported that at six months, 75% (474/632 eyes) were within 0.5 D and 93% (588/632 eyes) were within 1.0 D of the intended zero cylinder outcomes. Shen et al.[59] reported that 91.1% of participants treated with PARK were within 1.0 D of

astigmatism. Haw et al.[76] reported that 73.2% (52/71 eyes) of eyes had an under correction of astigmatism at 12 months.

Stability of corrected vision

Haw et al.[76] reported that there was a slight trend towards myopic regression until the six month follow-up. A mean of 0.27 D of myopic regression occurred between one and 12 months.

Re-treatment

Haw et al.[75] reported that 24 months after treatment, 25.8% (24/93 eyes) had undergone a re-treatment procedure after their initial treatment with PARK.

5 LASEK RESULTS

5.1 Type and quantity of available evidence

Full-text prospective case series of LASEK with 25 or more eyes, as well as abstracts and retrospective case series, with 50 or more eyes were included. Non-randomised comparative studies in which at least one arm assessed the efficacy and/ or safety of LASEK were also included (with sufficient eyes), and the LASEK arm treated as a case series. For studies with multiple publications, only the most up to date full text report was considered. Best efforts were made to avoid including duplicated data, including contacting authors for information, however some abstracts without contact details provided very little information regarding the setting and dates of LASEK treatment. The primary studies along with their related references are listed in Appendix 4.

5.2 Number and type of included studies

Twenty-six primary case series from 40 papers were included. Seventeen were full-text papers[20-23,25,26,78-101] and nine were abstracts.[102-111] Tables 27 and 28 show respectively the lists of full text studies and studies reported only in abstract format. The study characteristics are described in Appendix 7.

There were 21 case series, one study was an RCT of alternative topical agents for analgesia, both arms have been included and the study treated as a case series.[80] Three were non-randomised comparative studies comparing LASEK and LASIK[89,102,107] or LASEK and PRK,[93] in each case the LASEK arm was treated as a case series.

Participants with myopia or myopic astigmatism were included in all studies, only three studies included some participants with hyperopia,[23,98,100] the inclusion criteria were unclear in a further two studies.[105,109] Two studies included participants who were unsuitable for LASIK because of thin corneas or corneal topography suspicious of forme fruste keratoconus.[83,106] Data were presented for low/moderate myopia participants (<6.0 D) in seven studies,[78,80,93,95,102,104,110] and for high myopia (>6.0 D) in five studies.[20,78,82,89,104]

Six of the primary studies were set in the USA, four in Italy, two in the UK, two in Poland, two in South Korea and one only in Austria, Belgium, Germany, Ireland, Iran,

Russia, Saudi Arabia, Switzerland and Turkey, the location was not provided in one abstract.

The source of funding was unclear in 22/26 studies, although no proprietary interest in the instruments or techniques was noted in six of these studies. Ophthalmic Foundations provided funding in two studies,[78,107] technical assistance was provided by one manufacture,[88] and government funding was provided for one study.[89]

In total, the 26 studies included over 3000 participants (5091 eyes) with a mean age for each study between 26 and 42 years. The study sample size ranged from 36 to 603 eyes. Where reported the percentage of women ranged from 52 to 73%. Treatment dates were unclear in 16 studies. The earliest reported procedures were carried out from 1996 to July 2000.[95] Seven studies only reported treatments carried out after January 2000.[78,80,82,83,89,94,97] All treatments used an alcohol solution to loosen the epithelium. Average follow-up was between three months[102] to 27 months[20] and ranged from one month[94] to 38 months.[20]

Table 27 Included studies – LASEK case series, full text

Study id	Number of Participants	Number of eyes	Mean age (years)	Follow-up (months)	Pre-operative spherical equivalent (D)			Laser
Full-text					mean	SD	range	
Anderson 2002[78]	188	343	38	6	-5.42	2.62	-1.0 to -14.0	VISX Star S2
Badala 2004[80]	135	135	29	3	-3.05	NR	NR	Laserscan 2000
Bilgihan 2004[82]	36	61	32.3	12.1*	-7.33	1.00	-6.00 to –10.0	MEL 60
Camellin 2003[20]	56	76	37	26*	-11.7	3.30	-8.00 to -22.5	NIDEK EC-5000
Claringbold 2002[26]	127	222	39	12	-4.89	NR	-1.25 to -11.25	VISX Star S2
Hashemi 2004[83]	56	71	29	3	-5.14	1.66	-1.50 to –8.75	NIDEK EC-5000
Horwarth 2004[88]	21	37	32	6	-4.90	NR	-1.0 to –8.0	Keratome 1
Kim 2004[89]	73	146	27.9	12	-8.01	1.85	-6.00 to –12.50	NIDEK EC-5000
Lee 2002[25]	48	84	26.4	6	-4.72	1.08	-3.25 to –7.00	Keratome II
Lin 2004[23]	52	90	40.9	6	-5.46	3.74	+4.88 to –12.00	LADARVision ® 4000
Partal 2004[92]	56	102	NR	12	-7.03	2.60	–1.25 to -11.63 to	Bausch & Lomb Technolas 217
Shah 2001[93]	36	36	33.5	12	-3.49	1.36	-1.00 to –6.10	NIDEK EC-5000
Shahnian 2002[94]	83	146	42	12	NR	NR	-1.25 to -14.38	VISX or NIDEK
Taneri 2004[95]	105	171	36	8*	-2.99	1.43	-0.38 to –7.75	VISX Star S2/Apex SVS/Technolas 217A
Vandorselaer 2003[97]	27	45	33	9*	NR	NR	-1.75 to –9.75	INPRO Gauss or NIDEK EC-5000
Vinciguerra 2003[98]	452	773	34.3	12	-5.30	3.70	-22.50 to +5.50	NIDEK EC-5000
Vinciguerra 2004[100]	167	297	35	12	-5.46	2.57	-14.13 to +3.50	NIDEK EC-5000 with CATz software

*mean value

Table 28 Included studies – LASEK case series, abstracts

Study id	Number of participants	Number of eyes	Mean age (years)	Follow-up (months)	Pre-operative spherical equivalent (D)			Laser
Abstracts					mean	SD	range	
Condon 2003[102]	NR	509	NR	3	NR	NR	<6.0	NR
Gabler 2002[104]	NR	100	NR	6	NR	NR	<6.0	Keracor 217
	NR	60			NR	NR	-6.0 to –12.0	
Gierek 2002[105]	200	320	NR	12	NR	NR	NR	MEL 70
Kornstein 2003[106]	24	43	NR	5*	-7.21	3.20	NR	NR
Kotb 2004[107]	NR	86	NR	6	NR	NR	-1.0 to –13.75	Keracor 217 Z
Liberek 2002[108]	150	260	NR	12	NR	NR	-2.00 to –12.00	MEL 70
Molnar 2002[109]	NR	603	NR	12	-12.00	3.50	NR	NIDEK EC-5000
Vorotnikova 2004[110]	32	56	27.6	12	-2.48	NR	-0.62 to -4.75	NIDEK EC-5000
Wren 2003[111]	NR	219	NR	7.6*	-4.90	NR	-1.25 to –12.50	Summit Technology Apex Plus

* mean value

5.3 Number and type of excluded studies

From 278 screened papers, 85 were identified as being potentially relevant. Thirty-nine studies met the inclusion criteria and from this 26 separate studies were identified. Commonest reasons for exclusion were: fewer than 25 eyes and LASEK treatments with non-standard adjunctive treatment such as trials of mitomycin-C for the treatment of haze.

5.4 Quality of available evidence

A summary of the quality assessment of the 17 full-text non-randomised studies is presented in Table 29 and the detailed quality assessment results for included studies can be seen in Appendix 8.

Table 29 Summary of the quality assessment of the LASEK case series

Criteria		Yes	No	Unclear
1.	Were participants a representative sample selected from a relevant population?	10	0	7
2.	Are the inclusion/exclusion criteria of the participants in the study clearly described?	11	6	0
4.	Was selection of participants consecutive?	11	3	3
5.	Was data collection undertaken prospectively?	13	4	0
7.	Was the intervention (and comparison) clearly defined?	17	0	0
8.	Was the intervention undertaken by someone experienced in the procedure?	1	2	14
9.	Were the staff, place, and facilities where the participants were treated appropriate for performing the procedure?	17	0	0
10.	Were all important outcomes considered?	13	4	0
11.	Were objective (valid and reliable) outcome measures used?	17	0	0
13.	Was the follow-up long enough to detect important effects on outcomes of interest?	17	0	0
14.	Was information provided on non-respondents and dropouts?	13	4	0
15.	Were participants lost to follow up likely to introduce bias?	7	8	2
17.	Were all important prognostic factors identified?	10	4	3
19.	Was the paired nature of eyes taken into account in the analyses?	2	12	3

Note: questions 3, 6, 12, 16 and 18 were not relevant to either case series or this intervention

When studies reported information on participants lost to follow-up there was often a high drop out rate. The direction of bias that may result from this is unclear, but those returning for repeated follow-up appointments may have higher complication rates. Important prognostic factors such as the degree of myopia and pre-existing eye and skin

problems before treatment with LASEK, had been taken into account in ten of the studies. At least two studies were carried out in people who may be considered unsuitable for LASIK eye surgery, for example, people with a thin cornea.[83,106]

5.5 Overview of safety findings

5.5.1 Potentially serious complications

Ectasia

One study [95] with 171 eyes reported no cases of ectasia.

Other potentially serious complications

Perioperative complications reported (see Table 30) included one case of decentration of ablation which occurred in a participant with high myopia, leading to one or two line loss of BSCVA,[89] one case of keratitis in a high myopia participant (not defined as microbial keratitis), the keratitis resolved in a few days and the participant achieved a BSCVA of 20/20 at six months.[82] Fourteen cases of infection were reported although the exact site and severity were not stated.[102,105] Two eyes of participants with high myopia developed irregular astigmatism leading to a loss of one or two lines of BSCVA.[89] There were three cases of recurrent erosion reported (1%); no further details were provided.[105] One eye developed a macular cyst leading to loss of two lines of BSCVA (to 20/40).[78]

Table 30 LASEK case series: Potentially serious complications

Potentially serious complications	Reference	Rate	%
Perforation	Taneri 2004[95]	0/171	0
Decentration of ablation	[a]Kim 2004[89]	1/146	0.7
	Taneri 2004[95]	0/171	0
Acute epithelial complications	[b]Shah 2001[93]	0/36	0
Recurrent erosion	Claringbold 2002[26]	0/222	0
	[c]Gierek-Ciaciura 2002[105]	3/320	1.0
	Lee 2002[25]	0/84	0
Keratitis	[d]Bilgihan 2000[82]	1/39	2.6
Infection	Lee 2002[25]	0/84	0
	[e]Condon 2003[102]	3/509	0.6
	[f]Gierek-Ciaciura 2002[105]	11/320	3.4
Stromal melting	Taneri 2004[95]	0/171	0
Scarring	Taneri 2004[95]	0/171	0
Irregular astigmatism	[g]Kim 2004[89]	2/146	1.4
Ectasia	Taneri 2004[95]	0/171	0
Macular cyst	Anderson 2002[78]	1/343	0.3

[a] high myopia patients, decentration of ablation leading to 1 or 2 line loss of BSCVA
[b] no epithelial defects or infiltrates
[c] no details provided
[d] high myopia patients, states keratitis but unclear whether bacterial keratitis, resolved in a few days and achieved BSCVA 20/20 at 6 months
[e] site and severity of infection not specified
[f] site and severity of infection not specified
[g] all high myopia patients, irregular astigmatism leading to a loss of one or two lines of BSCVA

5.5.2 Undesired consequences

Peri-operative complications

Problems during the procedure included alcohol leakage in 3/84 eyes, difficulty with detaching the flap reported in five studies with a rate of 39/949 (median 2%; range 0% to 14%); this led to conversion to PRK,[83] but was also suggested to lead to development of greater than grade two haze accompanied by regression.[105] In one study, small flap tears during surgery which did not appear to affect the surgical outcome at the time, led to minor symptoms at three and 12 months (occasional pain, scratchy sensation, slight pulling sensation, and slight foreign body sensation).[94] Formation of a central island was traced back to poor laser maintenance.[94] Corticosteroid induced, raised IOP was reported in one study, which was controlled with a beta-blocker (Table 31).

Refractive complications

Table 32 provides details of reduced BSCVA. The rate of loss of one line of BSCVA was 50/1722 (2.9%, median 2.2%; range 0% to 16%), and for two lines 22/2545 (0.9% median 0%; range 0% to 8.2%). The three studies[20,82,89] that reported 19 of the 22 cases of loss of two or more lines of BSCVA were studies of participants with high myopia and astigmatism. Three studies[23,100,108] which used newer generation equipment (MEL 70,

LADARvision 4000, NIDEK EC-5000 with CATz software) reported no loss of two or more lines from a total of 445 eyes.

Table 31 LASEK case series: Undesired consequences

Undesired consequences	Reference	rate	%
Peri-operative			
Flap complications	[a]Camellin 2003[20]	9/76	12
	Claringbold 2002[26]	0/222	0
	[b]Gierek-Ciaciura 2002[105]	4/320	1.0
	[c]Hashemi 2004[83]	3/73	4.1
	[d]Lee 2002[25]	3/84	4.0
	Partal 2004[92]	0/102	0
	Shah 2001[93]	0/36	0
	[e]Shahinian 2002[94]	20/46	14
	[f]Wren 2003[111]	NR	2.0
Alcohol leakage	Lee 2002[25]	3/84	4.0
Central island	[g]Shahanian 2002[94]	1/55	1.9
Raised intraocular pressure	[h]Lee 2002[25]	1/84	1.2
Patient reported outcomes			
Strong/Severe pain (Grade 4)	Camellin 2003[20]	1/76	1.5
Severe pain	[i]Kotb 2004[107]	16/86	19
Grade 3 pain (severe)	[j]Lee 2002[25]	4/84	4.8
	Molnar 2002[109]	0/603	0
Severe pain	[k]Taneri 2004[95]	NR	4.0
Dry eyes syndrome	Claringbold 2002[26]	0/222	0
	Horwarth-Winter 2004[88]	0/37	0
	[l]Lee 2002[25]	5/84	6.0
	[m] Shahanian 2002[94]	48/146	33

[a] high myopia patients, flap difficult to detach with breaks in and irregularity of the hinge
[b] flaps difficult to detach, after surgery both patients (4 eyes) had >2+ haze accompanied by regression with BSCVA 20/25 at 6 mo (Both patients had BSCVA 20/20 before surgery)
[c] 3 of the 73 eyes converted to PRK because of flap abortion
[d] tear or button hole in epithelial flap after first 10 procedures
[e] small flap tears at time of surgery, the tears did not appear to affect the surgical outcome. 5 patients with such changes had minor symptoms at 3 and 12 months, occasional pain, scratchy sensation, slight pulling sensation, and slight foreign body sensation, respectively
[f] unspecified
[g] traced back to poor laser maintenance
[h] corticosteroid induced, controlled with a beta-blocker
[i] first post-op day
[j] post-op pain score
[k] first post-op day
[l] all over 35 years old, two eyes had filamentary keratitis associated with contact lens intolerance after application of pressure patch following the cessation of eye drops including lubricant solution
[m] minor tear film changes similar to those in basement membrane dystrophy, these changes were subtle and often transient and did not affect vision

Table 32 LASEK case series: Reduced BSCVA

Study id		Lost Snellen lines of BSCVA			
	Months	1 line		≥ 2 lines	
Eyes		Rate	%	Rate	%
Full-text					
[a]Anderson 2002[78]	6	NR	NR	1/343	0.3
*Bilgihan 2004[82]	12	NR	NR	2/39	5
*Camellin 2003[20]	26#	NR	NR	6/76	8.2
Claringbold 2002[26]	12	0/84	0	0/84	0
Hashemi 2004[83]	3	NR	NR	0/48	0
*[b]Kim 2004[89]	12	10/146	6.9	11/146	7.5
Lee 2002[25]	6	1/84	1.4	0/84	0
Lin 2004[23]	6	2/90	2.2	0/ 90	0
Partal 2004[92]	12	NR	5	NR	0
Shah 2001[93]	12	5/36	14	0/36	0
Shahanian 2002[94]	12	9/55	16	0/55	0
Taneri 2004[95]	24	NR	NR	0/13	0
Vandorselaer 2003[97]	3	1/45	2.2	0/45	0
Vinciguerra 2003[98]	12	2/542	0.3	0/542	0
Vinciguerra 2004[100]	12	0/95	0	0/95	0
Abstracts					
Condon 2003[102]	3	19/242	8	0/242	0
Gabler 2002[104]	6	NR	NR	0/85	0
Kornstein 2003[106]	5#	1/43	2.3	0/43	0
Kotb 2004[107]	6	NR	NR	NR	NR
Liberek 2002[108]	NR	0/260	0	0/260	0
Wren 2003[111]	7.6#	NR	NR	2/219	1

* all participants with preop high myopia (>6.0D)

\# mean

[a] Due to development of a macular cyst

[b] Stromal opacity and myopic regression in 18 eyes, irregular astigmatism in 2 eyes and eccentric ablation in one eye

Corneal Haze

In general, haze was assessed by slit-lamp examination using a four point scale, grade 2 haze considered as having the potential to reduce the quality of vision. Table 33 provides details of participants with ≥ grade two corneal haze. The rate of ≥ grade two corneal haze was 42/2093 (median 0%; range 0% to 25%). Four out of 16 studies reporting haze incidence had cases of ≥ grade two haze.[83,89,92,106] Most reported cases of ≥ grade two haze (37/42) come from the study by Kim 2004, this was a generally high quality study in patients with high myopia, although no explanation of the comparatively high rate of corneal haze was given.[89] Two studies were of participants with thin corneas or suspicious for forme fruste keratoconus who were not considered suitable for LASIK,[83,106] and one study was limited to participants with high myopia Haze occurring in one eye in the remaining study was related to a post-operative epithelial defect.

Table 33 LASEK case series: Corneal haze (≥ grade 2)

Undesired complications	Reference	Rate	%	Follow-up
Corneal haze (≥ grade 2)	*Camellin 2003[20]	0/76	0	12 mo
	Clarinbold 2002[26]	0/84	0	12 mo
	Gabler 2002[104]	0/85	0	6 mo
	#[a]Hashemi 2004)[83] (≥2)	1/48	2	3 mo
	*[b]Kim 2004)[89] (≥2	37/146	25	12 mo
	#[c]Kornstein 2003[106] (2)	3/43	7	≥ 3 mo
	Kotb 2004[107]	0/86	0	6 mo
	Liberek 2002[108]	0/260	0	≥ 3 mo
	[d]Lin 2004[23] (2)	0/90	0	>6 mo
	*[e]Molnar 2002[109]	0/603	0	12 mo
	[f]Partal 2004[92] (2)	1/102	1	11 mo
	Shahinian 2002[94] (≥2)	0/55	0	12 mo
	Vandorselaer 2003[97]	0/45	0	3 mo
	Vinciguerra 2004[100]	0/95	0	12 mo
	Vorotnikova 2004[110]	0/56	0	12 mo
	Wren 2003[111]	0/219	0	7.6 mo*

*high myopia
suspicious for forme fruste keratoconus or thin corneas
[a] patients with thin corneas
[b] in these patients with high myopia (>-6.0 D), stromal opacity with myopic regression led to a decrease of 1 or 2 lines of BSCVA at 12 mo in 18 patients (12.3%)
[c] LASEK in patients suspicious for forme fruste keratoconus or thin corneas
[d] states all cases of clinically significant haze resolved (>6 months)
[e] haze grade did not exceed trace
[f] one eye of a 27 year old woman (pre op refraction –7.5 D; ablation depth 178 um), developed grade 2-3 haze by the first post-operative month. Postoperatively the eye was noted to have an epithelial defect, which healed by day 5. Treated with Pred Forte and Flarex, PTK with mitomycin-C performed at 11 months. 14.5 mo the central corneal continued to have grade 1 haze but patient reported markedly improved vision BSCVA 20/20, UCVA 20/25

Participant reported outcomes

Strong/severe pain (see Table 31) was reported by between 0% and 19% of participants in five studies usually on the first postoperative day. Three studies provided data on dry eye syndrome. Lee[25] reported contact lens intolerance (which may be related to dry eye syndrome) in 6% of participants (all over 35 years old) following the cessation of eye drops including lubricant solution. Horwarth-Winter[88] found that the subjective score for dry eye at three and six months was not significantly higher (worse symptoms) than the pre-op score 1.8 (SD 1.6) versus 2.2 (SD 1.5) at three months and 1.8 (SD 1.6) versus 1.8 (SD 1.1) at six months. Minor tear film changes similar to those in basement membrane dystrophy, were reported in the study by Shahanian[94] these changes were described as subtle and often transient and did not affect vision.

5.6 Overview of efficacy findings

5.6.1 Accuracy

Fourteen studies provided refractions at three to six months for eyes treated with LASEK mainly for myopia and myopic astigmatism (Table 34). A median rate of 75% (range, 19% to 98%) of all eyes were within 0.5 D of their intended correction and 92% (range, 67% to 96%) were within 1.0 D. For participants with low to moderate myopia (three studies), 76% (range, 72% to 85%) and 90% (range, 88% to 93%) were within 0.5 and 1.0 D of their intended correction. For participants with high myopia (two studies), 78% (range 72% to 84%) and 87% (range 82% to 92%) achieved within 0.5 and 1.0 D of their intended correction.

Nine studies provided results beyond six months (mainly 12 months), a median rate of 82% (range, 42% to 96%) of all eyes were within 0.5 D of their intended correction and 90% (range, 67% to 97%) were within 1.0 D. In eyes treated for low to moderate myopia or myopic astigmatism, 42% (one study) and 67% (one study) were within 0.5 and 1.0 D of their intended correction, respectively. For participants with high myopia, 68% (range 55% to 82%) and 75% (range 69% to 90%) achieved within 0.5 and 1.0 D of their intended correction.

