Femtosecond Lasers for LASIK Flap Creation

A Report by the American Academy of Ophthalmology

Ayad A. Farjo, MD,[1] Alan Sugar, MD, MS,[2] Steven C. Schallhorn, MD,[3] Parag A. Majmudar, MD,[4] David J. Tanzer, MD,[5] William B. Trattler, MD,[6] John B. Cason, MD,[7] Kendall E. Donaldson, MD, MS[8] George D. Kymionis, MD, PhD[9]

Objective: To review the published literature to assess the safety, efficacy, and predictability of femtosecond lasers for the creation of corneal flaps for LASIK; to assess the reported outcomes of LASIK when femtosecond lasers are used to create corneal flaps; and to compare the differences in outcomes between femtosecond lasers and mechanical microkeratomes.

Methods: Literature searches of the PubMed and Cochrane Library databases were last conducted on October 12, 2011, without language or date limitations. The searches retrieved a total of 636 references. Of these, panel members selected 58 articles that they considered to be of high or medium clinical relevance, and the panel methodologist rated each article according to the strength of evidence. Four studies were rated as level I evidence, 14 studies were rated as level II evidence, and the remaining studies were rated as level III evidence.

Results: The majority of published studies evaluated a single laser platform. Flap reproducibility varied by device and the generation of the device. Standard deviations in flap thicknesses ranged from 4 to 18.4 μm. Visual acuities and complications reported with LASIK flaps created using femtosecond lasers are within Food and Drug Administration safety and efficacy limits. Of all complications, diffuse lamellar keratitis is the most common after surgery but is generally mild and self-limited. Corneal sensation was reported to normalize by 1 year after surgery. Unique complications of femtosecond lasers included transient light-sensitivity syndrome, rainbow glare, opaque bubble layer, epithelial breakthrough of gas bubbles, and gas bubbles within the anterior chamber.

Conclusions: Available evidence (levels I and II) indicates that femtosecond lasers are efficacious devices for creating LASIK flaps, with accompanying good visual results. Overall, femtosecond lasers were found to be as good as or better than mechanical microkeratomes for creating LASIK flaps. There are unique complications that can occur with femtosecond lasers, and long-term follow-up is needed to evaluate the technology fully.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an assessment is to systematically review the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. This assessment evaluated the safety, efficacy, and predictability of femtosecond lasers for the creation of corneal flaps for LASIK; assessed the reported outcomes of LASIK when femtosecond lasers are used to create corneal flaps; and compared the differences in outcomes between femtosecond lasers and mechanical microkeratomes.

Background and Description of Technology

Femtosecond lasers that are used for LASIK procedures are solid-state focusable photodisruptive lasers that operate in the infrared spectrum at approximately 1000 to 1053 nm wavelengths. The threshold for photodisruption occurs when a high-intensity, highly focused laser beam is absorbed by the target tissue.[1,2] This ionizes the tissue, releasing free electrons and creating plasma (electrically charged particles). Depending on energy intensities, plasma ignition occurs and creates cavitation and gas bubbles. Compared with the photodisruptive neodymium: yttrium-aluminum-garnet lasers, which have pulse durations in the nanosecond (10^{-9} second) range, femtosecond (10^{-15} second) lasers have a shorter pulse duration. This allows femtosecond lasers to be useful for corneal applications because they reduce the size of the cavitation bubble formation and resultant accompanying shock wave. There are 2 general categories of commercially available femtosecond lasers: higher energy–lower frequency and lower energy–higher frequency.

Higher-energy lasers operate in the microjoule (μJ) range, whereas the lower-energy lasers operate in the nanojoule range. In higher-energy systems, where repetition frequencies are in the kilohertz (kHz) range, each laser spot creates an expansile bubble that aids in the disruption process by allowing for a greater separation of laser pulses.

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Lower-energy systems, conversely, require closer spacing of the laser pulses and repetition frequencies in the megahertz (MHz) range. The pattern of placement and spacing of the spots are designed to take advantage of the expanding gas bubbles, which can lead to less total energy delivered for higher pulse energy systems relative to lower pulse energy systems. Ultimately, in both methods the laser spots create a potential geometric shape or plane that is then manually dissected to complete the process.