Two studies provided changes of cylinder correction at three to six months for eyes treated with LASEK for myopic astigmatism (0.0 to 6.0 D) (Table 35). A median rate of 78% (range, 74% to 82%) of all eyes were within 0.5 D of their intended correction and 93% (range, 89% to 97%) were within 1.0 D. Three studies provided results for 12 or 24 months, a median rate of 58% (range, 55% to 93%) of all eyes were within 0.5 D of their intended correction and 75% (range, 75% to 96%) were within 1.0 D.

Table 34 LASEK case series: Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id	3 to 6 months				Last follow-up				
	≤ ±0.5 D		≤ ±1.0 D		≤ ±0.5 D		≤ ±1.0 D		Mo
Eyes	Rate	%	Rate	%	Rate	%	Rate	%	
Kotb 2004[107]	16/86	19	71/86	82					
Partal 2004[92]	75/102	74	91/102	89	NR	83	NR	97	12
Kornstein 2003[106]	18/43	41	29/43	67					
Vandorselaer 2003[97]	27/45	60	42/45	93					
Vinciguerra 2003[98]	NR	NR	NR	NR	450/542	83	NR	NR	12
Wren 2003[111]	NR	NR	NR	NR	173/219	79	204/219	93	7.6*
Anderson 2002[78]	98/115	92	108/115	94					
Hashemi 2004[83]	36/48	75	46/48	96					
Claringbold 2002[26]	217/222	98	NR	NR	81/84	96	NR	NR	12
Liberek 2002[108]	220/260	84	NR	NR					
Lee 2002[25]	42/84	50	173/184	94					
Shahanian 2002[94]	90/117	77	108/177	92	46/55	84	51/55	93	12
Low/moderate myopia									
Condon 2003[102]	433/509	85	NR	NR					
Taneri 2004[95]	54/71	76	66/71	93	5/13	42	9/13	67	24
Gabler 2002[104] <-6.0	32/45	72	40/45	88					
High myopia									
Bilgihan 2004[82]	51/61	84	56/61	92	32/39	82	35/39	90	12
Kim 2004[89]	NR	NR	NR	NR	80/146	55	109/146	75	12
#Camellin 2003[20]	NR	NR	NR	NR	NR	NR	52/76	69	26*
Gabler 2002[104]≥-6.0	29/40	72	33/40	82					

* mean

not all eyes achieved attempted correction because some corneas were too thin to leave a 300 um residual bed

Table 35 LASEK case series: Refractions within 0.5 D and 1.0 D of intended cylinder correction

Study id	3 to 6 months				Last follow-up				
	≤ ±0.5 D		≤ ±1.0 D		≤ ±0.5 D		≤ ±1.0 D		Month
Eyes	Rate	%	Rate	%	Rate	%	Rate	%	
Kim 2004[89]	NR	NR	NR	NR	80/146	55	109/146	75	12
#Partal 2004[92]	NR	74	NR	89	NR	93	NR	96	12
Taneri 2004[95]	58/71	82	69/71	97	7/12	58	9/12	75	24

vector analysis, astigmatism in eyes with ≥ 1 D (range –1.0 to –4.5 D)

Refractive complications

Reported refractive complications are summarised in Table 36. Over or under correction for myopia was reported in one study with a rate of 4.0%. Gierek Ciaciura[105] also reported that refraction stabilised between two and four weeks postoperatively. Molnar[109] found that 85% achieved refractive stability within two to three weeks. Camellin 2003[20] suggested that stability following LASEK was reached in approximately 60 days. Shahanian[94] reported that the mean refraction was close to zero from one to 12 months indicating no significant regression towards myopia or postoperative

astigmatism in the treated population. Taneri[95] however suggested that changes in the cylinder correction did not reach a plateau until after 12 weeks.

Gabler[104] reported that the maximum regression at six months was –1.75 D. Five studies reported regression in 0% to 12.3% of eyes. Only one study reported the rate of regression towards myopia or hyperopia of >1.0 D: Partal[92] and colleagues reported four eyes (4%) with consecutive hyperopia (>1.5 D) at three and six months.

Seven studies reported rates of retreatment of between 0% and 5.5%,[20,26,92,94,95,100,102] reasons given included over/under correction or monocular diplopia, haze, and enhancement.

5.6.2 Uncorrected visual acuity (UCVA)

Three to six months after treatment with LASEK, a median rate of 66% (range, 39% to 100%) of all eyes had a UCVA of 20/20 or better and 96% (range, 95% to 100%) had a UCVA of 20/40 or better (Table 37). For studies of low/moderate myopia the rates were 72% (range 65% to 85%) and 96% respectively (range, 95% to 100%). For studies of high myopia the median achieving UCVA of 20/20 or better was 57% (range, 51% to 69%) and 95% (range, 95% to 98%) for 20/40 or better.

At last follow up (12 months in most cases), a median rate of 62% (range, 38% to 89%) and 92% (range, 77% to 100%) of eyes had a UCVA of 20/20 and 20/40, respectively. In eyes with low to moderate hyperopia, 38% (one study) and 77% (one study) had a UCVA of 20/20 and 20/40, respectively. In eyes with high myopia, 62% (range, 60% to 64%) had a UCVA of 20/20 or better and 92.0% (range, 91% to 92%) had a UCVA of 20/40 or better.

Table 36 LASEK case series: Refractive complications

Refractive complications	Study	Rate	%
Over or under correction	Gierek-Ciaciura 2002[105]	13/320	4.0
Regression	[a]Camellin 2003[20] >1.0D	0/76	0
	[b]Kim 2004[89]	18/146	12.3
	Kotb 2004[107]	0/86	0
	[c]Partal 2004[92]	4/102	4.0
	[d]Shahinian 2002[94]	0/55	0
Retreatment	[e]Camellin 2003[20]	1/76	1.3
	Claringbold 2002[26]	0/222	0
	[f]Condon 2003[102]	NR	1.0
	[g]Partal 2004[92]	1/ 102	1.0
	[h]Shahinian 2002[94]	3/55	5.5
	[i]Taneri 2004[95]	5/171	2.9
	Vinciguerra 2004[100]	0/297	0

[a] high myopia patients. Stability reached in approximately 60 days, refractive regression from two weeks to 720 days was less than 1.00 D, highly variable from 15 days to 1 year, predictability decreased as amount of myopia increased. The average loss of correction from 60 days to 1 year was approximately 0.25 D.

[b] high myopia patients, stromal opacity with myopic regression

[c] consecutive hyperopia (SE>1.5) at 3 and 6 months. One eye had hyperopic treatment at 12 months, the other 3 eyes were lost to follow-up at the 12 months examination

[d] the mean refraction was stable and close to 0 from 1 to12 months post operatively (including post-op astigmatism which was approx one third of the preop value)

[e] all high myopia patients, contact lens and epithelium fell off 2 days after surgery, developed 4+ haze which required future PTK/LASEK

[f] reoperation rate for enhancement

[g] consecutive hyperopia (SE>1.5) at 3 and 6 months. One eye had hyperopic treatment at 12 months, the other 3 eyes were lost to follow-up at the 12 months examination

[h] 3 eyes treated once at 7,10 and 10 months

[i] retreated with LASEK because of over/under correction or monocular diplopia, 1 eye was overcorrected by >1.0 D

Table 37 LASEK case series: Eyes achieving Snellen acuity 20/20 or better and 20/40 or better

Study id	3 to 6 months				Last follow-up				
	20/20 or better		20/40 or better		20/20 or better		20/40 or better		Mo
	Rate	%	Rate	%	Rate	%	Rate	%	
Anderson 2002[78]	102/122	84	119/122	98					
Claringbold 2002[26]	193/222	86	NR	NR	69/84	82			12
Hashemi 2004[83]	37/48	77	46/48	96					
Kotb 2004[107]	51/86	59	NR	NR					
Lee 2002[25]	33/84	39	NR	NR					
Partal 2004[92]	67/102	66	100/102	98	NR	83	NR	100	12
Shahanian 2002[94]	58/117	50	111/117	95	31/55	56	53/55	96	12
Vinciguerra 2004[100]	207/207	100	207/207	100	85/95	89	85/95	89	12
Vandorselaer 2003[97]	25/45	56	45/45	100					
Vinciguerra 2003[98]					304/542	56	509/542	94	12
Low/moderate myopia									
Anderson 2002[78]<-6.0 D	179/211	85	202/211	96					
Condon 2003[102]	331/509	65	483/509	95					
Gabler 2002[104] <-6.0	31/45	68	45/45	100					
Taneri 2004[95]	58/78	75	75/78	96	5/13	38	10/13	77	24
High myopia									
Anderson 2002[78] ≥-6.0 D	58/84	69	80/84	95					
Bilgihan 2004[82]	31/61	51	58/61	98	25/39	64	36/39	92	12
Kim 2004[89]					88/146	60	133/146	91	12
Gabler 2002[104] ≥-6.0	23/40	57	38/40	95					

6 LASIK RESULTS

6.1 Type and quantity of available evidence

The literature searches identified a total of 2020 papers that were screened for inclusion. Of these, 505 full-text papers were ordered and assessed in detail. Full-text prospective case series of LASIK with at least 300 eyes, and retrospective case series of LASIK with at least 500 eyes, were included. Other study designs (RCTs or comparative studies) were also included if at least 300 eyes for prospective studies, or 500 eyes for retrospective studies, received LASIK. All eyes receiving LASIK within each of these studies were treated as single case series. For studies with multiple publications, the most up-to-date report was considered. Primary studies, and their related references, are listed in Appendix 4. Analysis of additional, unpublished, data provided by a laser eye surgeon are presented separately.

6.2 Number and type of included studies

Sixty-four studies published in 73 reports were included in the LASIK review. Nineteen studies,[43,112-132] including seven FDA reports, were prospective case series and 32 were retrospective case series.[57,133-169] In a further two case series, it was unclear whether they were prospective or retrospective.[170,171] In addition, there were four prospective comparative studies,[63,89,172,173] six retrospective comparative studies[174-179] and one RCT.[180] The RCT compared use of corticosteroids and artificial tears for post-operative care and both arms of this trial were treated as a single case-series. The primary studies included in this review are listed in Table 38 and detailed characteristics are shown in Appendix 9.

Thirty-two of the primary studies were set in the USA, six in Canada, one in the USA and Canada, one in the USA and Brazil, and one in the USA and Mexico. Seven were set in South America (one in Argentina, two each in Brazil and Venezuala). Nine studies were set in Europe (one each in Crete, Germany and Spain, and two each in Turkey, UK and Russia). In addition, four studies were set in Japan, two in Australia and one each in Iran, South Korea and Thailand. Four of the studies were funded by government grants, ten by manufacturers and 38 studies did not declare their source of funding. The remaining 11 studies were funded by a range of private sources including seven funded or part-funded by the charity Research to Prevent Blindness (New York).

Thirty-three studies included participants with myopia or myopic astigmatism, two studies included participants with hyperopia or hyperopic astigmatism,[115,127] nine studies included participants with both myopia and hyperopia,[120,126,142,143,152,163,170,175,176] and 20 studies did not report whether participants had myopia or hyperopia. A total of 293,278 eyes were considered in 60 studies, the remaining four studies did not report number of eyes but enrolled a futher 4,063 participants. Sample sizes ranged from 300 to 84,711 eyes and the percentage of women from 41% to 67%. Mean age was 53[127] and 53.1[115] for studies of hyperopia (age range 21 to 74 years), and between 25.3 and 44.1 years (age range 16 to 75 years) for the remaining studies.

Follow-up varied between one day and 89 months; the median length of follow-up across all the studies was six months. Recruitment periods ranged from one and a half months[173] to eight years and eight months[57] and took place between April 1992[57] and March 2004.[154] However, the study recruiting from April 1992 also included participants with PRK,[57] the earliest recruitment date for a LASIK-only study was May 1993.[122] Recruitment dates were unclear in 12 studies. Twelve studies started to recruit participants after January 2000 and a further 20 studies included participants treated after this date.

The most frequently used microkeratomes were the Hansatome (26 studies) and the Automated Corneal Shaper (23 studies) followed by the MK-2000 (nine studies), Carriazo-Barraquer (eight studies), LSK-One (seven studies) and Summit Krumeich Barraquer (four studies). Other microkeratomes used included Flapmaker, Innovatome, K-3000, and Moria One and M2. The Nidek EC-5000 was the most commonly used laser (17 studies) followed by the Apex Plus (11 studies). Over 20 different lasers or modifications of lasers were used across the studies.

Table 38 Included studies – LASIK case series

Study id	Number of eyes	Mean age (years)	Follow-up (months)	Pre-operative spherical equivalent (D)			Microkeratome	Laser
				Mean	SD	Range		
Albietz 2004[133]	565	36	12	-4.00	2.26	NR	Automated Corneal Shaper	Nidek EC-5000
Arevalo 2002[137]	38823	36	48*	-6.00	NR	-0.75 to -29.00	Automated Corneal Shaper; Moria One	Chiron Technolas Keracor 217; Coherent Schwind Keratom II
Asano-Kato 2002[138]	4867	34.5	NR	-6.08	2.58	NR	LSK-One; MK-2000	Apex Plus; EC-5000
Bailey 2003[140]	NR	43.0	18.6*	-4.99	3.14	NR	NR	Summit Apex Plus; VISX Star S2
Bowers 2004[141]	755	39	1	-3.63	1.84	-0.50 to -9.50[a]	Automated Corneal Shaper; Hansatome	Technolas 217A
Flanagan 2003[174]	1776	40.4	8*	-5.86	3.25	NR	Automated Corneal Shaper	NR
	2652	41.5	4.4*	-3.70	2.8	NR	Summit Krumeich Barraquer	
Giledi 2004[175]	641	38.7	NR	-3.9	4.5	+7.40 to -25.00	Hansatome	NR
	116	43.8	NR	-4.4	3.75	+7.10 to -2.90		
Goldberg 2003[142]	NR	NR	24	NR	NR	NR	NR	NR
Hersh 2003[143]	2845	NR	12	NR	NR	NR	Hansatome; Alcon SKBM	Apex Plus; LADARVision
Hoffman 2003[118]	1000	NR	1 week	NR	NR	NR	Hansatome	VISX S2 or S3
Holland 2000[119]	NR	NR	3	NR	NR	NR	NR	NR
Hovanesian 2001[43]	NR	NR	≥ 6	NR	NR	NR	Automated Corneal Shaper	Summit SVS Apex
Ito 2004[144]	3751	34.7	≥ 6	NR	NR	–0.13 to -17.25	MK-2000; LSK One; Flapmaker; K-3000	EC-5000; Apex Plus
Jacobs 2002[145]	84711	NR	NR	NR	NR	NR	Automated Corneal Shaper; Hansatome Moria; Innovative; Flapmaker	VISX Star S2; Technolas 217
Johnson 2001[146]	2711	NR	NR	NR	NR	NR	Automated Corneal Shaper; Hansatome	Summit Apex Plus; VISX Star
Kenyon 2004[120]	411	47	≥ 1	-3.8	NR	-1.5 to -10.25	Moria LSK-One	VISX Star S-2
	89			+2.7	NR	+0.5 to +6.75		
Kim 2004[89]	324	28.4	12	-7.91	1.26	-6.00 to -11.50	Hansatome	Nidek EC-5000
Kremer 2001[122]	2482	NR	12	-5.60	2.90	-1.00 to -15.00	Automated Corneal Shaper	Kremer Excimer Laser
Lin 2003[147]	1131	NR	2	-5.64[a]	NR	-1.50 to -14.50	MK-2000	EC-5000
Lui 2003[148]	580	NR	6	NR	NR	NR	Carriazo-Barraquer	EC-5000
Lyle 2001[123]	332	39.9	12*	-11.69	1.46	-10.00 to -18.00	Automated Corneal Shaper; Hansatome	VISX Star
McDonald 2001[124]	177	42.5	6	-4.29	2.09	NR	Hansatome; Innovative Optics	LADARVision
	170	43.1	6	-4.73	2.24	NR	Innovatome	
McLeod 2003[149]	1632	NR	NR	NR	NR	NR	Automated Corneal Shaper; Carriazo-Barraquer	NR
Merchea 2002[151]	3499	NR	6	-3.80	2.09	-0.75 to -14.00[a]	Moria	Nidek EC-5000
	2239			-3.73	2.05	-0.25 to -15.50[a]		Meditec Mel-70 G-Scan

Study id	Number of eyes	Mean age (years)	Follow-up (months)	Pre-operative spherical equivalent (D)			Microkeratome	Laser
				Mean	SD	Range		
Miranda 2002[176]	813	44.1	NR	-4.21[a]	2.34	-0.5 to –13.5[a]	Hansatome; Carriazo-Barraquer; SKBM	LADARVision model 4000
				+2.18[a]	2.04	+0.5 to +5.0[a]		
Mirshahi 2004[152]	1650	NR	1	NR	NR	NR	Hansatome	Technolas C-LASIK 217
Mulhern 2002[153]	1496	NR	≥ 3	NR	NR	NR	Hansatome	NR
Nakano 2004[154]	47094	NR	NR	NR	NR	NR	Hansatome; Automated Corneal Shaper; Nidek MK-2000	NR
Noda-Tsuruya 2004[155]	5708	34.3	NR	NR	NR	NR	LSK-One; MK-2000	Apex-plus; Nidek EC-5000
Pallikaris 2001[156]	2873	NR	NR	NR	NR	NR	Flapmaker	MEL 60
Patel 2000[157]	1071	NR	3	NR	NR	NR	Automated Corneal Shaper; Hansatome	Summit Omnimed; Summit Apex Plus
Pop 2004[158]	1488	36	12	-4.32	1.78	≤ -9.75[a]	LSK One	Nidek EC-5000
Price 2001[180]	449	41.7	12	-5.36	2.78	-0.75 to –15.75	Automated Corneal Shaper	Keracor Technolas 116
	448	40.8	12	-5.53	2.78	-0.38 to –14.13		
Rad 2004[159]	6941	25.3	NR	NR	NR	NR	Moria CB	Nidek EC-5000
Recep 2000[160]	1481	NR	6	NR	NR	NR	Moria	VISX Twenty/Twenty B
Reviglio 2000[126]	300	35.2	5.1	-2.21	0.88	NR	Automated Corneal Shaper	LaserSight Compac-200
				-4.59	0.60			
				-7.63	1.09			
				-12.70	2.81			
				+2.25	2.81			
				+4.25	0.88			
Ruiz-Moreno 2003[57]	3009	32.0	64.1*	-13.50	3.30	-8.00 to –27.00	Automated Corneal Shaper	VISX 20/20; Technolas 217-C
Salz 2002[127]	152	53	12	2.56	1.19	+1.00 to +6.00[a]	Hansatome; Paradigm Innovatome	LADARVision
	143			2.84	1.58	+1.00 to +6.00[a]		
	65			0.22	1.54	+0.25 to +5.00[a]		
Sanders 2003[172]	559	38.8	12	-9.1	0.97	-8.00 to –12.00	Carriazo-Barraquer	VISX S2 or S3
Sarkisian 2001[170]	1220	NR	3	NR	NR	+9.00 to –25.00	Nidek MK-2000	EC-5000
Schumer 2001[128]	370	NR	NR	NR	NR	NR	Nidek MK-2000	NR
Smirennaia 2001[171]	5896	NR	NR	-7.00[a]	NR	-1.25 to –15.50[a]	HT-230 Hansatome	Nidek EC-5000
Solomon 2004[173]	1634	39.4	NR	NR	NR	NR	AMO Amadeus; Hansatome; MK-2000; M2; Carriazo-Barraquer; Summet Krumeich-Barraquer	VISX; LadarVision; Nidek
Stulting 2004[162]	11232	NR	NR	NR	NR	NR	Automated Corneal Shaper; Hansatome	Summit; Nidek; Autonomous
Suarez 2002[163]	18488	36	36	-2.23[a]	NR	+4.25 to –10.25	Automated Corneal Shaper; Moria One	Chiron; Coherent Schwind Keratom 2
Tham 2000[164]	3998	NR	5*	NR	NR	NR	Automated Corneal Shaper; Hansatome	VISX Star; Summit Apex Plus
Thammano 2003[177]	1122	41	≥ 1	NR	NR	NR	LSK-One; Carriazo-Barraquer	VISX S2; LADARVision

Study id	Number of eyes	Mean age (years)	Follow-up (months)	Pre-operative spherical equivalent (D)			Microkeratome	Laser
				Mean	SD	Range		
Toda 2002[131]	168	33.1	12	-7.24	3.09	NR	LSK One; MK 2000	Apex-plus; EC-5000
	300			-6.5	2.85	NR		
	75			-6.5	2.54	NR		
Tole 2001[63]	314	37	6	-2.26	0.48	-1.25 to –3.00	Automated Corneal Shaper	Nidek EC-5000
		38.2		-4.61	0.85	-3.13 to –6.00		
Vongthongsri 2001[178]	2021	33.7	≥ 6	-5.69	2.90	-1.00 to –17.50	Carriazo-Barraquer	Nidek EC-5000
		31.8		5.96	2.93	-1.00 to –16.25		
Walker 2000a[179]	598	42	NR	-7.10	1.80	-1.00 to –14.00	System ALK Automated Corneal	NR
	90	41		-8.10	0.90		Shaper; Hansatome	
Walker 2000b[165]	783	NR	6	NR	NR	NR	Automated Corneal Shaper; Hansatome	NR
Wang 2000[166]	3786	NR	NR	NR	NR	NR	Automated Corneal Shaper; Hansatome	VISX Star; Summit Apex or Apex Plus
Wang 2002[132]	353	40	NR	-5.86	2.96	-0.75 to –16.75[a]	Automated Corneal Shaper; Hansatome	VISX Star
Watson 2005[167]	1000	37	2[b]	-4.2	1.9	NR	Hansatome	VISX Star S2 to S4 Waveprint system
				2.4	0.9	NR		
				NR	NR	NR		
Wilson 2002[168]	1352	NR	6	NR	NR	NR	Hansatome	VISX S2 or S3
Yildirim 2001[169]	630	30.3	12.6*	-8.81	4.51	-2.00 to –13.25	Hansatome	Summit Apex Plus
FDA 2000a[117]	110	37.9	6	-3.82	1.52	-1.00 to –7.00[a]	NR	Technolas 217A
	276			-3.05	1.46			
FDA 2000b[125]	1126	42.6	12	NR	NR	NR	NR	Nidek EC-5000
FDA 2002a[114]	308	38.2	6	-8.19	1.23	-7.25 to –12.25[a]	NR	Technolas 217A
FDA 2002b[112]	426	38.1	6	NR	NR	0.00 to –7.00	NR	LADARVision 4000
FDA 2003a[115]	358	53.1	24	+2.17	0.82	+0.50 to +4.00[a]	NR	Technolas 217A
FDA 2003b[116]	324	34.4	6	-2.81	1.62	-0.46 to –7.15	NR	Technolas 217z
FDA 2003c[130]	901	38.1	12	NR	NR	0.00 to –13.00	NR	WaveLight Allegretto Wave

NR not reported
*mean
[a]spherical refraction
[b]median

6.3 Number and type of excluded studies

Four hundred and thirty-two reports, originally identified as being potentially relevant, did not meet the inclusion criteria for the LASIK review. The commonest reasons for exclusion were: too few eyes included; inappropriate type of intervention; inappropriate study design (e.g. letters, editorials, discussion papers); and no efficacy or safety data reported. Studies of participants receiving LASIK after keratoplasty or previous refractive surgery, including LASIK retreatments, were excluded.

6.4 Quality of available evidence

A summary of the quality assessment of the 64 included LASIK case series is presented in Table 39, the detailed quality assessment results shown in Appendix 11.

Table 39 Summary of the quality assessment of LASIK case series

Criteria		Yes	No	Unclear
1.	Were participants a representative sample selected from a relevant population?	43	2	19
2.	Are the inclusion/exclusion criteria of the participants in the study clearly described?	28	34	2
4.	Was selection of participants consecutive?	31	0	33
5.	Was data collection undertaken prospectively?	23	39	2
7.	Was the intervention (and comparison) clearly defined?	10	51	3
8.	Was the intervention undertaken by someone experienced in the procedure?	30	0	34
9.	Were the staff, place, and facilities where the participants were treated appropriate for performing the procedure?	43	0	21
10.	Were all important outcomes considered?	18	46	0
11.	Were objective (valid and reliable) outcome measures used?	62	2	0
13.	Was the follow-up long enough to detect important effects on outcomes of interest?	41	3	20
14.	Was information provided on non-respondents and dropouts?	20	43	1
15.	Were participants lost to follow up likely to introduce bias?	5	23	36
17.	Were all important prognostic factors identified?	24	27	13
19.	Was the paired nature of eyes taken into account in the analyses?	20	44	0

Note: questions 3, 6, 12, 16 and 18 were not relevant to either case series or this intervention

In 43 studies (67%), participants were a representative sample of a relevant population. Two studies[131,133] were judged not to be from a relevant population and it was unclear in the remaining 19 studies. However, the inclusion or exclusion criteria of participants

were clearly described in only 28 studies, including the seven FDA reports.[57,63,112,114-117,120,122-127,130,132,133,137,140,141,156,157,160,164,170,176,178,180] Data collection was prospective in 23 studies,[43,63,89,112,114-117,119,120,122,123,125-128,130-132,149,172,173,180] unclear in two studies,[170,171] and retrospective in the remaining 39. In approximately half of the included studies it was unclear whether selection of eyes was consecutive; it was reported as consecutive in the remaining 31 studies.

Only ten studies[63,123,124,126,127,156-158,172,178] clearly defined the intervention by reporting microkeratome, laser, ablation zone, and post-operative treatment. Most of the remaining studies only reported laser and/or microkeratome used. The procedure was reported to have been undertaken by an experienced surgeon in 30 studies, this information was unclear in 34. Staff, place, and facilities were considered to be appropriate in 43 studies and unclear in the remaining studies.

Forty-six studies did not report all the outcome measures pre-identified in the protocol for this review; many studies reported only one or two adverse events.[57,118,119,132,137,138,140,141,143,146,149,152,153,155,156,159,160,162,163,165,168,171,175,177] Two studies[140,142] failed to use objective outcome measures.

In three studies[141,147,173] follow-up was not long enough to detect important effects on outcomes of interest to that study; it was unclear whether follow-up was long enough in a further 20 studies. Only 20 studies provided information on non-respondents or drop-outs including all the FDA reports, which reported this information in detail. Loss to follow-up was only considered likely to introduce bias in five studies,[43,123,124,140,151] although it was unclear whether loss to follow-up may have introduced bias in 36 of the studies.

The paired nature of eyes was taken into account in 20 studies.[43,118,120,133,138,145,146,149,152,153,156,158,159,162,164,166,168,173,174,177] However, this was generally through inclusion of a single eye or assessment of bilateral occurrences of adverse events rather than statistical analysis.

6.5 Overview of safety findings

Creation of the flap in LASIK may lead to keratomileusis-related complications, these are addressed first in this section, followed by the potentially serious complications and undesired consequences.

6.5.1 Keratomileusis-related complications

Flap complications

Intra-operative and post-operative flap complications were documented amongst a total of 159,177 eyes in 28 studies and are presented in Table 40.

Problems may occur in the creation of the flap, these include buttonholing or tearing of the flap or an incomplete flap, the creation of a free cap rather than a hinged flap, and a flap that is thicker than intended. Buttonhole flaps were reported in nine studies, occurring in 0% to 0.53% of eyes treated. Overall, buttonhole flaps were created in 136 out of 140,316 eyes (0.10%, median 0.13%). Fifteen studies reported rates of free caps and these varied from 0% to 2.00% (median 0.13%). There were five occurrances of torn flaps noted in two studies from a total of 8,179 treated eyes (0.06%).[144,174] Nineteen studies reported numbers of eyes where the flap was partial, small, short, irregular, incomplete or where the microkeratome stopped during creation of the flap; these are grouped as 'incomplete flaps'. A total of 273 out of 152,794 eyes treated had incomplete flaps, 0.18%, median 0.28% (range 0% to 2.86%). One study, Ito et al.,[144] reported a single case of a thick flap (0.03%).

Thin flaps, dislodged flaps, and flap folds and striae are undesired consequences of LASIK. Thin flaps occurred for a median of 0.23% (range 0% to 0.86%) of eyes. One hundred and thirty-nine eyes out of 10,679 eyes (1.3%, median 0.77%) in 14 studies had flap folds or striae. The rate of flap folds and striae ranged from 0.03% to 5.52%; this variation in rates may partially reflect differences in reporting as some studies reported just flap folds or striae whereas others reported both together. Dislodged flaps may result in flap folds and striae. Dislodged flaps were identified for a median of 1.2% of eyes (range 0.29% to 2.41%). Flap folds and dislodged flaps may be repositioned; Reviglio et al.[126] repositioned flap folds within 24 hours although there was a temporary loss of more than two Snellen lines of BSCVA.

Ito et al.[144] found no statistically significant difference in rate of microkeratome-related flap complications between surgeons who had performed 100 or less cases and those who had performed 101 or more cases (p=0.20). However, Tham et al.[164] did find a significant difference in rate of microkeratome complications with experience; 1.3% in the first thousand eyes, 0.6% in the next thousand eyes and 0.4% for the third and fourth thousand eyes treated (p=0.048). The occurrence of microkeratome complications did not differ significantly between the first and second eye treated in participants scheduled to have bilateral treatment.[144,145,164] Solomon et al.[173] found participants who had bilateral surgery using the same blade had significantly thinner flap thickness (p<0.001) in the second operated eye; the mean flap thickness decreased from 150±35 µm to 141±36 µm.

Table 40 LASIK case series: Flap complications

Study id	Buttonhole flap		Free cap		Torn flap		Incomplete flap[a]		Thin flap		Flap folds/striae		Dislodged flap	
	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%
Watson 2005[167]	0/1000	0.20	0/1000	0	-	-	0/1000	0	-	-	4/1000	0.40	12/1000	1.2
Bowers 2004[141]	4/755	0.53	1/755	0.13	-	-	2/755	0.26	-	-	-	-	-	-
Ito 2004[144]	-	-	3/3751	0.08	1/3751	0.03	12/3751	0.32	7/3751	0.19	1/3751	0.03	-	-
Kim 2004[89]	-		-	-	-	-	-	-	-	-	-	-	4/324	1.23
Nakano 2004[154]	61/47094	0.13	39/47094	0.08	-	-	107/47094	0.23	36/47094	0.08	-	-	-	-
Flanagan 2003[174]	-	-	-	-	4/4428	0.09	10/4428	0.23	-	-	-	-	-	-
FDA 2003a[115]	-	-	-	-	-	-	1/358	0.28	-	-	4/358	1.12	-	-
Lin 2003[147]	-	-	-	-	-	-	0/1131	0	4/1131	0.35	7/1131	0.62	-	-
Lui 2003[148]	3/580	0.52	4/580	0.69	-	-	3/580	0.52	5/580	0.86	30/580	5.17	14/580	2.41
Sanders 2003[172]	-	-	1/559	0.18	-	-	-	-	-	-	17/559	3.04	-	-
FDA 2002a[114]	-	-	-	-	-	-	-	-	-	-	3/308	0.97	-	-
FDA 2002b[112]	-	-	-	-	-	-	1/427	0.23	-	-	2/426	0.47	-	-
Jacobs 2002[145]	59/84711	0.07	10/84711	0.01	-	-	84/84711	0.10	74/84711	0.09	-	-	-	-
Salz 2002[127]	-	-	-	-	-	-	3/360	0.83	-	-	2/360	0.56	-	-
Toda 2002[131]		-	-	-	-	-	-	-	-	-	30/543	5.52	-	-
Wang 2002[132]	-	-	1/300	0.33	-	-	-	-	-	-	-	-	2/300	0.67
Kremer 2001[122]	-	-	29/2482	1.17	-	-	-	-	-	-	-	-	-	-
Lyle 2001[123]	-	-	-	-	-	-	2/332	0.60	-	-	-	-	5/332[b]	1.51
McDonald 2001[124]	-	-	-	-	-	-	1/347	0.29	-	-	3/347	0.86	1/347	0.29
Sarkisian 2001[170]	0/1120	0	0/1220	0	-	-	1/1220	0.08	0/1220	0	-	-	-	-
Schumer 2001[128]	0/370	0	0/370	0	-	-	1/370	0.27	-	-	-	-	-	-
Tole 2001[63]	-	-	-	-	-	-	6/314	1.91	2/314	0.64	-	-	1/314[c]	0.32
Yildirim 2001[169]	-	-	1/630	0.16	-	-	18/630	2.86	-	-	32/630	5.08	8/630	1.26
FDA 2000a[117]	-	-	-	-	-	-	-	-	3/386	0.78	2/386	0.51	-	-
Recep 2000[160]	-	-	-	-	-	-	-	-	-	-	-	-	21/1481	1.42
Reviglio 2000[126]	-	-	6/300[d]	2.00	-	-	0/300	0	-	-	2/300	0.67	-	-
Tham 2000[164]	5/3998	0.13	2/3998	0.05	-	-	16/3998	0.40	9/3998	0.23	-	-	-	-
Walker 2000a[179]	2/688	0.29	1/688	0.15	-	-	5/688	0.73	-	-	-	-	-	-

[a]includes partial flap, small flap, short flap, irregular flap, miscreated flap, keratome stopped, improper keratectomy
[b]includes flap folds
[c]dislodge flap lost 4 lines BSCVA, the flap was replaced but left with significant folds and then went onto partial flap necrosis requiring amputation of the flap
[d]free caps all in hyperopic eyes

Epithelial complications

Rates of epithelial ingrowth and epithelial defects were noted in 30 studies that included 36,536 eyes. Epithelial complications are presented in Table 41 and are grouped, where possible, by myopia and hyperopia.

The rate of epithelial ingrowth ranged from 0% to 4.44% across all studies. The median rate of epithelial ingrowth was 1.4% of eyes (233 out of 17,715 eyes, 1.3%).

Epithelial defects occurred in between 0% and 10.20% of eyes, in total 510 out of 23,679 eyes (2.15%, median 1.7%) had epithelial defects. Sixty-one percent of epithelial defects identified by Kenyon et al.[120] and 83% of defects identified by Smirennaia et al.[171] were under 2 mm and 3 mm respectively. Sarkisian et al.[170] observed that the epithelial defects they identified were not visually significant.

Solomon et al.[173] reported epithelial defects occurred more frequently in the second operated eye (p=0.029). However, incidence of ingrowth did not differ between the first and second eye treated in eyes studied by Asano-Kato et al.[138]

Keratitis

Watson et al.[167] and Yildirim et al.[169] each identified a single case of microbial keratitis. A further four studies reported that they observed no cases of microbial keratitis (Table 42).

Diffuse lamellar keratitis was reported in 26 studies and occurred in between 0% and 7.72% of eyes (median 1.4% of eyes). Four of the studies[118,162,168,177] noted that no eyes lost more than two lines BSCVA after resolution of diffuse lamellar keratitis. However, Johnson et al.[146] found two eyes (6%) lost more than two lines of BSCVA after resolution of diffuse lamellar keratitis. Where reported, diffuse lamellar keratitis was identified within the first week after LASIK.[118,119,138,146,153,155,177]

Table 41 LASIK case series: Epithelial complications: epithelial ingrowth and epithelial defects

Study id	Follow-up (months)	Ingrowth Rate	Ingrowth %	Defects Rate	Defects %
Mixed refraction or refraction not reported					
Kenyon 2004[120]	>1	0/500	0	51/500	10.20
Mirshahi 2004[152]	1	-	-	22/1650	1.33
Solomon 2004[173]	NR	-	-	130/1634	7.96
Flanagan 2003[174]	NR	-	-	40/4428	0.90
Hoffman 2003[118]	1 week	-	-	27/1000	2.70
Lui 2003[148]	6	8/580	1.38	-	-
Thammano 2003[177]	≥1	-	-	0/1122	0
Miranda 2002[176]	NR	-	-	36/813	4.43
Toda 2002[131]	12	6/543	1.10	4/543	0.74
Sarkisian 2001[170]	3	-	-	38/1220	3.11
Reviglio 2000[126]	5	6/300[e]	2.00	0/300	0
Wang 2000[166]	NR	35/3786	0.92	-	-
Myopia and myopic astigmatism					
Watson 2005[167]	2[a]	10/1000	1.00	17/1000	1.70
Lin 2003[147]	2*	1/1131	0.09	4/1131	0.35
Asano-Kato 2002[138]	NR	64/4867[b]	1.31	-	-
Merchea 2002[151]	6	22/866[c]	2.54	-	-
Wang 2002[132]	NR	4/300	1.33	12/300	4.00
McDonald 2001[124]	6	5/347	1.44	-	-
Smirennaia 2001[171]	NR	-	-	95/5896	1.61
Yildirim 2001[169]	13*	21/630	3.33	-	-
Recep 2000[160]	5*	6/300	2.00	8/300	2.67
Walker 2000b[165]	6	3/783	0.38	-	-
Low/moderate myopia ± myopic astigmatism					
FDA 2003b[116]	6	-	-	0/340	0
FDA 2002b[112]	6	14/426	3.29	1/426	0.23
Tole 2001[63]	6	7/314[d]	2.23	-	-
FDA 2000a[117]	6	-	-	1/386	0.26
High myopia ± myopic astigmatism					
Kim 2004[89]	12	0/324	0	-	-
Lyle 2001[123]	13*	-	-	12/332	3.61
Hyperopia and hyperopic astigmatism					
FDA 2003a[115]	24	5/358	1.40	12/358	3.35
Salz 2002[127]	12	16/360	4.44	-	-

*mean

[a]median

[b]first detected at 1 week in 35 eyes; 1 week to 1 month in 16 eyes; 1 to 3 months in 10 eyes; 3 to 6 months in 1 eye; after 6 months in 2 eyes.

[c]7 eyes progressed to a corneal flap melt as a direct consequence

[d]1 eye lost ≥2 lines BSCVA

[e] in eyes with free caps

Table 42 LASIK case series: Keratitis: microbial keratitis and diffuse lamellar keratitis

Study id	Follow-up (months)	Microbial keratitis		Diffuse lamellar keratitis	
		Rate	%	Rate	%
Mixed refraction or refraction not reported					
Kenyon 2004[120]	>1	0/500	0	5/500	1.00
Noda-Tsuruya 2004[155]	NR	-	-	46/5708[b]	0.81
Stulting 2004[162]	NR	-	-	54/11232	0.48
Hoffman 2003[118]	1 week	-	-	40/1000[c]	4.00
Lui 2003[148]	6	-	-	4/580[d]	0.69
McLeod 2003[149]	NR	-	-	126/1632	7.72
Thammano 2003[177]	≥1	-	-	25/1122[e]	2.23
Mulhern 2002[153]	≥3	-	-	20/1436	1.39
Toda 2002[131]	12	-	-	1/543	0.18
Wilson 2002[168]	6	-	-	17/1352[f]	1.26
Johnson 2001[146]	NR	-	-	36/2711[g]	1.33
Holland 2000[119]	3	-	-	52/985	5.28
Reviglio 2000[126]	5*	0/300	0	-	-
Myopia and myopic astigmatism					
Watson 2005[167]	2[a]	1/1000	0.1	36/1000	3.6
Lin 2003[147]	2*	0/1131	0	1/1131	0.09
Asano-Kato 2002[138]	NR	-	-	61/4867	1.25
McDonald 2001[124]	6	-	-	3/347	0.86
Yildirim 2001[169]	13*	1/630	0.16	32/630[h]	5.08
Low/moderate myopia ± myopic astigmatism					
FDA 2003b[116]	6	-	-	1/340	0.29
FDA 2002b[112]	6	-	-	16/426	3.76
Tole 2001[63]	6			2/314	0.64
FDA 2000b[125]	12	0/938	0	-	-
High myopia ± myopic astigmatism					
Kim 2004[89]	12	-	-	0/324	0
Sanders 2003[172]	12	-	-	17/559	3.04
FDA 2002a[114]	6	-	-	6/308	1.95
Lyle 2001[123]	13	-	-	6/332	1.81
Hyperopia and hyperopic astigmatism					
FDA 2003a[115]	24			6/358	1.68
Salz 2002[127]	12	-	-	13/360[i]	3.61

*mean
[a]median
[b]24 (52%) in second eye treated
[c]bilateral in 30/40 (15/25 participants)
[d]'interface debris'
[e]18 participants, all diagnosed on postoperative day 1 and all responded to medical therapy.
[f]11 participants, 12/1352 (0.89%, 9 participants) stage 1, 5/1352 (0.37%, 4 participants) stage 2.
[g]21 (19 participants) type I, 15 (15 participants) type II. All cases were diagnosed by postoperative day 5, time to resolution was 1 to 38 days (mean 3.5 days type I and 12.1 days type II)
[h]includes 'interface debris'
[i]'peripheral sterile corneal infiltrates' and 'interface inflammation'

Comparison of keratomileusis-related complications by microkeratome

Eight studies[138,141,144,145,154,155,174,176] compared the rate of intraoperative, epithelial, and keratitis complications between microkeratomes.

Nakano et al.[154] observed higher rates of total intraoperative microkeratome-related complications in the Automated Corneal Shaper than the Hansatome ($p<0.001$) or the MK-2000 ($p=0.03$). Jacobs et al.[145] and Bowers et al.[141] also found higher rates of intraoperative complications in the Automated Corneal Shaper than the Hansatome ($p<0.005$ and $p<0.001$ respectively). Flanagan et al.[174] found incomplete flaps were more common in the Automated Corneal Shaper (0.51%) than the Summit Krumeich Barraquer (0.04%) ($p=0.002$). Ito et al.(Ito 2004) reported different rates of intraoperative flap complications between LSK-One (0.77%), MK-2000 (0.28%), Hansatome (1.22%), K-3000 (5.26%) and Flapmaker microkeratomes (100%). However, the Flapmaker microkeratome was only used twice.

Flanagan et. al.[174] found epithelial defects were more common in the Summit Krumeich Barraquer than the Automated Corneal Shaper (1.40% versus 0.23%, $p<0.001$). Miranda et al.[176] found higher rates of epithelial defects in the Hansatome (7.1%) than the Summit Krumeich Barraquer (1.2%) and the Carriazo-Barraquer (2.2%) ($p<0.001$). However, Watson et al.[167] found a reduction in the incidence of intraoperative epithelial defects with the Hansatome, from 3.98% to 0.17% ($p<0.001$), following the introduction of zero compression Hansatome heads. Asano-Kato et al.[138] reported more eyes had epithelial ingrowth with the MK-2000 (2.0%) than the LSK-One (0.9%) ($p=0.001$). Noda-Tsuruya et al.[155] also reported higher incidence of diffuse lamellar keratitis with the MK-2000 (1.12%) than the LSK-One (0.62%) microkeratomes ($p=0.041$).

6.5.2 Potentially serious complications

Ectasia

Ectasia was reported in only five studies123,126,127,156,159 (Table 43), median rate 0.2% (range 0% to 0.9%). Two of these studies, both retrospective case series, looked specifically for ectasia after LASIK.156,159 The pre-operative refraction and length of follow-up for all eyes was not reported in either of these two studies.

Pallikaris et al.[156] identified 20 participants with ectasia, six of these were excluded from the study due to preoperative high astimatism and corneal topographic and pachymetric

finding suspicious for keratoconus. Of the remaining 14 participants, five of developed bilateral ectasia. The mean attempted correction in these participants was between -8.25 and -22.00 D (mean -14.65±4.40 D) and the mean RST after creation of the flap and stomal ablation was 243.95±46.32 µm (range 175 to 325 µm). Thirteen out of 19 eyes with ectasia had RST less than 250 µm. Three eyes lost more than two lines BSCVA at final follow-up of between six and 42 months.

Rad et al.[159] identified 10 participants with ectasia, which was bilateral in four participants. The mean pre-operative spherical equivalent refraction for eyes with ectasia was –10.85±3.20 D (range –5.75 to –15.00 D). The mean calculated RST was 222.8±15.1 µm (range 200 to 249 µm). Ectasia developed within a mean of 14±0.3 months (range 11 to 17.5 months). Seven participants eventually underwent penetrating keratoplasty.

The single case of ectasia reported by Lyle et al.[123] occurred in a participant treated for myopia of –10.50 D. Ectasia occurred 18 months after retreatment for initial undercorrection. The calculated RST in this participant was 225 µm.

Table 43 LASIK case series: Ectasia

Study id	Follow-up (months)	Rate	%
Rad 2004[159]	NR	14/6941	0.20
Salz 2002[127]	12	0/360	0
Lyle 2001[123]	13*	1/332	0.30
Pallikaris 2001[156]	NR	25/2873[a]	0.87
Reviglio 2000[126]	5*	0/300	0

*mean

[a]including six participants with post-LASIK ectasia who had high astigmatism and corneal topographic and pachymetric finding suspicious for keratoconus preoperatively who were excluded from the study.

Raised intraocular pressure (IOP)

Raised IOP was reported in four studies.[112,124,125,127] A median rate of 0.14% of eyes (four eyes) experienced an increase in intraocular pressure (Table 44). In three of these eyes[124] raised intraocular pressure was reported to be related to use of steroids for regression and resolved on cessation of topical steroids. The remaining case occurred in a participant with mixed astigmatism but no additional details were given.

Table 44 LASIK case series: Raised intraocular pressure

Study id	Follow-up (months)	Rate	%
FDA 2002b[112]	6	0/426	0
Salz 2002[127]	12	1/360	0.28
McDonald 2001[124]	6	3/347	0.86
FDA 2000b[125]	12	0/938	0

Vitreo-retinal complications

Seven studies reported rates of vitreo-retinal complications (Table 45).[57,112,114,115,124,125,137] Only one study[115] involved participants with hyperopia; this study had a single case of vitreous detachment and two eyes with vitreal traction.

Ruiz-Moreno et al.[57] analysed the incidence of vitreo-retinal complications in 3009 eyes with high myopia. Eleven eyes had retinal detachments (0.37%), which occurred between two and 61 months after LASIK (mean 24.6±20.4 months), two of these eyes had prior treatment on the peripheral retina for flap tear and lattice degeneration. Arevalo et al.[137] also examined the incidence of retinal detachment after LASIK in myopic eyes. Retinal detachments were observed in 0.08% of eyes and occurred between 12 days and 60 months (mean 16 months) after LASIK.

Ruiz-Moreno et al. identified ten eyes (0.33%) with choroidal neovascularisation, after a mean of 30.2±19.3 months (range four to 60 months), one eye with a lacquer crack and one with a full thickness macular hole at 12 months.[57] McDonald et al.[124] reported a case of serious macular oedema. Two FDA reports of LASIK for myopia also identified one incidence of vitreous detachment[114] and one retinal horseshoe tear that was reported to be unrelated to the laser treatment.

Table 45 LASIK case series: Vitreo-retinal complications

Study id	Follow-up (months)	Rate	%
FDA 2003a[115]	24	3/358	0.84
Ruiz-Moreno 2003[57]	64*	23/3009	0.76
Arevalo 2002[137]	48*	33/38823	0.08
FDA 2002a[114]	6	1/308	0.32
FDA 2002b[112]	6	1/426	0.23
McDonald 2001[124]	6	1/347	0.29
FDA 2000b[125]	12	0/938	0

*mean

6.5.3 Undesired consequences

Refractive complications

Twenty-five studies reported eyes with a loss of two or more Snellen lines of BSCVA, as shown in Table 46. In eyes with low to moderate myopia, a median rate of 0.7% (range 0% to 1.6%) of eyes lost two or more lines. In the high myopia group, 0.9% (range 0% to 1.8%) of eyes lost two or more lines. Overall, a median rate of 0.6% (range 0% to 3.0%) of eyes with myopia or myopic astigmatism lost two of more lines. Two studies of eyes with hyperopia or hyperopic astigmatism reported that a median of 3.4% of eyes lost two or more lines of BSCVA (range 2.2% to 4.7%).

Incidence of induced astigmatism in spherical eyes was reported in seven studies. In total, a median 0% of myopic eyes (range 0% to 1.0%) and 0.6% of hyperopic eyes had induced astigmatisms of more than 2.00 D.

Table 46 LASIK case series: Refractive complications

Study id	Follow-up (months)	Loss ≥2 lines BSCVA		Induced astigmatism >2 D*	
		Rate	%	Rate	%
Mixed refraction or refraction not reported					
Toda 2002[131]	12	10/543	1.84	-	-
Reviglio 2000[126]	5*	0/300	0	-	-
Myopia and myopic astigmatism					
Ito 2004[144]	6	73/3732	1.96	-	-
Pop 2004[158]	12	0/1488	0	-	-
FDA 2003c[130]	12	4/813	0.49	1/249	0.40
Lin 2003[147]	2[a]	2/1131[b]	0.18	-	-
Wang 2002[132]	NR	0/300	0	-	-
Kremer 2001[122]	12	22/957	2.30	4/414	0.97
McDonald 2001[124]	6	2/347	0.58	1/347[c]	0.29
Vongthongsri 2001[178]	>6	0/2021	0	-	-
Yildirim 2001[169]	13*	5/630	0.79	-	-
Patel 2000[157]	3	27/900[d]	3.00	-	-
Low/moderate myopia ± myopic astigmatism					
FDA 2003b[116]	6	2/340	0.59	-	-
FDA 2002b[112]	6	0/426	0	0/426	0
Tole 2001[63]	6	2/139	1.44	-	-
Price 2001[180]	12	6/1063	0.56	-	-
FDA 2000a[117]	6	3/361	0.83	0/95	0
FDA 2000b[125]	12	8/499	1.60	-	-
High myopia ± myopic astigmatism					
Kim 2004[89]	12	2/324	0.62	-	-
Sanders 2003[172]	12	0/94	0	-	-
FDA 2002a[114]	6	4/263	1.52	0/65	0
Lyle 2001[123]	13*	6/332	1.81	-	-
Price 2001[180]	12	6/656	0.91	-	-
Hyperopia and hyperopic astigmatism					
FDA 2003a[115]	≥12	8/172	4.65	1/178	0.56
Salz 2002[127]	12	5/224	2.23	-	-

*Induced astigmatism in spherical eyes only
[a]mean
[b]eyes with loss of BSCVA had striae
[c]induced astigmatism due to flap decentration
[d]no participant experienced BSCVA <20/40

Corneal haze and oedema

These outcomes were reported in eleven studies as shown in Table 47. However, the definition of haze and oedema varied between studies. Three studies[63,89,126] reported no eyes with detectable or significant haze at last follow-up. Two FDA reports[114,125] noted late onset of haze with loss of more than two Snellen lines of BSCVA in 0% and 0.65% of eyes. Merchea et al.[150] observed haze greater than grade three in 2.08% of eyes treated. Price et al.[180] only noted the incidence or haze at one week; at this stage 0.18% of eyes had moderate or marked haze.

Corneal oedema between one week and one month was reported in two studies,[112,127] in 0.56% and 1.39% of eyes. The remaining two studies reported corneal oedema of the flap (0.56%) and corneal oedema of the bed (0.26%) both at more than one month.

Table 47 LASIK case series: Corneal haze or oedema

Study id	Follow-up (months)	Rate	%
Haze			
Kim 2004[89]	12	0/324[a]	0
FDA 2002a[114]	6	2/308[b]	0.65
Merchea 2001[150]	6	18/866[c]	2.08
Price 2001[180]	12	3/1710[d]	0.18
Tole 2001[63]	6	0/314[e]	0
FDA 2000b[125]	12	0/938[b]	0
Reviglio 2000[126]	5*	0/300[a]	0
Oedema			
FDA 2003a[115]	24	2/358[f]	0.56
FDA 2002b[112]	6	8/426[g]	1.88
Salz 2002[127]	12	5/360[g]	1.39
FDA 2000a[117]	6	1/386[h]	0.26

*mean
[a]detectable haze
[b]late onset of haze with loss of ≥2 lines BSCVA
[c]haze greater than grade 3
[d]moderate or marked haze at 1 week
[e]significant corneal haze
[f]corneal oedema (flap) at >1 month
[g]corneal oedema at 1 week to 1 month
[h]corneal oedema (bed) at > 1 month

Participant reported outcomes

Five FDA reports[112,114-117] analysed whether participant reported outcomes were better or worse at six months follow-up compared with baseline. A further two studies[124,127] analysed whether participant reported outcomes were significantly worse at follow-up. Blurring of vision was worse in 10.3% to 37.9% of participants and better in 14.4% to 41.2%. Burning was worse in 4.3% to 13.6% of participants and better in 12.1% to 16.5%. Double vision was worse in 2.6% to 14.7% of participants and better in 1.3% to 7.2%. Between 17.0% and 44.0% participants reported worse dry eye at follow-up compared with 9.8% to 28.6% reporting dry eye as better at follow-up. Fluctuation of vision was worse in 14.7% to 42.3% of participants and better in 7.5% to 12.1% of participants. Glare was worse at follow-up in 10.3% to 29.9% of participants and better in 10.9% to 24.6% of participants. Between 14.4% and 42.9% of participants reported halos as worse at follow-up compared with 6.0% to 15.6% of participants who reported this as better at follow-up. Light sensitivity was worse in 4.4% to 36.8% of participants and better in 23.0% to 42.4%

of participants. Night driving difficulty was worse at follow-up in 10.3% to 36.6% of participants and better in 22.7% to 40.3% of participants. Additional participants reported outcomes are given in Table 48.

Incidence of blurring of vision, burning, headaches, light sensitivity and variation of vision in bright light were higher at baseline than at follow-up in all studies reporting these outcomes (Table 49).[114-117,130] Incidence of glare and night driving difficulty were higher at baseline in four out of five studies and incidence of gritty feeling, pain and excessive tearing were higher at baseline in three out of the four studies reporting this outcome. Double vision, ghost images, and variation of vision in normal light were more frequent at follow-up in all studies. Incidence of halos and fluctuations of vision were higher at follow-up in four out of five studies and incidence of dry eye was higher at follow-up in three out of four studies.

Other complications

Suarez et al.[163] reported 35 out of 18,488 eyes (0.19%) developed anterior uveitis, which appeared 17 to 28 days after LASIK (mean 20.7 days) and resolved after a mean of three days on topical steroids and cycloplegic agents. There was a recurrent episode of anterior uveitis in seven eyes but this resolved after use of topical steroid and cycloplegic agents. Three eyes had a third case, which again resolved with treatment.

Two FDA reports examined changes in contrast sensitivity six months after LASIK in spherical myopes. One report[116] observed a decrease of more than two levels on CSV-1500 at two or more spatial frequencies in 3.5% of eyes in photopic conditions and 2.1% in mesopic conditions. The other FDA report[112] observed a decrease of more than two levels on CSV-1000 in 0.7% of eyes in photopic conditions and 5.8% of eyes in mesopic conditions.

Three FDA reports[114,115,117] found secondary surgical intervention other than excimer laser treatment was necessary in 1.1% of eyes (range 0.5% to 2.0%).

Table 48 LASIK case series: Participant reported outcomes better or worse at 6 months follow-up (Salz 2002[127] 12 months follow-up) compared with baseline

Study id	FDA 2003a[115]		FDA 2003b[116]		FDA 2002a[114]		FDA 2002b[112]		FDA 2000a[117]		*Salz 2002[127]		*McDonald 2001[124]	
Participant reported outcomes:	**Better** %	**Worse** %	**Better** %	**Worse** %	**Better** %	**Worse** %	**Better** %	**Worse** %	**Better** %	**Worse** %	**Better** %	**Worse** %	**Better** %	**Worse** %
Blurring of vision	26.6	30.5	22.3	18.5	41.2	37.9	-	19.1	14.4	10.3	-	0.5	-	1.6
Burning	14.4	13.6	14.4	7.9	16.5	9.8	-	7.4	12.1	4.3	-	0.5	-	-
Double vision	7.2	14.7	1.5	3.3	1.3	8.5	-	6.6	2.9	2.6	-	0	-	0.4
Discharge	-	-	-	-	0.4	0	-	-	0.6	0	-	-	-	-
Dryness	9.8	44.0	19.7	31.2	28.6	21.4	-	22.8	28.2	17.0	-	6.0	-	3.6
Eye strain	-	-	-	-	0	0.4	-	-	0	0	-	-	-	-
Floaters	-	-	-	-	3.6	0	-	-	0.6	0	-	-	-	-
Fluctuation of vision	9.4	42.3	7.5	24.2	12.1	36.6	-	17.6	7.5	14.7	-	1.8	-	2.0
Ghost images	6.4	18.2	4.4	4.4	7.1	18.8	-	-	1.1	2.3	-	-	-	-
Glare	24.2	28.7	20.9	15.3	24.6	29.9	-	14.7	10.9	10.3	-	0	-	6.0
Gritty feeling	11.3	20.8	8.5	6.2	8.9	12.1	-	10.3	12.9	6.0	-	-	-	-
Halos	15.5	21.1	13.6	14.4	15.6	42.9	-	13.2	6.0	18.4	-	0.9	-	-
Halos/starburst	-	-	-	-	-	-	-	-	-	-	-	-	-	5.2
Headaches	29.0	5.0	25.3	5.3	28.1	7.1	-	1.5	18.1	2.0	-	0	-	0.4
Itching	-	-	-	-	1.8	0	-	-	0	0	-	-	-	-
Light sensitivity	29.2	25.8	36.8	7.7	42.4	10.7	-	4.4	23.0	10.9	-	0	-	4.0
Night driving difficulty	38.8	18.5	40.3	10.3	21.0	36.6	-	19.1	22.7	11.5	-	0.9	-	9.6
Night vision	-	-	-	-	-	-	-	-	0	0	-	-	-	-
Oedema, lid	-	-	-	-	0	0	-	-	0.6	0	-	-	-	-
Pain	9.1	5.7	6.2	2.1	6.3	5.4	-	0.7	4.6	2.0	-	0.9	-	-
Redness	13.6	15.9	23.3	10.9	21.4	5.4	-	5.9	20.1	6.3	-	1.4	-	1.2
Starburst	-	-	-	-	0	0	-	-	-	-	-	-	-	-
Tearing	18.1	5.6	12.1	3.8	8.0	6.7	-	0	12.4	2.0	-	-	-	-
Twitch	-	-	-	-	0	0.4	-	-	-	-	-	-	-	-
Variation of vision in bright light	26.1	23.5	23.9	10.6	20.5	16.1	-	-	8.9	6.3	-	-	-	-
Variation of vision in normal light	12.1	26.5	9.5	11.2	9.4	27.7	-	-	4.0	5.7	-	-	-	-
Variation of vision in dim light	20.3	36.6	25.4	17.4	13.8	37.1	-	-	17.2	12.4	-	-	-	-

*significantly worse only

Table 49 LASIK case series: Incidence of moderate or severe participant reported outcomes at baseline and 6 months follow-up (FDA 2003c[130] 3 months follow-up)

Study id	FDA 2003a[115]		FDA 2003b[116]		FDA 2003c[130]		FDA 2002a[114]		FDA 2000a[117]	
Participant symptoms:	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
	%	%	%	%	%	%	%	%	%	%
Blurring of vision	21.4	18.6	11.5*	7.1	-	-	18.8	18.8	4.9	2.0
Burning	3.4	2.2	2.1	0.6	-	-	4.1	0.4	1.6	1.4
Double vision	3.1	5.5	0.3	2.4	-	-	2.0	4.7	0.5	0.6
Discharge	-	-	-	-	-	-	0.3	0	0	0
Dryness	10.0	21.9	7.9	5.9	-	-	16.4	12.0	16.6	6.9
Eye strain	-	-	-	-	-	-	0	0	-	-
Floaters	-	-	-	-	-	-	0.7	0	0	0
Fluctuation of vision	5.7	14.6	0.9	5.4	2.5	6.1	6.8	10.3	2.6	2.3
Ghost images	2.9	4.4	0.9	1.8	-	-	2.0	5.6	0	0.6
Glare	12.0	12.8	4.4	3.5	17.4	12.4	15.7	11.1	4.1	2.6
Gritty feeling	2.9	6.6	0.9	0.3	-	-	3.4	2.1	2.3	0.3
Halos	6.9	9.9	2.6	3.8	13.2	9.1	12.3	17.9	2.6	3.4
Headaches	11.7	2.9	9.7	4.1	-	-	10.2	6.8	10.1	1.7
Itching	-	-	-	-	-	-	0	0	0	0
Light sensitivity	23.1	19.7	18.5	2.6	12.3	8.3	30.0	8.1	11.9	5.2
Night driving difficulty	18.6	10.9	18.5	7.1	17.4	11.9	25.6	28.6	7.0	4.3
Pain	2.3	1.1	2.4	0	-	-	0.7	1.3	1.6	0.9
Redness	6.0	7.7	3.5	1.5	-	-	6.5	2.6	1.4	2.9
Starburst	-	-	-	-	-	-	0	0	-	-
Tearing	7.4	2.6	2.4	0.6	-	-	0.7	0.9	4.4	1.4
Variation of vision in bright light	11.7	9.9	7.4	1.2	-	-	9.9	5.6	3.1	1.4
Variation of vision in normal light	5.1	7.3	1.5	2.9	-	-	2.7	4.3	1.0	2.0
Variation of vision in dim light	18.3	27.7	11.5	10.6	-	-	15.0	25.2	4.1	4.0

6.6 Overview of efficacy findings

6.6.1 Myopia and myopic astigmatism

Accuracy

Seventeen studies reported the number of eyes with myopia or myopic astigmatism achieving intended spherical equivalent correction at between three and 12 months follow-up (Table 50). Overall, 7,309 out of 9,542 eyes, median 75.2% (range 53.4% to 90.4%), were within 0.5 D of intended correction and 8,109 out of 8,885, median 92.4% (range 74.7% to 100%) were within 1.0 D of intended correction. In eyes treated for low to moderate myopia, a median of 84.6% (range 74.8% to 90.4%) and a median of 96.3% (range 92.2% to 100%) were within 0.5 and 1.0 D of their intended corrections, respectively. In highly myopic eyes, a median of 62.3% (range 53.4% to 74.0%) and 80.6% (range 74.7% to 91.5%) respectively, achieved within 0.5 and 1.0 D of their intended corrections. Eyes treated for myopic astigmatism achieved within 0.5 and 1.0 D of their intended corrections for a median of 73.3% (range 56.2% to 87.2%) and 94.0% (range 83.3% to 98.9%) of eyes, respectively.

Table 50 LASIK case series: Participants with myopia and myopic astigmatism achieving refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id	Pre-operative refraction (D)	Follow-up (months)	≤ ±0.5 D Rate	%	≤ ±1.0 D Rate	%
Myopia or myopic astigmatism						
Ito 2004[144]	-0.13 to –17.25	6	3027/3732	81.1	3485/3732	93.4
Pop 2004[158]	< -10	12	NR	78	NR	92
Merchea 2002[151]	-0.75 to –15.50	6	668/866	77.1	NR	NR
Wang 2002[132]	-0.75 to –16.75	6	NR	67.9	NR	84.9
McDonald 2001[124]	spherical myopia	6	118/157	75.2	149/157	94.9
FDA 2000b[125]	-1.0 to –20.0	12	143/195	73.3	182/195	93.3
Low/moderate myopia						
FDA 2003b[116]	-0.46 to –7.15	6	99/117	84.6	113/117	96.6
FDA 2003c[130]	0 to –6.00	3	568/644	88.2	633/644	98.3
FDA 2002b[112]	0 to –7.00	6	104/139	74.8	133/139	95.7
Kremer 2001[122]	< -7.00	6	730/960	76.0	885/960	92.2
Tole 2001[63]	-0.50 to –6.00	6	109/139	78.4	129/139	92.8
FDA 2000a[117]	-1.0 to –7.0	6	81/95	85.3	95/95	100
Reviglio 2000[126]	-1.00 to –5.99	6	123/136	90.4	131/136	96.3
High myopia						
Kim 2004[89]	–6.00 to –11.50	12	205/324	63.3	261/324	80.6
FDA 2003c[130]	-6.01 to –13.00	3	148/200	74.0	183/200	91.5
Sanders 2003[172]	-8.00 to –12.00	12	57/100	57.0	79/100	79.0
FDA 2002a[114]	-7.25 to –12.25	6	161/263	61.2	216/263	82.1
Kremer 2001[122]	≥ -7.00	6	236/442	53.4	330/442	74.7
Lyle 2001[123]	-10.00 to –18.00	12*	NR	NR	167/209	80.3
Reviglio 2000[126]	-6.00 to –25.00	6	78/114	68.4	97/114	85.1
Myopic astigmatism						
FDA 2003b[116]	-0.46 to –7.15	6	159/223	71.3	206/223	92.4
McDonald 2001[124]	NR	6	85/113	75.2	108/113	95.6
FDA 2000a[117]	-1.0 to –7.0	6	232/266	87.2	263/266	98.9
FDA 2000b[125]	-1.0 to –20.0	12	178/317	56.2	264/317	83.3

*mean

Uncorrected visual acuity (UCVA)

This outcome was reported in eyes with myopia and myopic astigmatism, with between one and 24 months follow-up after LASIK (Table 51.). A median of 64.0% of eyes achieved an UCVA of 20/20 or better and a median of 94.0% had an UCVA of 20/40 or better. In eyes with low to moderate myopia, a median of 80.6% (range 44.1% to 90.1%) and 98.2% (range 93,5% to 100%) achieved UCVA of better than 20/20 and 20/40 respectively. UCVA of 20/20 or better and 20/40 or better was obtained in a median of 45.2% (range 14.7% to 74.3%) and 89.4% (76.2% to 97.4%) respectively of highly myopic eyes. Three studies reported UCVA in eyes corrected for myopic astigmatism; a median of 87.8% (range 52.0% to 90.1%) achieved 20/20 or better and 99.1% (range 94.1% to 99.6%) achieved 20/40 or better.

Table 51 LASIK case series: Participants with myopia and myopic astigmatism achieving uncorrected visual acuity (UCVA) of Snellen acuity 20/20 or better or 20/40 or better

Study id	Pre-operative refraction (D)	Follow-up months	≥ 20/20 Rate	%	≥ 20/40 Rate	%
Myopia and myopic astigmatism						
Bowers 2004[141]	–0.50 to –9.50	1	550/713	77	708/713	99
Ito 2004[144]	SE –0.13 to –17.25	6	3039/3732	81.4	3640/3732	97.5
Pop 2004[158]	< -10	12	NR	72	NR	94
Goldberg 2003[142]	myopia	<24	NR	64	NR	100
Lin 2003[147]	-1.50 to –14.50	2*	455/1131	40	1077/1131	95
Wang 2002[132]	-0.75 to –16.75	6	NR	59.6	NR	89.5
McDonald 2001[124]	spherical myopia	6	89/147	60.5	138/147	93.9
Vongthongsri 2001[178]	0.00 to –18.00	6	1334/1974	67.6	1879/1974	95.2
FDA 2000b[125]	-1.0 to –20.0	12	247/505	48.9	433/505	85.7
Patel 2000[157]	-0.75 to –14.38	3	346/900	38.4	856/900	95.1
Low/moderate myopia						
Price 2004[180]	0.00 to –6.0	12	827/1062	77.9	1041/1062	98.0
FDA 2003b[116]	-0.46 to –7.15	6	201/223	90.1	221/223	99.1
FDA 2003c[130]	0 to –6.00	3	544/622	87.5	611/622	98.2
FDA 2002b[112]	0 to –7.00	6	111/139	80.6	137/139	98.6
Kremer 2001[122]	< -7	6	361/818	44.1	765/818	93.5
Tole 2001[63]	-0.5 to –6.0	6	112/139	80.6	NR	NR
FDA 2000a[117]	-1.00 to –7.00	6	79/92	85.9	92/92	100
Reviglio 2000[126]	-1.00 to –5.99	6	73/136	53.7	133/136	97.8
High myopia						
Kim 2004[89]	–6.00 to –11.50	12	232/324	71.6	307/324	94.8
Price 2004[180]	-6.25 to –16.0	12	336/656	51.2	602/656	91.8
FDA 2003c[130]	-6.01 to –13.00	3	142/191	74.3	186/191	97.4
Sanders 2003[172]	-8.00 to –12.00	12	36/100	36.0	87/100	87.0
FDA 2002a[114]	-7.25 to –12.25	6	138/259	53.3	234/259	90.3
Kremer 2001[122]	≥ -7	6	50/341	14.7	260/341	76.2
Lyle 2001[123]	-10.00 to –18.00	12*	81/209	39.2	183/209	88.5
Reviglio 2000[126]	-6.00 to –25.00	6	21/114	18.4	95/114	83.3
Myopic astigmatism						
FDA 2003b[116]	-0.46 to –7.15	6	201/223	90.1	221/223	99.1
McDonald 2001[124]	NR	6	53/102	52.0	96/102	94.1
FDA 2000a[117]	-1.00 to –7.00	6	223/254	87.8	253/254	99.6

*mean

Stability of refraction

Stability of refraction between one and three months, and between three and six months, was reported in eight studies and is presented in Table 52. Between one and three months, the refraction of a median 86.5% of eyes (range 63.8% to 92.2%) with myopia and myopic astigmatism changed by less than 0.50 D and 99.4% of eyes (range 91.0% to 99.6%) changed by less than 1.0 D. Between three and six months, a median of 90.0%

(range 78.3% to 94.7%) and 98.5% (range 91.5% to 100%) of eyes changed by less than 0.50 and 1.0 D respectively. In addition, one study[133] reported regression in a median of 8.14% of eyes by 12 months follow-up.

Table 52 LASIK case series: Stability of refraction in participants with myopia and myopic astigmatism

Study id	1 to 3 months				3 to 6 months			
	≤ ±0.50 D		≤ ±1.0 D		≤ ±0.5 D		≤ +1.0 D	
	Rate	%	Rate	%	Rate	%	Rate	%
Myopia and myopic astigmatism								
FDA 2003c[130]	NR	NR	747/765	97.6	NR	NR	757/765	99.0
Wang 2002[132]	NR	84.1	NR	94.2	NR	89.0	NR	96.5
McDonald 2001[124]	NR	NR	NR	97.5	NR	NR	NR	100
Low/moderate myopia								
FDA 2003a[115]	295/340	86.8	327/340	96.2	309/340	90.9	335/340	98.5
FDA 2002a[114]	NR	NR	139/139	100	NR	NR	139/139	100
Price 2001[180]	509/589	86.4	NR	NR	449/510	88.0	NR	NR
FDA 2000a[117]	95/103	92.2	103/103	100	90/95	94.7	93/95	97.9
FDA 2000b[125]	NR	NR	NR	NR	NR	NR	155/157	98.7
High myopia								
FDA 2002a[114]	NR	NR	54/59	91.5	NR	NR	54/59	91.5
Price 2001[180]	150/235	63.8	NR	NR	144/184	78.3	NR	NR
FDA 2000b[125]	NR	NR	NR	NR	NR	NR	59/63	93.7
Myopic astigmatism								
FDA 2002a[114]	NR	NR	172/189	91.0	NR	NR	182/189	96.3
McDonald 2001[124]	NR	NR	NR	99.4	NR	NR	NR	100
FDA 2000a[117]	227/262	86.6	261/262	99.6	252/266	94.7	265/266	99.6
FDA 2000b[125]	NR	NR	NR	NR	NR	NR	376/392	95.9

*mean

6.6.2 Hyperopia, hyperopic astigmatism and mixed astigmatism

Accuracy

Three studies examined the number of eyes with hyperopia, hyperopic astigmatism or mixed astigmatism achieving refractions within 0.5 and 1.0 D of intended spherical equivalent correction at between six and 12 months follow-up (Table 53). In hyperopic eyes, 62.0% (range 59.0% to 74.1%) and 88.0% (range 86.0% to 91.4%) achieved refractions within 0.5 and 1.0 D of intended correction respectively. For eyes with hyperopic astigmatism, 67.3% (range 61.6% to 73.0%) and 88.4% (range 87.5% to 89.2%) achieved within 0.5 and 1.0 D of their intended correction. Salz et al.[127] also found 73.7% and 94.7% of eyes with mixed astigmatism achieved within 0.5 and 1.0 D respectively of intended refraction.

Table 53 LASIK case series: Participants with hyperopia, hyperopia astigmatism and mixed astigmatism achieving refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id	Pre-operative refraction (D)	Follow-up (months)	≤ ±0.5 D Rate	%	≤ ±1.0 D Rate	%
Hyperopia						
FDA 2003a[115]	+0.50 to +4.00	6	105/178	59.0	153/178	86.0
Salz 2002[127]	+1.00 to +6.00	12	86/116	74.1	106/116	91.4
Reviglio 2000[126]	+1.00 to +6.00	6	31/50	62.0	44/50	88.0
Hyperopic astigmatism						
FDA 2003a[115]	+0.50 to +4.00	6	69/112	61.6	98/112	87.5
Salz 2002[127]	+1.00 to +6.00	12	54/74	73.0	66/74	89.2
Mixed astigmatism						
Salz 2002[127]	+0.25 to +5.0	12	28/38	73.7	36/38	94.7

Uncorrected visual acuity (UCVA)

Three studies reported UCVA (Table 54). In hyperopic eyes, 51.5% (range 51% to 59.3%) reported an UCVA of 20/20 or better at between six and 24 months follow-up, and 95.9% (range 93.9% to 100%) had an UCVA of 20/40 or better. For eyes with hyperopic astigmatism, 59.0% (range 53.1% to 64.8%) and 93.5% (range 93.2% to 93.8%) had UCVA of 20/20 or better and 20/40 or better respectively. Eyes with mixed astigmatism were reported by one study to achieve 20/20 or better and 20/40 or better in 47.2% and 94.4% of eyes respectively.

Table 54 LASIK case series: Participants with hyperopia, hyperopic astigmatism and mixed astigmatism achieving uncorrected visual acuity (UCVA) of Snellen 20/20 or better or 20/40 or better

Study id	Preoperative Refraction (D)	Follow-up months	≥ 20/20 Rate	%	≥ 20/40 Rate	%
Hyperopia						
Goldberg 2003[142]	hyperopia	<24	NR	51	NR	100
FDA 2003a[115]	+0.50 to +4.00	6	86/145	59.3	139/145	95.9
Salz 2002[127]	+1.00 to +6.00	12	51/99	51.5	93/99	93.9
Hyperopic astigmatism						
FDA 2003a[115]	+0.50 to +4.00	6	57/88	64.8	82/88	93.2
Salz 2002[127]	+1.00 to +6.00	12	34/64	53.1	60/64	93.8
Mixed astigmatism						
Salz 2002[127]	+0.25 to +5.0	12	17/36	47.2	34/36	94.4

Stability of refraction

Two studies reported stability of refraction in participants with hyperopia, hyperopic astigmatism and mixed astigmatism between one and three months and between three

and six months (Table 55). A change of less than 1.0 D was observed in 96.6% (range 96.2% to 97.2%) of hyperopic eyes between one month and three months, and 96.2% (range 95.3% to 96.9%) of hyperopic eyes between three months and six months. In eyes with hyperopic astigmatism, a change of less than 1.0 D was observed in 98.3% (range 97.3% to 100%) and 97.2% (95.5% to 98.2%) between one month and three months and three months and six months respectively. No change of more than 1.0 D was noted in eyes with mixed astigmatism between one and six months after LASIK.

Table 55 LASIK case series: Stability of refraction in participants with hyperopia, hyperopic astigmatism and mixed astigmatism

Study id	1 to 3 months				3 to 6 months			
	≤ ±0.50 D		≤ ±1.0 D		≤ ±0.5 D		≤ +1.0 D	
	Rate	%	Rate	%	Rate	%	Rate	%
Hyperopia								
FDA 2003a[115]	NR	NR	151/157	96.2	NR	NR	154/159	96.9
Salz 2002[127]	NR	NR	103/106	97.2	NR	NR	101/106	95.3
Hyperopic astigmatism								
FDA 2003a[115]	NR	NR	107/110	97.3	NR	NR	108/110	98.2
Salz 2002[127]	NR	NR	66/66	100	NR	NR	63/66	95.5
Mixed astigmatism								
Salz 2002[127]	NR	NR	33/33	100	NR	NR	33/33	100

6.6.3 Astigmatism

Eight studies reported results of correction of astigmatism; six studies reported percent reduction of absolute cylinder (Table 56) and two studies reported number of participants achieving refractions within 0.5 and 1.0 D or intended cylinder correction (Table 57). In eyes with myopic astigmatism, between 49.26% and 70.31% reduction of absolute cylinder was achieved. Between 28.63% and 109% reduction of absolute cylinder was achieved in eyes with hyperopic astigmatism, and 91% reduction in eyes with mixed astigmatism. Kim et al.[89] noted that 76.5% of eyes with myopic astigmatism achieved within 0.5 D of intended cylinder correction. Between 87.7% and 91.1% of eyes with myopic astigmatism achieved within 1.0 D of intended cylinder correction.

Table 56 LASIK case series: Percent reduction of absolute cylinder (astigmatic eyes)

Study id	Pre-operative Astigmatism	Follow-up (months)	Reduction (%) Mean	SD
Myopic astigmatism				
FDA 2003b[116]	0.02 to 3.12*	3	64.00	43.00
FDA 2003c[130]	NR	3	78.2	
FDA 2002a[114]	0 to 3.5	6	49.26	74.46
FDA 2000a[117]	0.25 to 3.5	6	70.31	41.72
Hyperopic astigmatism				
FDA 2003a[115]	0 to 4.00	6	28.63	72.91
Salz 2002[127]	-0.50 to –6.00	12	109	
Mixed astigmatism				
Salz 2002[127]	-1.25 to –6.00	12	91	

*attempted cylindrical (astigmatism) correction

Table 57 LASIK case series: Participants achieving refractions within 0.5 D and 1.0 D of intended cylinder correction

Study id	Astigmatism Diopters (D)	Follow-up (months)	≤ ±0.5 D Rate	%	≤ ±1.0 D Rate	%
Myopic astigmatism						
Kim 2004[89]	0 to +4.50	12	248/324	76.5	295/324	91.1
Wang 2002[132]	0 to +4.75	6	NR	NR	NR	87.7

6.6.4 Retreatments

Ninteen studies reported the rate of LASIK retreatments as shown in Table 58. These retreatments were generally due to under or overcorrection and were not planned prior to primary LASIK. A median of 10.7% of eyes with myopia or myopic astigmatism had retreatment. In eyes with low to moderate myopia, a median of 3.4% (range 1.6% to 5.1%) were retreated. Highly myopic eyes were retreated in a median of 22.6% (range 2.6% to 37.0%) of cases. A single study reported 11.2% of eyes with myopic astigmatism were retreated. In eyes with hyperopia and hyperopic astigmatism, a median of 12.1% (range 0% to 23.6%) of eyes were retreated.

Table 58 LASIK case series: Unintended retreatments

Study id	Pre-operative Refraction (D)	Follow-up (months)	Retreatment Rate	%
Mixed refraction				
Kenyon 2004[120]	+6.75 to –10.25	>1	26/500	5.2
Myopia and myopic astigmatism				
Watson 2005[167]	-1.0 to –11.0	2[a]	49/1000	4.9
Pop 2004[158]	<-10	12	136/1488	9.1
FDA 2003c[130]	0 to –13.00	3	33/901	3.7
Goldberg 2003[142]	myopia	<24	NR	11.7
Hersh 2003[143]	myopia	12	282/2322[b]	12.1
Wang 2002[132]	-0.75 to –16.75	NR	40/353	11.3
Kremer 2001[122]	-1.0 to –15.0	12	253/2482[c]	10.2
McDonald 2001[124]	spherical myopia	6	18/177	10.2
FDA 2000b[125]	-1.0 to –20.0	12	197/1126	17.5
Patel 2000[157]	-0.75 to –14.38	17	171/1071	15.9
Reviglio 2000[126]	-1.0 to –25.0	5*	15/300[d]	5.0
Low/moderate myopia				
Price 2001[180]	0 to –6	12	54/1062	5.1
Tole 2001[63]	-0.5 to –6.0	6	5/314	1.6
High myopia				
Sanders 2003[172]	-8 to –12	12	128/559	22.9
FDA 2002a[114]	-7.25 to –12.24	6	8/308	2.6
Lyle 2001[123]	-10 to –18	12*	123/332	37.0
Price 2001[180]	-6 to –16	12	146/656	22.2
Myopic astigmatism				
McDonald 2001[124]	-0.5 to –5.0 D	6	19/170	11.2
Hyperopia and hyperopic astigmatism				
Goldberg 2003[142]	hyperopia	<24	NR	14.7
Hersh 2003[143]	hyperopia	12	10/163[b]	6.1
FDA 2003a[115]	+0.5 to +4.0	24	18/358	5.0
Reviglio 2000[126]	+1 to +6	5*	0/50	0.0
Salz 2002[127]	+1 to +6	12	85/360	23.6

*mean

[a]median

[b]85% of retreatments took place within 1 year. Higher degrees of myopia and astigmatism were independent predictors of the need for retreatment.

[c]retreatment for overcorrection 44/2483 (1.8%), undercorrection 209/2482 (8.4%)

[d]all retreatments were in the extreme myopia group (-10 to-25 D)

6.7 Unpublished data

Unpublished data from three, prospective case series was received from one source (personal communication, Reinstein 2005). Details of the study design, interventions and outcomes are reported in detail in Appendix 11.

6.7.1 Safety

Refractive complications

Reduction of BSCVA varied according to the level and type of refractive error and across laser type (Table 59). In the earlier series using the Technolas 217c and VISX excimer lasers for ablation, 18.2% and 16.9%, had loss of one Snellen line of BSCVA for both low and high preoperative myopia respectively. Loss of two or more lines BSCVA was 0.6% and 2.2% for low and high preoperative myopia respectively. In the more recent, but much smaller, single surgeon series, 3.2% and 6.5% treated with the MEL 70, and 2.4% and 0.0% treated with the MEL 80, had loss of one line BSCVA for low and high preoperative myopia, respectively. No eyes loss two or more lines BSCVA for both low and high preoperative myopia, with either the MEL 70 or MEL 80.

Similarly for preoperative hyperopia, in the earlier series using the Technolas 217c and VISX excimer lasers for ablation, 24% and 2.6% of eyes had lost one and two lines BSCVA respectively. In the single, but much smaller surgeon series, with the MEL 70, 14.4% and 1.0% lost one and two Snellen lines of BSCVA respectively and with the MEL 80, 10.7% lost one lines BSCVA and no eyes lost two lines.

Table 59 LASIK case series, unpublished data: Refractive complications

Study id	Follow-up (months)*	Loss ≥1 line BSCVA		Loss ≥2 lines BSCVA	
		Rate	%	Rate	%
Low/moderate myopia (≤-6 D)					
Reinstein 2005 (1)					
Technolas 217c	3.0	5575/29522	18.9	154/29522	0.5
VISX	2.2	1385/7977	17.4	56/7977	0.7
Reinstein 2005 (3)					
MEL 70	10.5	6/185	3.2	0/185	0
MEL 80	8.0	4/167	2.4	0/167	0
High myopia (> -6 D)					
Reinstein 2005 (1)					
Technolas 217c	3.25	814/5096	16.0	57/5096	1.1
VISX	2.3	269/1522	17.7	51/1522	3.4
Reinstein 2005 (3)					
MEL 70	11.7	2/31	6.5	0/31	0
MEL 80	8.3	0/46	0	0/46	0
Hyperopia up to +5 D					
Reinstein 2005 (1)					
Technolas 217c	3.0	519/2391	21.7	64/2391	2.7
VISX	2.0	64/241	26.6	6/241	2.5
Reinstein 2005 (3)					
MEL 70	10.3	14/97	14.4	1/97	1.0
MEL 80	9.1	16/149	10.7	0/149	0

*Median

Ectasia and Flap complication

A single surgeon series, performed from 1998 to 2005, recorded flap complications and the incidence of ectasia on all cases performed, (Reinstein 2, 2005). There were no cases of ectasia. Flap complications occurred in 7/8448 (0.08%) of surgeries and none of these cases lost a line of BSCVA.

Other safety outcomes

In a sub series of 778 primary treatments and 94 enhancements 3/778 (0.4%) eyes had epithelial ingrowth requiring further action, 77/778 (10%) of eyes had an epithelial defect that occurred intra-operatively, and 6/778 (0.3%) eyes developed diffuse lamellar keratitis. One eye out of 778 primary treatments had post-operative monocular diplopia. Of these complications, 1/103 (0.97%) of eyes lost one line of BSCVA and no eye lost two or more lines of BSCVA.

6.7.2 Efficacy

Accuracy

The proportion of eyes achieving within 0.5 and 1.0 D of predicted refraction for myopia varied according to the level and type of refractive error and between one and six months follow up but was similar across the four lasers. After six months follow up, for lower pre-operative myopia the proportion of eyes within 0.5 and 1.0 D of predicted refraction were approximately 72% to 87% and 93% to 98% and for myopia of greater than –6 D the respective accuracies were lower at approximately 30% to 57% and 72% to 87%. For hyperopic corrections, at six month follow up; approximately 49% to 75% and 74% to 100% of treatments were within 0.5 and 1.0 D of the predicted refraction respectively.

The accuracy was lower, as expected on account of tissue healing, after six months follow up than after one month for all four lasers and for all levels and types of refractive error (Table 60). This difference in accuracy was greatest for high myopia. The change in accuracy was minimal between time points for both the MEL 70 and MEL 80 for myopia up to and including –6 D and may be due to the improved treatment profiles giving greater stability but this is not certain due to the small study size.

Table 60 LASIK case series, unpublished data: Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id	≤ ±0.5 D				≤ ±1.0 D			
	1 month		6 months		1 month		6 months	
	Rate	%	Rate	%	Rate	%	Rate	%
Low/moderate myopia (≤-6 D)								
Reinstein 2005 (1)								
Technolas 217c	24175/27499	87.9	2009/2810	71.5	26834/27499	97.6	2603/2810	92.6
VISX	6968/7598	91.7	84/107	78.5	7465/7598	98.2	102/107	95.3
Reinstein 2005 (3)								
MEL 70	145/180	80.6	135/172	78.5	168/180	93.3	163/172	94.8
MEL 80	133/159	83.6	132/152	86.8	154/159	96.9	149/152	98.0
High myopia (>-6 D)								
Reinstein 2005 (1)								
Technolas 217c	3282/4746	69.2	374/743	50.3	4176/4746	88.0	567/743	76.3
VISX	1047/1448	72.4	13/23	56.5	1295/1448	89.4	20/23	87.0
Reinstein 2005 (3)								
MEL 70	19/31	61.3	8/26	30.8	25/31	80.6	21/26	80.8
MEL 80	24/44	54.5	23/43	53.5	36/44	81.8	31/43	72.1
Hyperopia up to +5 D								
Reinstein 2005 (1)								
Technolas 217c	1510/2185	69.1	168/276	60.9	1940/2185	88.8	228/276	82.6
VISX	159/221	71.9	6/8	75.0	204/221	92.3	8/8	100
Reinstein 2005 (3)								
MEL 70	55/95	57.9	41/83	49.4	76/95	80.0	61/83	73.5
MEL 80	105/140	75.0	94/133	70.7	124/140	88.6	94/116	87.2

Uncorrected Visual Acuity (UCVA)

The analysis of final UCVA (Table 61) excluded eyes where monovision was the intended outcome. Again the results varied according to the level and type of refractive error and across laser type. In the earlier series using the Technolas 217c and VISX excimer lasers for ablation at latest follow up (six to 12 months), for myopia of up to and including –6 D of error, the percentage of eyes achieving 20/20 vision or better and 20/40 vision or better was approximately 60% and 90% of eyes. For myopia of greater than –6 D, approximately 42% and 88% achieved the respective vision. In the single surgeon series with the MEL 70 the respective visions were achieved in 89% and 99% of eyes for myopia up to and including –6 D and 45% and 70% for myopia greater than –6 D. For the MEL 80, the respective visions were achieved in 95% and 100% of eyes for myopia up to and including –6 D and 67% and 100% for myopia greater than –6 D.

Similarly for preoperative hyperopia, in the earlier series using the Technolas 217c for ablation, approximately 52% and 97% achieved 20/20 vision or better and 20/40 vision or better at latest follow up between six to 12 months. In the single surgeon series with the MEL 70 the respective visions were achieved in 62.5% and 97.5% of eyes, and for 77% and 100% of eyes treated with the MEL 80.

Table 61 LASIK case series, unpublished data: Eyes achieving uncorrected Snellen visual acuity (UCVA) of 20/20 and 20/40 or better

Study id	6 months				12 months			
	≥ 20/20		≥ 20/40		≥ 20/20		≥ 20/40	
	Rate	%	Rate	%	Rate	%	Rate	%
Low/moderate myopia (≤-6 D)								
Reinstein 2005 (1)								
Technolas 217c	1702/2837	60.0	2671/2837	94.1	177/310	57.1	280/310	90.3
VISX	70/113	61.9	107/113	94.7				
Reinstein 2005 (3)								
MEL 70	156/173	90.2	173/173	100	111/125	88.8	124/125	99.2
MEL 80	121/128	94.5	128/128	100	39/41	95.1	41/41	100
High myopia (>-6 D)								
Reinstein 2005 (1)								
Technolas 217c	307/752	40.8	621/752	82.6	32/77	41.6	68/77	88.3
VISX	7/27	25.9	24/27	89.9				
Reinstein 2005 (3)								
MEL 70	14/26	53.8	23/26	88.5	9/20	45.0	14/20	70
MEL 80	19/29	65.5	29/29	100	8/12	66.7	12/12	100
Hyperopia up to +5 D								
Reinstein 2005 (1)								
Technolas 217c	96/272	35.3	250/272	91.9	15/29	51.7	28/29	96.5
VISX	3/7	42.9	6/7	85.7				
Reinstein 2005 (3)								
MEL 70	41/55	74.5	53/55	96.4	25/40	62.5	39/40	97.5
MEL 80	46/64	71.9	64/64	100	30/39	76.9	39/39	100

7 EVIDENCE FROM RCTS COMPARING PRK, LASEK AND LASIK

7.1 Type and quantity of available evidence

Randomised controlled clinical trials of PRK versus LASEK, LASEK versus LASIK, and LASIK versus PRK were identified. Where studies had multiple publications, only the most up to date (preferably full text) report was considered. The 16 primary studies along with their related references are listed in Appendix 4.

7.2 Number and type of included studies

Six full text studies[36,181-187] and four abstracts,[188-191] compared LASEK with PRK for the correction of myopia, or myopic astigmatism. One full text study compared LASEK with PRK for hyperopia.[37] Two full text studies[192,193] and one abstract[194] compared LASEK with LASIK for myopia or myopic astigmatism. Finally, two full text studies compared LASIK with PRK in people with myopia or myopic astigmatism.[195,196] Tables 62, 63 and 64 show the included studies for each of the three comparisons. The detailed characteristics of included studies are described in Appendix 12.

All trials but two[193,195] were within-person comparisons. Most studies included participants with low to moderate myopia. Two studies[189,195] only included participants with high myopia.

Two of the studies were set in the Czech Republic, two in Saudi Arabia, two in South Korea, one only in China, England India, Iran, Italy, Mexico, Netherlands, Turkey and the USA. The setting was unclear in one.

The source of funding was unclear in 13 out of 16 studies, although no proprietary interest in the instruments or techniques was noted in five of these studies. University hospital funding was provided in two studies[36,37,195] and funding provided by the manufacturer in one.[195]

The comparison of LASEK and PRK included 1016 eyes in total, LASEK versus LASIK included 498 eyes, and PRK versus LASIK included 310 eyes. The sample size ranged

from 28 eyes to 394 eyes. The mean age was between 20 and 39 years. Where reported the percentage of women ranged from 30% to 79%. Treatment dates were unclear in 10 studies. Three studies reported treatments carried out after January 2000.[37,182,193] Length of follow–up ranged from 48 hours (one study of pain) to 24 months.

Table 62 Included studies – RCTs: LASEK vs PRK

Study id		Preoperative spherical equivalent (D) mean	SD	range	Eyes	F/up (mo)	Age (yrs)	Laser
Full text								
Autrata 2003a[37]	LASEK	+3.76	1.29	+2.00 to +5.00	216	24	38.7	NIDEK
	PRK	+3.58	1.29					
Autrata 2003b[36]	LASEK	-4.90	3.01	-1.75 to –7.50	184	24	27.4	NIDEK
	PRK	-4.78	2.93					
Hashemi 2004[182]	LASEK	-3.57	1.25	-1.50 to –6.50	84	3	29.1	NIDEK or Techno 217C
	PRK	-3.44	1.13	-1.60 to –6.00				
Lee 2001[183]	LASEK	-4.69	0.96	-3.00 to –6.50	54	3	25.0	Keratome II
	PRK	-4.82	1.07					
Litwak 2002[185]	LASEK	-3.1	2.0	-0.75 to –7.75	50	1	28.7	NIDEK
	PRK	-3.0	1.9	0.87 to –7.13				
Pirouzian 2004[186]	LASEK	NR	NR	-1.00 to -8.75	32	1	21-46	VISX Star 3
	PRK	NR	NR					
Saleh 2003[187]	LASEK	-2.27	NR	-1.12 to –3.38	28	0	32	NIDEK
	PRK	-2.04	NR					
Abstracts								
Al Fayez 2002[188]	LASEK	NR	NR	-1.50 to -6.50	196	12	NR	Techno 217C
	PRK	NR	NR					
Al Fayez 2004[189]	LASEK	NR	NR	-6.50 to -12.00	68	12	NR	Techno 217C
	PRK	NR	NR					
Ghirlando 2002[190]	LASEK	-3.95	1.29	NR	68	NR	NR	NR
	PRK	-4.37	1.35					
Rooij 2003[191]	LASEK	NR	NR	-1.75 to –6.50	36	6	NR	Kerato 217
	PRK	NR	NR					

Table 63 Included studies – RCTs: LASEK vs LASIK

Study id		Preoperative spherical equivalent (D) mean	SD	range	Eyes	F/up (months)	Age (years)	Laser
Full Text								
Kaya 2004[192]	LASEK	-2.69	1.31	-1.00 to –6.00	64	6-12	26.8	LaserSight LSX
	LASIK	-3.08	1.85					
Sheng 2004[193]	LASEK	-7.52	2.44	-4.00 to –12.00	394	6	24	Keratome Multiscan
	LASIK	-7.23	2.23	-4.00 to –13.00				
Abstracts								
Bansal 2003[194]	LASEK	-6.5	1.25	NR	40	3	20.5	NR
	LASIK	-6.8	1.75	NR				

Table 64 Included studies – RCTs: PRK vs LASIK

Study id		Preoperative spherical equivalent (D) mean	SD	range	Eyes	F/up (months)	Age (years)	Laser
Full Text								
Lee 2001a[196]	PRK	-4.54	0.80	NR	45	NR	NR	Keratome II
	LASIK	-4.82	1.10		45			
Hersh 2000[195]	PRK	-9.23	1.76	-6.00 to -14.38	105	NR	39	Summit Apex
	LASIK	-9.30	1.70	-6.00 to -13.88	115		38	

7.3 Number and type of excluded studies; reasons for exclusion

Abstracts were only included in the search for trials involving LASEK as this is a recently introduced procedure with only a small number of full text studies meeting our inclusion criteria.

7.4 Quality of available evidence

A summary of the quality assessment of the 11 full-text randomised studies is presented in Table 65 and the detailed quality assessment results for included studies can be seen in Appendix 13.

Table 65 Summary of the quality assessment of randomised controlled trials

Criteria		Yes	No	Unclear
1.	Was the assignment to the treatment groups really random?	3	0	8
2.	Was the treatment allocation concealed?	0	3	8
3.	Were the groups similar at baseline in terms of prognostic factors?	11	0	0
4.	Were the eligibility criteria specified/	9	2	0
5.	Were the interventions clearly defined?	11	0	0
6.	Were the groups treated in the same way apart from the intervention received?	10	0	1
7.	Was the operation undertaken by somebody experienced in performing the procedure?	1	0	10
8.	Was the outcome assessor masked to the treatment allocation?	4	0	7
9.	Was the care provider masked?	2	0	9
10.	Were the participants masked?	6	1	4
11.	Was follow-up long enough to detect important effects on outcomes of interest	8	3	0
12.	Were the point estimates and measures of variability presented for the primary outcome measures?	11	0	0
13.	Was the withdrawal/drop-out rate likely to cause bias?	0	8	3
14.	Did the analyses include an intention-to-treat analysis?	6	4	1
15.	Was the paired nature of eyes taken into account in the analysis?	10	0	1

Treatment assignment appeared to be adequately randomised in three trials (random tables or computer generated).[182,186,192] The remaining trials[36,37,183,185,187,193,195,196] did not provide information on the method of randomisation used. Treatment allocation was not definitely concealed in three studies[183,186,187] and this information was unclear in the remaining eight studies (ie no description of robust methods to prevent foreknowledge of allocation sequence).

The two treatment groups were similar at baseline for prognostic factors in all eleven trials (all trials but two[193,195] were within-person comparisons). Two trials failed to clearly describe the inclusion and exclusion criteria.[186,196] All provided details about the refractive surgery technique used. Both treatment groups within each trial were treated in the same way apart from the intervention received excluding one study[193] where this was unclear. It was reported in only one study that the surgeon had previous experience of both procedures.[182]

In four studies the outcome assessor was masked to the treatment allocation[185-187,193] but this was unclear in the other seven.[36,37,182,183,192,195,196] Six studies reported that participants were masked to the treatment allocation.[36,37,182,185,186,193] After surgery follow-up was only one month in two trials[185,186] and only 48 hours in one trial in which the only outcome was pain after surgery.[187]

All eleven RCTs presented point estimates and measures of variability for the primary outcome measures. It was unclear whether the number of dropouts or withdrawal was likely to cause bias in three studies.[182,195,196]

Out of the eleven studies, four did not undertake an intention-to-treat analysis[36,186,192,195] and in one study this was unclear.[196] All studies except one,[196] which did not report any statistical methods, took into account the paired nature of eyes.

7.5 Overview of safety findings

7.5.1 LASEK versus PRK safety findings

Myopia

Ten trials[36,182,183,185-191] compared LASEK with PRK for myopia or myopic astigmatism.

Potentially serious complications

Autrata[36] and Lee[183] reported no post-operative complications such as infection or recurrent erosion syndrome.

Undesired consequences

In the study by Autrata,[36] 8% of eyes were converted to PRK because of flap disintegration; these converted eyes were excluded from further evaluation. In the study by Hashemi[182] the LASEK procedure failed in 2/42 (4.7%) eyes that were converted to PRK. In the study by Lee,[183] there was more pain reported in five LASEK eyes compared with PRK eyes due to a problem with flap formation in 1/27 eyes (3.7%), alcohol leakage occurred in 3/27 eyes (11.1%) and tight contact lens syndrome in 1/27 (3.7%) eyes.

Rate of reduced BSCVA for LASEK and PRK treated eyes from four trials[36,182,185,186] are shown in Table 66. The rate of loss of one line BSCVA was 1/181 (median 0%, range 0% to 3.0%) for LASEK compared with 6/181 (median 2.2%, range 0% to 6.0%)) for PRK. No eye lost two or more lines (Table 66).

Table 66 LASEK vs PRK: Number of Snellen lines of BSCVA lost

Study id	Months	LASEK		PRK	
		Rate	%	Rate	%
1 line					
Autrata 2003b[36]	24	0/92	0	4/92	4.5
Hashemi 2004[182]	3	1/32	3	2/32	6
Litwak 2002[185]	1	0/25	0	0/25	0
Pirouzian 2004[186]	1	0/32	0	0/32	0
≥ 2 lines					
Autrata 2003b[36]	24	0/92	0	0/92	0
Hashemi 2004[182]	3	0/32	0	0/32	0

In general, haze was measured by slit-lamp examination using a four-point scale. See Table 67 for corneal haze levels for LASEK and PRK treated eyes from two trials.[36,183] Both reported significantly lower levels of corneal haze for LASEK treated eyes ($p<0.05$).

In addition, two abstracts by Al Fayez describing participants with low to moderate myopia[188] and high myopia[189] reported that LASEK eyes had less corneal haze than PRK eyes ($p<0.05$). However, no statistically significant difference was found by Hashemi[182] in the number of eyes with grade one haze at three months (4/32 versus 1/32 for LASEK and PRK respectively). Also, Litwak[185] reported no difference between LASEK and PRK eyes in the development of post-operative haze at one month in 25 participants.

Table 67 LASEK vs PRK: Corneal haze

Study id			Corneal haze (four point scale)				
		Months	LASEK		PRK		P value
	N		mean	SD	mean	SD	P=
Autrata 2003b[36]	92/92	24	0.21	0.24	0.43	0.29	P<0.05
Lee 2001[183]	27/27	3	0.29	0.26	0.45	0.27	P<0.05

Participant reported outcomes

In the study by Hashemi[182] glare and halo were self-assessed using a five point Likert scale. There was no difference at three months between LASEK and PRK eyes for the mean (SD) glare score (1.79 (1.18) versus 1.83 (1.13)), or for the mean (SD) halo score (1.62 (1.31) versus 1.71 (1.27)).

Table 68 shows mean postoperative pain levels from six trials. Two trials[36,183] reported that pain was significantly less with LASEK than PRK. Two additional abstracts by Al Fayez providing limited data[188,189] also reported that LASEK treated eyes had less pain than PRK eyes ($p<0.05$). Four trials however,[182,186,187,191] showed no significant difference. Conversely, more discomfort with LASEK was reported in two trials: Ghirlando[190] with 34 participants reported more pain in the LASEK eyes ($p=0.02$). Litwak[185] with 25 participants included, reported that 20/25 LASEK eyes had discomfort at three days compared with only 1/25 PRK eyes; reasons for more pain in the LASEK eyes suggested by the authors include longer alcohol exposure (40 seconds) required for their (Hispanic) participants, a slightly larger ablation zone, and sloughing of the epithelial flap. Data were combined from five of the trials that provided sufficient data for meta-analysis using a random effects model (I^2 70.8%). There was no significant difference in the standard mean difference for early post-operative pain between LASEK and PRK respectively –0.21 (95% confidence interval -0.63, 0.20).

Table 68 LASEK vs PRK: Post-operative pain

Study id			Post-operative pain (4 point scale)				
			LASEK		PRK		P value
	N		mean	SD	mean	SD	P=
Autrata 2003b[36]	92/92	Day 1-3	0.61	5.3	1.26	0.91	p<0.05
Hashemi 2004[182]	42/42	Day 1	1.00	0.7	0.80	0.70	ns
Lee 2001[183]	27/27	Day 1-7	1.63	0.81	2.36	0.67	p<0.05
*Pirouzian 2004[186]	30/30	Day 3	2.17	NR	2.27	NR	ns
#Rooij 2003[191]	18/18	Day 3	28.0	26.0	41.0	28.0	ns
*Saleh 2003[187]	14/14	Day 2	2.86	3.43	2.21	2.55	ns

* ten point scale
# 100mm visual analogue scale

Hyperopia

One full text trial by Autrata[37] examined people with hyperopia.

Potentially serious complications

No post-operative complications such as infection, corneal melt, and recurrent erosion syndrome were reported.

Undesired consequences

There was a loss of one or more lines of BSCVA in 14% of LASEK eyes and 12% of PRK eyes. No eyes lost two or more lines.

There was significantly less haze (p<0.05) at 24 months in the LASEK group. Mean haze was 0.20 (SD 0.27) versus 0.45 (SD 0.31) (measured on a four point scale)

Participant reported outcomes

There was significantly less pain (p<0.05) in the LASEK group. The overall mean (SD) pain score for days one to three was 0.59 (SD 0.52) versus 1.13 (SD 0.95).

7.5.2 LASEK versus LASIK safety findings

Potentially serious complications

No data were reported in the trials comparing LASEK and LASIK

Undesired consequences

Three trials[192-194] compared LASEK with LASIK for myopia and reported safety outcomes. Table 69 describes undesired consequences.

30/184 (16%) of eyes in the LASEK group in the study by Sheng[193] had a punctate corneal defect, all had recovered in two weeks. Three eyes (9%) had complications during LASEK flap preparation in the study by Kaya[192] and were excluded from the trial. IOP was 21 mmHg or more at one to two months after surgery in three high myopic LASEK eyes (1.6%) when topical cortico-steroid eye drops were used. IOP returned to normal after corticosteroids were discontinued and topical beta-blockers administered. In the LASIK group flap complications were reported by Sheng,[193] leading to loss of one to two lines in 2/210 (0.95%).

Refractive complications

The rate of reduced BSCVA, one or two Snellen lines, for LASEK and LASIK treated eyes from the three trials[192-194] was 4/236 (median 0%, range 0% to 20.0%) for LASEK and 2/262 (median 0%, range 0% to 0.95%) for LASIK.

Haze

Bansal[194] reported that 7/20 LASEK eyes had ≥ grade two haze at three months. In the trial by Sheng[193] 17/184 (9%) LASEK eyes had grade one haze at three months which were treated with flourometholone for four weeks. No further treatment was necessary in any eye at six months. No cases of haze were reported for LASIK treated eyes.

Participant reported outcomes

No data reported for any of the trials.

Table 69 LASEK vs LASIK: Undesired consequences:

	Undesired consequences: LASEK vs LASIK				
	Study id	LASEK		LASIK	
		Rate	%	Rate	%
Perioperative					
Punctate corneal defect	[i]Sheng 2004[193]	30/184	16		
LASEK flap complications	[b]Kaya 2004[192]	3/32	9		
LASIK Flap complications:					
Buttton hole flap	[c]Sheng 2004[193]			1/210	0.48
Incomplete LASIK flap	[d]Sheng 2004[193]			1/210	0.48
Epithelial ingrowth	[e]Sheng 2004[193]			1/210	0.48
Increased intra ocular pressure	[f]Sheng 2004[193]	3/184	1.6		
Lost Snellen lines:					
1 line	[g]Bansal 2003[194]	4/20	20	0/20	0
1 line	Kaya 2004[192]	0/32	0	0/32	0
1 or 2 lines	Sheng 2004[193]	0/184	0	2/210	0.95

[a]all recovered in two weeks
[b]3 eyes excluded from the study due to complications during flap preparation
[c]button hole 0.48% (loss of 1-2 lines BSCVA)
[d]incomplete flap 0.48% (loss of 1-2 lines BSCVA)
[e]Epithelial ingrowth 0.48 (no loss BSCVA)
[f]all occurred in high myopic eyes when a topical corticosteroid was used. Intraocular pressure returned to normal in all eyes after topical corticosteroids were discontinued and topical beta blockers administered
[g]no reason given

7.5.3 LASIK versus PRK safety findings

Potentially serious complications

No such complications were reported in the two studies comparing PRK and LASIK.

Undesired consequences

Lee et al.[196] reported that the following complications occurred in the LASIK group: stopping of the microkeratome in the middle of the pass (one eye, 2.2%); free cap (one eye, 2.2%); and interface foreign body (two eyes, 4.4%). One eye (2.2%) in the PRK group had delayed epithelisation until day six after the procedure.[196] In the LASIK group, epithelial ingrowth occurred in three eyes (6.7%) and in one eye had to be mechanically removed.[196]

Haze

Subepithelial corneal haze levels were detected by slit-lamp examination and graded according to Hanna's method (0 to 4). At six months, 84.4% (38/45 eyes) of eyes in the PRK group had zero or 0.5 grade haze, 13.3% (6/45 eyes) of eyes had grade one haze and one eye had grade two haze. LASIK-treated eyes were graded zero in all examinations.

Raised intraoperative pressure (IOP)

Raised IOP was seen in one eye (2.2%) in the PRK group, secondary to steroid treatment.[196]

Participant reported outcomes

Hersh et al.[195] reported halo and glare symptoms at six months: in the PRK group and LASIK group, respectively 41.4% (24/58 participants) and 21.6% (11/51 participants) of participants reported a worsening of glare symptoms after surgery (Table 70). There was no statistically significant difference between the PRK and LASIK groups in terms of change in glare symptoms. In the PRK group, 58.6% (34/58 participants) of participants reported a worsening of halo symptoms compared with 50.0% (26/52 participants) of participants in the LASIK group. There was no statistically significant difference between the PRK and LASIK groups in terms of change in halo symptoms.

Table 70 PRK vs LASIK: Change in glare and halo symptoms at 6 months

	Change in glare symptoms			Change in halo symptoms		
	Less	**No change**	**Worse**	**Less**	**No change**	**Worse**
PRK	25/58 (43.1%)	9/58 (15.5%)	24/58 (41.4%)	9/58 (15.5%)	15/58 (25.9%)	34/58 (58.6%)
LASIK	29/51 (56.9%)	11/51 (21.6%)	11/51 (21.6%)	17/52 (32.7%)	9/52 (17.3%)	26/52 (50.0%)

When preoperative to postoperative changes in glare and halo symptoms in individual participants were considered, participants treated with PRK showed a significantly greater likelihood of an increase in symptoms (p=0.048, chi-square test).

Monocular diplopia

Hersh et al.[195] reported diplopia symptoms at six months (Table 71). In the PRK group, 44.8% (26/58 participants) of participants reported a worsening of diplopia symptoms compared with 35.8% (19/53 participants) in the LASIK group. There was no statistically significant difference between PRK and LASIK in terms of change in diplopia symptoms (double-vision index) at six months.

Table 71 PRK vs LASIK: Change in diplopia symptoms at 6 months

	Change in diplopia symptoms		
	Less	**No change**	**Worse**
PRK	11/58 (19.0%)	21/58 (36.2%)	26/58 (44.8%)
LASIK	8/53 (15.1%)	26/53 (49.1%)	19/53 (35.8%)

7.6 Overview of efficacy findings

7.6.1 LASEK versus PRK efficacy findings

Postoperative refraction

A median of 80% (range 62% to 95%) of LASEK eyes and 64% (range 57% to 72%) of PRK eyes were within 0.5 D of their intended correction. This difference was statistically significant in one study of hyperopic participants.[37] For LASEK and PRK eyes respectively a median of 92% (range 91% to 92%) and 91% (range 86% to 94%) were within 1.0 D (Table 72).

Table 72 LASEK vs PRK: Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id		Achieving ≤ ±0.5 D					Achieving ≤ ±1.0 D				
	Mo	LASEK		PRK			LASEK		PRK		
Eyes		Rate	%	Rate	%	P=	Rate	%	Rate	%	P=
Hashemi2004[182]	3	26/32	81	23/32	72	ns	29/32	91	30/32	94	ns
Pirouzian 2004[186]	1	NR	NR	NR	NR	ns	NR	NR	NR	NR	ns
*Autrata 2003a[37]	24	85/108	78	62/108	57	0.04	99/108	92	93/108	86	0.13
Autrata 2003b[36]	24	57/92	62	52/92	57	ns	85/92	92	84/92	91	ns
Rooij 2003[191]	6	NR	95	NR	72	NR	NR	NR	NR	NR	NR

* participants with hyperopia

In the study by Autrata[36] of participants with myopia, three PRK eyes (3.2%) and two LASEK eyes (2.1%) were overcorrected 1.0 D to 2.0 D. No eye in either group was overcorrected by more than 2.0 D. No participant required retreatment.

In the study by Autrata[37] including only participants with hyperopia, one month after treatment, the mean SE refraction was greater than -1.0 D in both groups. The spherical equivalent refraction reached stability at nine months in the PRK eyes and six months in the LASEK eyes. Eight PRK eyes have received retreatment due to significant regression; no LASEK eye had required retreatment

Uncorrected visual acuity (UCVA)

No study reported any significant difference in UCVA between LASEK and PRK treated eyes (Table 73). A median of 100% (range, 91% to 100%) of LASEK eyes and 97% (range 81% to 100%) of PRK eyes had a Snellen acuity of 20/40 or better. For LASEK and PRK eyes respectively a median of 70% (range, 30% to 79%) and 70% (range 26% to 82%) were 20/20 or better.

Table 73 LASEK vs PRK: Snellen acuity 20/40 or better and 20/20 or better

Study id		20/40 or better					20/20 or better				
	Mo	LASEK		PRK			LASEK		PRK		
Eyes		Rate	%	Rate	%	P =	Rate	%	Rate	%	P =
Hashemi 2004[182]	3	32/32	100	31/32	97	NR	25/32	79	26/32	82	
Pirouzian 2004[186]	1	NR	NR	NR	NR	ns	NR	NR	NR	NR	ns
#Autrata 2003a[37]	24	98/108	91	87/108	81	NR	72/108	67	79/108	73	
Autrata 2003b[36]	24	92/92	100	92/92	100	ns	67/92	73	62/92	67	ns
Ghirlando 2002[190]	NR	NR	NR	NR	NR	ns	NR	NR	NR	NR	ns
Litwak 2002[185]	1	NR	NR	NR	NR	ns	NR	NR	NR	NR	ns
Lee 2001[183]	3	NR	NR	NR	NR	NR	8/27	30	7/27	26	ns

hyperopic participants

7.6.2 LASEK versus LASIK efficacy findings

Postoperative refraction

No statistically significant differences between LASEK and LASIK were reported for accuracy of postoperative refraction after treatment for myopia or myopic astigmatism (Table 74). One study by Bansal[194] reported that 65% of LASEK eyes and 95% of LASIK eyes were within 0.5 D of their intended correction. In a larger study, Sheng[193] found that 85% and 84% of LASEK and LASIK eyes respectively were within 1.0 D.

Table 74 LASEK vs LASIK: Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id		Achieving ≤ ±0.5 D					Achieving ≤ ±1.0 D				
	Mo	LASEK		LASIK			LASEK		LASIK		
Eyes		Rate	%	Rate	%	P=	Rate	%	Rate	%	P=
Sheng 2004 [193]	6	NR	NR	NR	NR	NR	156/184	85	176/210	84	ns
Bansal 2003[194]	3	13/20	65	19/20	95		NR	NR	NR	NR	NR

Myopic astigmatism

Sheng[193] reports the changes of astigmatism dioptre six months after LASEK and LASIK. The proportion of eyes achieving within 1.0 D for LASEK and LASIK was 69.1% and 64.7% respectively, the proportion of eyes achieving within 0.5 D for LASEK and LASIK was 19.6% and 27.6% respectively.

Uncorrected visual acuity (UCVA)

No study reported any significant difference in UCVA between LASEK and LASIK treated eyes. One study by Bansal[194] reported that 70% of LASEK eyes and 95% of LASIK eyes had a Snellen acuity of 20/40 or better. One study[193] found that 85% and 84% of eyes were 20/20 or better for LASEK and LASIK eyes respectively (Table 75).

Table 75 LASEK vs LASIK: Snellen acuity 20/40 or better and 20/20 or better

Study id		20/40 or better*					20/20 or better				
	Mo	LASEK		LASIK			LASEK		LASIK		
Eyes		Rate	%	Rate	%	P=	Rate	%	Rate	%	P=
Sheng 2004[193]	6	NR	NR	NR	NR	NR	156/184	85	176/210	84	0.64
Bansal 2003[194]	3	14/20	70	19/20	95	NR	NR	NR	NR	NR	NR

7.6.3 LASIK versus PRK efficacy findings

Postoperative refraction

Lee et al.[196] reported post-operative refraction at three and six months. At three months follow-up, 57.8% (26/45 eyes) of eyes in the PRK group were within 0.5 D of the intended correction compared with 51.1% (23/45 eyes) in the LASIK group (Table 76). In both the PRK and LASIK groups, 86.7% (39/45 eyes) of eyes were within 1.0 D. At six months follow-up, 62.2% (28/45 eyes) of eyes in the PRK group were within 0.5 D compared with 53.4% (24/45 eyes) of eyes in the LASIK group (p=0.39). In the PRK group, 86.7% (39/45 eyes) of eyes were within 1.0 D of the intended correction compared with 84.4% (38/45 eyes) of eyes in the LASIK group.

Table 76 PRK vs LASIK: Refractions within 0.5 D and 1.0 D of intended spherical equivalent correction

Study id		Achieving ≤ ±0.5 D					Achieving ≤ ±1.0 D				
	Mo	PRK		LASIK			PRK		LASIK		
Eyes		Rate	%	Rate	%	P=	Rate	%	Rate	%	P=
Lee 2001a[196]	3	26/45	57.8	23/45	51.1	NR	39/45	86.7	39/45	86.7	NR
Lee 2001a[196]	6	28/45	62.2	24/45	53.4	.393	39/45	86.7	38/45	84.4	NR

Uncorrected visual acuity (UCVA)

Lee et al.[196] reported UCVA at three and six months. At three months, 84.4% (38/45 eyes) of eyes in the PRK group achieved a UCVA of 20/20 or better compared with 71.1% (32/45 eyes) of eyes in the LASIK group (Table 77). At six months, 77.8% (35/45 eyes) of eyes and 62.2% (28/45 eyes) of eyes in the PRK and LASIK groups, respectively, achieved a UCVA of 20/20 or better.

Table 77 PRK vs LASIK: Snellen acuity 20/20 or better

Study id	3 months					6 months				
	PRK		LASIK			PRK		LASIK		
Eyes	Rate	%	Rate	%	P=	Rate	%	Rate	%	P=
Lee 2001a[196]	38/45	84.4	32/45	71.1	NR	35/45	77.8	28/45	62.2	NR

8 DISCUSSION

This systematic review was initiated because of concerns about the long-term safety of photorefractive surgery. The interventional procedures programme has issued guidance on LASIK for the treatment of refractive errors[102,197]; this expressed concern about the procedure's safety in the long term, and additionally that the effects of the procedure can make it more difficult to detect glaucoma and to measure accurately the intraocular lens power required for cataract surgery. PRK and LASEK are contemporary excimer laser refractive surgery techniques and are also included in this systematic review. In view of the rapidly changing technologies and expertise in laser refractive surgery, the review has only included studies published from 2000. Inevitably, more recent developments have limited length of follow-up, studies with longer term follow-up include people treated earlier in the techniques' development. Many of the publications recruited participants in the mid to late 1990s, and refer to early laser delivery systems and older microkeratomes, which may no longer be in use.

In addition to the systematic review, the diagnostic performance of IOP testing and intraocular lens (IOL) power calculation following refractive surgery are described. A diagnostic accuracy systematic review was beyond the scope of this review and therefore IOP testing and IOL power calculation have not been reviewed systematically.

8.1 Assumptions, limitations and uncertainties

In this report, PRK, LASIK and LASEK are described separately. Most of the evidence consisted of case series studies, which are known to be more prone to biases than other research designs. In particular, selection bias (participants treated and cases reported both chosen by the investigators), findings not adjusted for confounding factors (e.g. degree of refraction, age, dry eye), and dropout/withdrawal rates may affect the reliability and magnitude of the treatment effect in case series studies. Comparisons between the PRK, LASEK and LASIK should therefore be made with care.

Many of the concerns about photorefractive surgery relate to rare serious complications. Because these events are uncommon their estimated frequencies are prone to random error (imprecision). Larger case case series are more likely to identify rare adverse

events. More evidence was available for LASIK, therefore larger case series were included than for PRK and LASEK (median number of eyes were 1122 for LASIK, 200 for PRK, and 102 for LASEK). In addition, nine out of the 26 LASEK case series were only published in abstract form and therefore only reported limited data.

Generalisability of some results may be difficult as some of the included studies recruited participants with higher refractive errors than may be common in routine practice, and these participants are less likely to achieve successful outcomes following the procedure and may be at a greater risk of complications.

Some studies had a high drop-out rate. In the LASEK review, losses to final follow-up ranged from 30% to 93% in at least seven studies, and in the PRK review at least four studies had losses to final follow-up over 50%. The direction of the bias was unclear, as participants returning for later follow-up appointments may be pleased with their treatment or conversely be more likely to be having problems.

This review aimed to consider participants who had had primary refractive surgery treatment, however it is possible that some retreated eyes may be included. Retreatment may increase the risk of adverse event but this was not assessed by this review.

In general, long-term safety was not documented; few studies reported results after long-term follow-up. Data for LASIK extended up to five and a half years and only seven studies provided results at more than one- year follow-up. One PRK study reported 12 years follow-up and another study reported findings at eight years.

Participant reported outcomes were not uniformly reported across the included studies. For example for glare and halo symptoms some authors presented a mean score or index and others reported the percentage of participants with symptoms. Similarly for haze different grading scales were used. In addition, some of the participant reported outcomes were not informative because no preoperative data were presented for comparison.

Most studies did not describe the clinical experience and skill of the surgeon; all three procedures require a high level of skill and training, which may impact on the safety and

efficacy of the procedure. The experience of the surgeon undertaking LASIK was unclear in over half the studies and two studies of LASEK were based on surgeons early experiences of the technique. Surgical protocols differed between studies and techniques are changing rapidly. In addition, it is uncertain from this review whether age has any effect on the safety or efficacy of LASIK, LASEK or PRK.

Direct comparisons of techniques can be made using evidence from RCTs. However, the RCTs were not of adequate size to identify a difference in the rate of rare adverse events. The data available from RCTs were limited with only three small trials of LASEK versus LASIK, two trials of LASIK versus PRK and there were 11 small trials comparing LASEK versus PRK. Most trials were within person comparisons, which did not report the method of randomisation used. It was not clear in any study that treatment allocation had been concealed, and in most studies it was unclear whether the outcome assessor was masked to the treatment allocation. However, in around half of the studies participants were masked to the treatment allocation and again, in around half of the studies, an intention to treat analysis had been carried out.

The median event rates were presented for each outcome along with the range of observed study rates to summarise the data. Standard approaches to generating confidence intervals for event rates would have produced overly precise and potentially misleading estimates. A meta-analysis model which realistically represents uncertainty around the estimates could potentially have been used. However, such an approach is not straight-forward particularly given that most data were generally very heterogenous.

Evolution in the technology and techniques of photo-refractive surgery (such as wavefront-guided customised ablation) may have improved the safety and efficacy of the procedures; one unpublished single surgeon case series suggested improved efficacy using latest generation lasers. In the PRK review, only 5% of studies reported data only on participants recruited from 2000 onwards. For LASIK and LASEK the proportions were 19% and 27% respectively. Only three studies included wavefront-guided surgery, one of the FDA reports of LASIK and two studies of PRK in patients with myopia and hyperopia, respectively. There were no other studies including only wavefront-guided refractive surgery which met the inclusion criteria, and the review is therefore not able to

fully assess the impact and role of technological improvements, such as wavefront-guided ablations on adverse events and visual outcomes.

8.2 Safety

8.2.1 Ectasia

Ectasia is a condition in which the eye becomes progressively more myopic with irregular astigmatism and corneal thinning. Ectasia is the most serious of all complications related to refractive surgery and can lead to serious loss of vision. The creation of a flap in LASIK as opposed to surface based treatments (PRK and LASEK) has the potential to undermine the biomechanical properties of the cornea affecting long-term refractive stability. Although certain biomechanical properties of the cornea are measurable, the relevance of measurements to predict ectasia after refractive surgery are uncertain.[198] This review may have under or over-estimated incidence of ectasia. Retrospective case series may not have identified all cases, whereas studies not reporting ectasia may have had no ectasia and if this were the case the overall rate of ectasia would be lower.

One LASEK study reported no cases of ectasia in 171 eyes. None of the studies included in the PRK review reported incidence of ectasia.

In the LASIK review, only five studies reported incidence of ectasia, two of these were retrospective case series specifically investigating cases of ectasia and included 39 of the cases. The overall rate of ectasia was 40/10806 (median 0.2%, range 0% to 0.87%). Of these, six eyes had preoperative topography suspicious of pre-existing keratoconus, which is a contraindication to LASIK. This highlights the importance of detailed preoperative corneal topography assessment. The remaining cases occurred in eyes with between –5.75 and -22.0 D myopia and 28 of these cases occurred in eyes with less than 250 µm of RST (this is recognised as a risk factor for corneal ectasia). Risk factors were not identified for the remaining six eyes and this apparently much lower rate of 6/10806 (median 0%) is consistent with the rate presented by the unpublished data (0/8448) (Reinstein, personal communication, 2005). Nine participants developed bilateral ectasia. In one study, seven of the fourteen eyes required a corneal graft. Corneal grafting is a complex intraocular microsurgical procedure requiring long-term follow-up.

Known risk factors for the development of ectasia are high myopia, keratoconus and low RST.[16] The calculation of the predicted RST relies on the accuracy of measurement of corneal thickness, flap thickness and ablation depth. Measurement of each of these variables is subject to error; the potential error in each measurement needs to be accounted for when predicting a safe RST for an individual.[199]A model taking into account the imprecision of these variables predicted that the routine use of a 130 µm flap would reduce the risk of LASIK induced ectasia to a third of the rate of routinely using 180 µm flaps. Correctly identifying eyes at risk and an understanding of the accuracy of microkeratomes could reduce the risk of ectasia.

8.2.2 Loss of Best Spectacle Corrected Visual Acuity (BSCVA)

Loss of visual function as a consequence of refractive surgery is generally measured as loss of BSCVA.

PRK and LASEK

Data from the included studies indicated that, for myopia, a median rate of around 0.5% (range 0% to 20.5%) of PRK-treated eyes lost two or more lines. Participants with myopia greater than 6.0 D were more likely to lose lines of BSCVA than participants with low to moderate myopia. In H-PRK treatment of hyperopia, overall, 7.0% (range 0% to 13.5%) lost two or more lines. Participants with higher levels of hyperopia (>+3.5 D) were more likely to lose lines of BSCVA than participants with lower levels of hyperopia. When PARK was used for the treatment of astigmatism, overall, 0.6% (range 0% to 1.6%) lost two or more lines of BSCVA.

For myopia or myopic astigmatism treated by LASEK, a median rate of 0.0% (range 0% to 8.2%) of eyes lost two or more lines at last follow-up; evidence suggests that participants with high myopia (greater than -6.0 D) are more at risk. Three studies that reported the highest rates (5.0%, 7.5% and 8.2% respectively) were studies in participants with high myopia and myopic astigmatism. There was one report of irregular astigmatism (1.4%) in participants with high myopia, leading to a loss of BSCVA.

In the four RCTs comparing LASEK with PRK for myopia or myopic astigmatism, more PRK-treated eyes than LASEK-treated eyes lost one line of BSCVA (0% versus 2.2%) at

follow-up (range, one and 24 months). No participants in either group lost two or more lines during follow-up ranging from three to 24 months.

LASIK

Using LASIK, a median rate of 0.6% (range 0% to 3.0%) of eyes with myopia or myopic astigmatism lost two or more lines of BSCVA. Overall, the proportion of eyes losing two or more lines of BSCVA was slightly higher in participants with high myopia (0.9%, range 0% to 1.8%) than participants with low myopia (0.7%, range 2.2% to 4.6%), however, this may simply reflect variation between studies. In eyes with hyperopia or hyperopic astigmatism, 3.4% (range 2.2% to 4.6%) of eyes lost two or more lines of BSCVA. Unpublished case series data were consistent with these findings and results varied according to level and type of refractive error and laser type; 0% to 0.7% of eyes with myopia less than or equal to -6.0 D, and 0% to 3.4% with myopia greater than -6.0 D, lost two or more lines of BSCVA. In hyperopia, 0% to 2.7% of eyes lost two or more lines of BSCVA (Reinstein, personal communication).

Induced astigmatism was reported in seven studies. Astigmatism of greater than 2.0 D was induced in 0% (range 0% to 1.0%) of eyes with predominantly spherical myopia and 0.56% of eyes with predominantly spherical hyperopia.

8.2.3 Inflammation

Microbial keratitis is an infection of the cornea; this is potentially serious if inappropriately managed and can lead to considerable loss of vision. None of the studies of PRK and its variants reported cases of microbial keratitis. In the LASEK review, there was an infection rate of between 0% and 3.4% reported in four studies; however the site and severity were not specified. In the LASIK review, two studies each identified a single case of microbial keratitis, median rate 0% (range 0% to 0.16%). A further four studies, involving 2869 LASIK-treated eyes, reported that they observed no cases of microbial keratitis. The risk of microbial keratitis in daily wear contact lenses has been reported to be between 0.01% and 0.04%.[11]

Diffuse lamellar keratitis is a sterile inflammatory condition in which white blood cells migrate along the stromal interface after surgery; the infiltrates result from instrumentation at the time of surgery. An epithelial defect is associated with an

increased risk of diffuse lamellar keratitis.[21] Diffuse lamellar keratitis is treated with topical steroids, and usually resolves. Severe cases can result in stromal melt and subsequent irregular astigmatism with loss of BSCVA. In this review of LASIK treatment, diffuse lamellar keratitis was reported by 26 studies and occurred in between 0% and 7.7% of eyes (overall 1.4% of eyes). Four of the studies noted that no eyes lost more than two lines BSCVA after resolution of diffuse lamellar keratitis. However, one study found two eyes (6% of eyes with diffuse lamellar keratitis) lost more than two lines of BSCVA after resolution of diffuse lameller keratitis. The one unpublished case series (Reinstein, personal communication 2005), identified six cases of diffuse lamellar keratitis (0.3%) and one eye lost a line of BSCVA, no eyes had reduced BSCVA of two lines or more. No cases of diffuse lamellar keratitis were reported in the reviews of PRK and LASEK.

8.2.4 Flap complications

LASIK has emerged as a more popular technique than PRK because it potentially offers faster visual recovery, less pain, reduced need for post-operative steroid therapy and therefore less risk of raised IOP, and easier re-treatment compared with PRK; but it has the potential for complications related to creation of a corneal flap. There are concerns that replacement of the epithelium in LASEK, comprising tissue cells in decay, may be a potential risk factor for infection.

In eyes treated with LASEK minor complications during the procedure, namely difficulty with detaching the flap, were reported in nine case series, and found in 2.0% (range 0% to 14.0%) of eyes. Five trials involving LASEK also reported flap complications for between 3.7% and 9.0% of eyes. Flap complications produced no long-term adverse effects in most participants, however two studies[105,193] reported a loss of one or two lines of BSCVA for 1.0% of participants as a result of flap complications.

In LASIK the flap is generally between 130 to 180 µm thick. The creation of the flap can result in complications such as buttonhole flaps and incomplete flaps. These are generally managed by replacing the flap without continuing with the ablation and waiting for the flap to heal for three to six months. Once the flap has healed, it may be re-cut or the surgeon may proceed to surface based ablation. Where a free cap has been created, ablation is sometimes carried out and the cap replaced. Overall, a median rate

of 0.1% (range 0% to 0.5%) of eyes had buttonhole flaps, 0.3% (range 0% to 2.9%) had incomplete flaps and 0.1% (range 0% to 2.0%) had free caps.

After LASIK, the flap may be dislodged, for example by the participants rubbing their eyes. Dislodged flaps may result in folds and striae that reduce BSCVA. In the case series, 1.2% (range 0.3% to 2.4%) of eyes had dislodged flaps and 0.8% (range 0% to 5.5%) of eyes had flap folds or striae. Lifting and repositioning the flap is the recommended management for dislodged flaps and flap folds. The experience of the surgeon in recognising and managing flap complications appropriately is likely to affect the final visual outcome.

The incidence of flap complications did not differ significantly between the first and second eye treated in participants scheduled to have bilateral treatment. However, incidence of flap complications did differ between microkeratomes, though this may be partly accounted for by differences in sample populations and experience of the surgeon.

8.2.5 Epithelial complications

PRK and LASEK

In PRK treatment, three studies reported that delayed epithelialisation delayed healing for an additional one to two days. Delayed healing would increase time to visual rehabilitation and comfort. In LASEK treated eyes, three cases of recurrent erosion were reported (1%); no further details were provided. Recurrent erosion is a recurring epithelial defect provoked by minor trauma such as eyelid opening on wakening. It can cause considerable recurrent participant discomfort. Erosions may be, but are not necessarily, related to the LASEK intervention.

LASIK

Epithelial defects associated with LASIK can be associated with a chain of postoperative complications including diffuse lamellar keratitis and epithelial ingrowth. Epithelial ingrowth describes a condition where epithelial cells grow into the flap, either introduced at the time of the lamellar cut or grow in from the peripheral corneal epithelium usually as a result of a poorly adherent flap. Progressive epithelial ingrowth affecting vision is managed by lifting the flap and removing the proliferating cells.

Epithelial defects occurred in between 0% and 10.2% of eyes (median 1.6%) receiving LASIK. Epithelial ingrowth occurred in 1.4% (range 0% to 4.4%) of eyes. Rates of epithelial defects and epithelial ingrowth varied between microkeratome. Epithelial defects and ingrowth, if managed appropriately, may not reduce visual outcome. Three studies reported that epithelial ingrowth adversely affected visual outcome, two eyes with ingrowth lost more than two lines BSCVA,[63,166] and in a separate study 0.3% (7/22) of eyes[151] progressed to a corneal flap melt as a direct consequence of epithelial ingrowth. In the unpublished series (Reinstein personal communication, 2005) epithelial ingrowth was reported in 0.4% cases with no loss of final BSCVA. One study reported that identified epithelial defects did not affect visual outcome.[170]

8.2.6 Participant reported outcomes

Participants can experience problems with glare, difficulties in low light conditions and fluctuating vision after refractive surgery. Some of these problems can occur before surgery, related to either contact lens or spectacle correction of the refractive error. Corneal haze can occur post operatively particularly after PRK and LASEK, and may take months to resolve completely. Disturbance of the epithelium in surface-based treatments (PRK and LASEK) may result in early post-operative pain.

PRK and LASEK

Following PRK for myopia, in one study with 690 participants, just over 50% of participants reported that daytime glare sensitivity was worse after treatment, around 30% of participants also reported that night vision was worse. Similar numbers reported more difficulty with night driving after treatment. However, a study following PRK participants over 12 years reported a subjective improvement in night vision over that time.

In the treatment for astigmatism, in one study after treatment with PARK just under 40% of participants had an increase in 'haloes' compared with pre-operatively. Twenty-seven percent of participants also experienced an increase in glare score from baseline. One comparative study reported glare symptoms occurred less frequently in participants who had had wavefront-guided H-PRK, however baseline data was not provided.

Grade two haze may affect quality of vision and was reported for between 0% to 31.4% (median 0%) of eyes treated with PRK. In two studies with eight and 12 years follow-up, respectively, no eyes had evidence of grade two or more haze.

Two studies reported pain outcomes in the first week after PRK; most participants experienced some discomfort with 1.5% and 0.8% of participants, respectively, reporting 'horrible' and 'excruciating' levels of pain. Ocular symptoms such as epiphora, photophobia, itching and foreign body sensation were also experienced by approximately 30% to 40% of participants in the first week after treatment.

Corneal haze can be a concern following LASEK. There were cases of grade two or more corneal haze at final follow-up in four out of 16 of the LASEK case series (median rate 0%, range 0% to 25%). Two of these studies included participants who were not considered suitable for LASIK, one study with the highest rate (25%) included only participants with high myopia. Grade two haze occurring in one eye in the fourth study may have been related to a post-operative epithelial defect. Treatments such as Mitomycin C are being explored to prevent haze in surface-based treatments.

In the LASEK review some participants reported pain and dry eye syndrome. Results reported in five case series suggest strong or severe early post-operative pain for between 0% and 19% of participants.

In the RCTs comparing LASEK with PRK, significantly less corneal haze in the LASEK treated eyes was reported in four trials, two other trials found no difference between LASEK and PRK treated eyes. Participant assessment of glare and halo symptoms indicated that there was no difference between LASEK and PRK treated eyes. Pain outcomes were difficult to interpret as the studies reported conflicting results.

LASIK

The incidence of blurring of vision, burning, headaches, light sensitivity and variation of vision in bright light were less common six months after LASIK than before in all case series reporting these outcomes. Glare, night driving difficulty, gritty feeling, pain and excessive tearing were also less common after LASIK in the majority of studies. Double

vision, ghost images, halos, dry eye, fluctuations of vision, and variation in vision in normal light were all more common six months after LASIK.

In seven studies participants were asked whether symptoms were better or worse (or significantly worse) six to 12 months after LASIK compared with before LASIK. Double vision was reported as unchanged six months after LASIK in most participants, but 2.6% to 14.7% reported it as worse and 1.3% to 7.2% reported it as better. Ghost images and halos were reported as worse by 2.3% to 18.8% and better in 14.4% to 42.9% of participants respectively. Between 7.0% and 44.0% of participants reported worse dry eye at follow-up compared with 9.8% to 28.6% reporting this as better. Fluctuation of vision was worse in 14.7% to 42.3% of participants.

Only seven studies of LASIK reported haze and the definition varied between these studies. Four of the studies reported no eyes with detectable or significant haze at last follow-up; one study found 2.1% of eyes had haze greater than grade three.

In the two RCTs comparing LASIK with PRK there was no statistically significant difference in the incidence of increased glare or halo symptoms after surgery. In the three RCTs comparing LASEK with LASIK subjective quality of vision outcomes were not reported.

8.2.7 Vitreo-retinal complications

Myopes have an increased incidence of retinal detachment compared with non-myopes, and the risk increases with increasing levels of myopia. In high myopia the risk is estimated at 0.5% over five years.[200] In PRK treated myopic eyes, two studies of eyes with myopia and myopic astigmatism up to –14 D reported retinal detachment rates of 0.15% and 0.13% respectively, which is lower than the reported rate of retinal detachment eyes with high myopia. There were no reports of retinal detachment following H-PRK treatment for hyperopia. No cases of retinal detachment were reported in the LASEK review.

Vitreo-retinal complications occurred in 0.29% (range 0% to 0.84%) of eyes in the seven studies of LASIK in which this complication was reported; only one study involved a participant with hyperopia who developed vitro-retinal traction. Two retrospective case

series reported the incidence of retinal detachment, with rates ranging from 0.08% and 0.37% up to five years post surgery. None of the LASIK studies in hyperopes reported cases of retinal detachment.

8.2.8 Risk of developing glaucoma after photo refractive surgery

Raised intraocular pressure (IOP) is a major risk factor for developing glaucoma. Postoperative steroids usage is associated with an increased risk of raised IOP. Postoperative steroids are used after photo refractive surgery and if use is prolonged for example, to treat diffuse lamellar keratitis a secondary rise in IOP may occur and require additional topical treatment to lower IOP. A prolonged, high IOP can lead to glaucoma if not recognised and treated.

Eyes treated with LASEK and PRK tend to be given corticosteroid drops for longer periods than for LASIK; in this review, in PRK treatment for myopia, increases in IOP were uncommon (median 1.9%, range 0% to 7.6%) of eyes and most cases resolved after corticosteroids were discontinued. In two studies of hyperopic treatments, increases in IOP were reported in 8.5% and 8.6% of eyes but resolved after discontinuation of corticosteroid therapy. Two studies noted corticosteroid induced raised IOP for 1.2% and 1.6% of LASEK treated eyes for myopia; IOP returned to normal when corticosteroids were discontinued and topical beta-blockers administered. Raised IOP was reported in four out of 2071 eyes receiving LASIK. In three of these eyes IOP returned to normal on cessation of topical steroids. No details were given about the remaining eye.

8.2.9 Other safety considerations

Intraocular pressure monitoring after photorefractive surgery

Measurement of IOP is one of the key diagnostic assessments to detect and monitor glaucoma, together with an assessment of the optic nerve and visual field.

IOP measurement is influenced by the central corneal thickness. Central corneal thickness is reduced after photo refractive surgery and this may account for an underestimation of the actual IOP. IOP results may therefore be misleading to the unaware observer. Central corneal thickness is an important variable in any case of potential glaucoma. Corneal thickness varies even between individuals who have not

undergone refractive surgery, and is increasingly being included in the evaluation of a person's IOP.[201] An adjustment for central corneal thickness should be made during routine IOP measurement for glaucoma detection, if the participant has had prior refractive surgery.

Hyperopia is a risk factor for developing narrow angle glaucoma. An assessment of the depth of the anterior chamber and the chamber angle (gonioscopy) is an important diagnostic assessment for all participants at risk of or who have glaucoma. People who have undergone a refractive procedure for hyperopia will retain the configuration of an eye with hyperopia and therefore the assessment of the depth of the anterior chamber and chamber angle remains important as a risk assessment for narrow angle glaucoma.

Cataract surgery after refractive corneal surgery

Cataract surgery involves removing the cataractous lens and insertion of an Intraocular lens (IOL) implant. The power of the IOL to be inserted to achieve the desired visual outcome is determined preoperatively. The IOL power calculation depends on the corneal curvature, assessed by keratometry readings and a measurement of the axial length of the eye and anterior chamber depth. The length of the eye and anterior chamber depth rarely change after refractive surgery, however the keratometry readings are affected by refractive surgery and if the post refractive surgery keratometry readings were used for the IOL power calculation a miscalculation of the strength of the IOL lens required would occur.

Refined methods of accurate IOL power prediction are therefore required for people who have had refractive surgery and subsequently require cataract surgery. Several methods for assessing the keratometry readings after refractive surgery have been developed; these can be based on pre-refractive surgery keratometry readings and post refractive surgery refraction. Recent research into methods of developing formula to allow calculation of IOL power based on K-readings after refractive surgery is ongoing.[202]

8.3 Efficacy

8.3.1 Accuracy

PRK and LASEK

Data from over 2000 eyes treated with PRK for myopia, showed that a median rate of 68% of eyes had achieved within 0.5 D of their intended spherical equivalent correction and that around 86% achieved within 1.0 D, at last follow-up. Participants with low to moderate myopia were more likely to achieve their intended correction than participants with high myopia. For over 300 eyes treated with H-PRK, a rate of 61% and 79% of eyes, respectively, achieved within 0.5 and 1.0 D of their intended spherical equivalent correction, 12 months or more after treatment. Participants with hyperopia of less than +3.5 D were more likely to achieve the intended correction than those with more severe hyperopia. Following treatment in over 700 eyes with PARK for astigmatism, a rate of 55% and 84% of eyes, respectively, achieved within 0.5 and 1.0 D of their intended spherical equivalent after 12 months or more of follow-up. A rate of between 91% and 93% of eyes achieved within 1.0 D of their intended astigmatic correction.

A single study reported that around 40% of eyes treated with PRK for myopia had a change in their corrected vision more than 1.0 D in the first year after surgery. In one study, there was no significant change in refractive stability over 12 years of follow-up, combining data from two studies, around 2% of eyes required a re-treatment procedure. Stability of the post-surgical correction with H-PRK for hyperopia was 76% in one study and 96% in another where all eyes changing 1.0 D or less of manifest refractive spherical equivalent were considered. A re-treatment procedure was undertaken in 0.7% of eyes in one study. There was no data regarding stability of vision following treatment with PARK for astigmatism but in one study with two years follow-up, 26% of participants required a re-treatment procedure.

Data from over 1800 eyes included in the LASEK case series show that a rate of 75% and 92% of eyes treated for myopia or myopic astigmatism were within 0.5 D and 1.0 D of their intended correction at three to six months. Outcomes at 12 months were 82% and 90% for within 0.5 D and 1.0 D respectively. Data were too limited to assess whether there are similar trends in the predictability of post-operative refraction at different levels of myopia.

Data regarding rates of refractive change following LASEK were limited. Those reported included over/under correction, late onset regression, stability and re-treatment. One abstract[105] reported over/ under correction in 4.0% of participants. Regression towards hyperopia of more than 1.0 D in four eyes (4%) was reported in one study.[92] Five studies of myopia and myopic astigmatism reported stability of refraction between two weeks and two months after surgery for the spherical correction, and between one month and three months for the cylinder correction. Seven studies reported re-treatment rates of between 0.0% and 5.5%, however the reasons for re-treatment were not always provided.

In five RCTs, that compared LASEK with PRK the median percentage of eyes achieving within 0.5 D of their intended correction was 80% and 64% respectively, only one study was of participants with hyperopia and this showed a statistically significant difference in favour of LASEK. The median percentage of eyes within 1.0 D for LASEK and PRK was 92% and 91% respectively.

LASIK

Three to 12 months after LASIK, a median rate of 75% of eyes treated for myopia and myopic astigmatism were within 0.5 D of their intended spherical equivalent correction, and 92% were within 1.0 D. Eyes with low to moderate myopia were more likely to achieve their intended correction than eyes with high myopia. Only three studies reported accuracy of LASIK in eyes with hyperopia or hyperopic astigmatism. Overall, a rate of 62% and 88% of eyes with hyperopia and hyperopic astigmatism achieved refractions within 0.5 D and 1.0 D of intended spherical equivalent correction respectively. The unpublished data reported in section 6.7 were consistent with these results.

Stability of refraction was presented as change in refraction between one and three months and between three and six months. In myopic eyes there was a change of less than 1.0 D in 99% of eyes from one to three months and between three and six months. In hyperopic eyes, the corresponding rates were 97% and 96%. Accuracy may be lower at six months compared with one month as tissue healing modifies refraction over a period of three months.

LASIK participants may be retreated for under or overcorrection. Criteria for re-treatment varied between studies. Where incidence of re-treatment was reported, a median rate of 11% of eyes with myopia and myopic astigmatism were retreated (3% in eyes with low myopia and 23% in eyes with high myopia). In total, 12% of hyperopic eyes or eyes with hyperopic astigmatism were retreated. The higher retreatment rate for LASIK does not necessarily imply less accuracy as retreatment is easier and less painful in LASIK than in PRK and LASEK.

There was no evidence to suggest that any procedure resulted in more superior outcomes in terms of post-operative refraction or UCVA in the trials comparing LASIK with PRK, and LASIK with LASEK.

8.3.2 Post-operative uncorrected visual acuity (UCVA)

Uncorrected vision may be a misleading outcome because a small proportion of participants with presbyopia opt for under correction in one eye. This means that intentional mild myopia (for example of 20/30 to 20/40) in the non-dominant eye is a desired outcome.

PRK and LASEK

At last follow-up, a median rate of 70% of case series participants treated with PRK for myopia had achieved Snellen acuity of 20/20 or better and 93% had Snellen acuity of 20/40 or better. Once more, findings indicated that participants with low to moderate myopia were more likely to achieve a Snellen visual acuity of 20/20 or better, or 20/40 or better, than participants with high myopia. Overall, a rate of 59% of participants treated with H-PRK for hyperopia had a UCVA of 20/20 or better and 86% achieved 20/40 or better. Eyes with hyperopia less than +3.5 D were more likely to achieve a UCVA of 20/20 or 20/40 or better. Following treatment with PARK for astigmatism, 60% of eyes had a UCVA of 20/20 or better and 84% of eyes had a UCVA of 20/40 or better.

At three to six months after LASEK, the median rate achieving UCVA 20/40 or better was 96% with 67% achieving 20/20. At 12 months or longer UCVA was 20/40 or better and 20/20 or better in 92% and 62% of eyes respectively. Data were again too limited to test for possible trends in the efficacy of LASEK at different levels of myopia.

LASIK

The rate of eyes with myopia and myopic astigmatism achieving an UCVA of 20/20 or better and 20/40 or better, excluding eyes treated with monovision for presbyopia, was 64% and 94% respectively. Eyes with low to moderate myopia were more likely to achieve a UCVA of 20/20 or better, or 20/40 or better, than eyes with high myopia. In eyes with hyperopia or hyperopic astigmatism, 52% achieved a UCVA of 20/20 or better and 96% achieved 20/40 or better. Results from the unpublished case series at up to twelve months follow up were consistent with these findings for myopia and hyperopia.

9 CONCLUSIONS

Refractive errors are common, and in the UK the demand for elective refractive surgery has increased considerably over the last five years. PRK, LASEK and LASIK are widely available in the private sector but are not performed as an NHS procedure unless indicated for therapeutic reasons. More evidence, including larger case series, was available for LASIK than for PRK or LASEK. Comparisons between LASIK, PRK and LASEK case series must be made with care as sample sizes, participant populations, length of follow–up, surgeon experience, and technologies used differ. The review was limited to publication from 2000, with a view to reporting outcomes of the more recent generation lasers and microkeratomes, and being able to evaluate longer-term outcomes. However, the equipment and techniques used in photorefractive surgery are changing rapidly, and some of the included studies relate to lasers and microkeratomes that may no longer be in current use.

9.1 Safety

The data from this review estimate the risk of ectasia following LASIK as 0.2%. However, on review, the surgery received was inappropriate in the majority of cases and with 'good practice' one would expect the rate to be lower. Rates of ectasia were not reported following PRK and no cases of ectasia were reported following LASEK.

Microbial keratitis was only reported in LASIK studies and occurred in between 0% and 0.16% of eyes which is in line with, or less than, the reported incidence for contact lens wear associated microbial keratitis.

Combining data on early post-operative pain outcomes for LASEK and PRK from five trials did not suggest a significant difference between treatments. No LASIK studies reported rates of early post-operative pain.

The median rate of reduced BSCVA of at least two Snellen lines following LASIK, LASEK and PRK ranged from 0% to 0.6%. In hyperopia, more eyes lost BSCVA, and this may be higher for PRK (7.0%, range 0% to 13.5%) than LASIK (3.4%, range 2.2% to 4.7%). It was reported in one small RCT that included eyes with hyperopia treated by LASEK

compared with PRK that no eyes lost more than two lines BSCVA at two years. The visual outcomes were less good for higher pre-operative refractive error, (>-6 D for myopia and >+3.5 D for hyperopia) than lower levels of refractive error.

Flap complications of varying consequence occur in LASIK (0% to 1.3%) and LASEK (2%, range 0% to 14%). Flap complications may result in postponement of ablation, conversion to PRK, or occasionally loss of BSCVA. Epithelial ingrowth occurs following LASIK in 0% to 4.4% of eyes and the limited data on subsequent visual outcome suggest that such complications rarely lead to reduced vision, once resolved.

The evidence that PRK, LASEK or LASIK surgery either exacerbated or improved visual symptoms such as day time glare, night vision problems, dry eye and fluctuations in vision was limited. Trial evidence suggests that worsening symptoms of daytime glare and haloes are more likely following PRK than LASIK. Night vision problems may be worse following PRK; however, data from one study with follow up to 12 years suggest that theses symptoms improve with time.

The data suggest that any rise in IOP following surgery is short-term; no cases of glaucoma were reported following the surgeries. The incidence of retinal detachment was lower than that reported for similar degrees of myopia.

9.2 Efficacy

Overall, for the correction of myopia and myopic astigmatism, the median rate of eyes which achieved within 0.5 D of their intended spherical equivalent correction was 68% to 75%. A rate of around 86% to 92% of eyes achieved within 1.0 D. There were no significant differences between the three procedures for myopia or myopic astigmatism in any of the RCTs. The accuracy of PRK and LASIK in hyperopia is lower, with a rate of 61% and 62% of eyes achieving within 0.5 D of intended correction, and 79% and 88% within 1.0 D. One RCT in hyperopic eyes found LASEK to be significantly more accurate than PRK.

Final uncorrected visual acuity (UCVA) outcome was similar across all three techniques. The median rate of eyes achieving a UCVA of 20/20 or better was 64% to 70% of eyes.

Overall, the median rate was 93% to 96% for a UCVA of 20/40 or better. The results were less good for high myopia and hyperopia.

Around 98% of eyes following LASIK maintained stability within 1.0 D of the early post-operative outcome at three to six months, longer-term data were not available. The data suggest that following PRK for myopia, 20% to 40% of eyes may regress towards the pre-operative error within the first year, and that regression is more common in high myopia. In the longer-term evidence from two small studies suggest that the refraction is stable. Variable data suggest that refractive stability is achieved in LASEK within two weeks to 60 days, but may be longer for astigmatic correction, and regression was reported in 0% to 12.3% of eyes.

9.3 Patient selection

This review confirmed the importance of patient selection. Not only were the results less good the worse the underlying refractive error, but most cases of the serious complication, ectasia, followed inappropriate selection or treatment of patients.

10 NEED FOR FURTHER AUDIT OR RESEARCH

At present, there are limited data available from good quality large prospective case studies with long-term safety outcomes for PRK, LASEK and LASIK. In particular, there are few large published prospective case series of LASEK. It is important that evidence of the long-term safety, refractive stability, efficacy, and vision specific health related quality of life outcomes are provided. More data on the comparable efficacy and safety of the three techniques for people with different degrees of myopia, hyperopia and astigmatism, within recognised treatment limits, are also required. Good quality RCTs with long-term follow-up are necessary to directly compare PRK, LASEK and LASIK. Investigators should use appropriate methods to randomise patients and steps taken to ensure allocation is concealed from patients and outcome assessors. Better reporting and adherence to the CONSORT statement would also substantially improve the quality of future studies. In addition, systematic audit and evaluation should be carried out to establish the safety and efficacy of refractive surgery in everyday practice.

Data are required to establish the advantages and disadvantages of different lasers, microkeratomes (for LASIK) and specific techniques. There have been rapid developments in refractive surgery, including new generation excimer lasers, scanning eye tracking systems, wavefront-guided technology, femtosecond lasers for cutting thin flaps in LASIK and the development of methods for epithelial flap formation such as epi-LASIK (the creation of an epithelial flap without use of alcohol). Although these developments are expected to improve overall safety and efficacy, good quality data from prospective cohort studies and RCTs are required to establish this.

Further research is required to identify, pre-operatively, characteristics of the eye that increase the risk of complications. This should include potentially serious complications, such as ectasia, and undesired consequences such as problems with flap formation during LASIK and LASEK, delayed healing, corneal haze and patient reported outcomes such as early postoperative pain.

It is also essential to have comparable data regarding the safety of contact lens wear, the alternative for people who may wish to reduce or eliminate the use of spectacles. Issues

related to the accurate measurement of intraocular lens power required for cataract surgery, after people have had refractive eye surgery, also need to be addressed.

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