Theoretically, femtosecond laser surgery offers a safety advantage over microkeratome-based LASIK procedures because the corneal tissue does not need to be dissected if an aberrant flap is created, allowing the corneal tissue to revert to its previous shape and clarity on dissolution of the gas bubbles. The lasers also can create precise cutting geometries to allow variation of flap width, flap depth, hinge width, variable diameter (oval vs. circular), and side-cut angles that may lead to better surgical results. As with any new technology, unforeseen complications may occur.

Femtosecond laser platforms can perform other corneal procedures, including crafting a precise, interlocking graft–host junction for penetrating keratoplasty; creating donor lamellar buttons for both anterior (superficial and deep) and posterior (endothelial) lamellar keratoplasty; dissecting tunnels for intracorneal ring insertion; creating flaps or pockets for corneal inlays; cutting astigmatic keratotomy incisions; and dissecting a midstromal lenticule for the treatment of myopia.

Femtosecond laser systems that have received Food and Drug Administration clearance for marketing in the United States are listed in Table 1. Each laser is capable of creating a planar LASIK flap using computer-controlled, infrared laser energy as described previously. There are notable differences among the lasers in physical characteristics, laser-delivery properties, and performance specifications.

A modified suction ring is used for all systems to seat an applanation plate and to align and stabilize the eye during the laser surgery procedure. Once suction is achieved, the laser is docked in most laser systems. Depending on the laser, a flat or curved contact surface is used. A flat contact surface simplifies the creation of a planar dissection, and spiral or raster patterns can be used for the laser cut. However, a flat contact surface requires a higher level of suction and a greater elevation in intraocular pressure (IOP). This elevation in IOP can temporarily reduce vision during the creation of the flap. Conversely, a curved contact surface is a better approximation of the contour of the cornea, requires less suction, and can allow the patient to maintain fixation while the suction ring is seated. However, a curved contact surface makes the creation of a planar flap more technologically challenging, and suction loss may occur more readily with eye movement. Current-generation femtosecond laser systems generally take 10 to 40 seconds to create a lamellar corneal flap, but this does not include docking and undocking times, which will likely vary by surgeon experience. After flap creation, the plane must be manually dissected, usually with a blunt spatula that takes more time and effort than lifting a mechanical microkeratome-created LASIK flap. The remainder of the excimer laser surgery procedure is the same as for standard LASIK. The gas bubbles created in the stroma by femtosecond lasers can occasionally limit the ability of eye tracking or iris-tracking systems to register properly.

Flap centration, diameter, hinge angle and width, and flap thickness are programmable and adjustable in all systems that use the higher energy–lower frequency lasers. The lower energy–higher frequency system (FEMTO LDV, Ziemer Ophthalmic Systems AG, Port, Switzerland) relies on mechanical centration, a selection of suction rings to determine the flap diameter, a set of foils to set the flap thickness, and limited ability to adjust the side-cut angle. This mobile femtosecond system uses a segmented raster pattern for the laser cut, using a lower pulse energy/higher frequency delivery. It also requires the use of a masking agent and generally cannot be reengaged if there is a loss of suction during the creation of the flap. However, this laser can be used directly under the excimer laser, similar to a microkeratome, whereas the other systems require that the patient be moved between the stand-alone femtosecond laser and the excimer laser. Thus, for the other systems, the surgeon must decide whether to create both flaps and then perform the excimer ablations ("Flap, Flap, Zap, Zap" technique) or to perform the excimer ablation after each flap is created ("Flap, Zap, Flap, Zap" technique).

Resource Requirements

In addition to the resources required to perform LASIK, the procurement of a femtosecond laser requires extra space, time, and expenditure. Because femtosecond lasers are generally stand-alone units, existing laser rooms may not be sufficiently sized to accommodate the units. Likewise, proper temperature control for the room is essential, and the addition of the femtosecond laser should not exceed the cooling capacity of the laser room. For surgeons who are experienced with microkeratomes, femtosecond lasers typically add at least a few minutes to the overall case time per patient, which may be more problematic for higher-volume centers. Finally, femtosecond lasers generally cost substantially more than microkeratomes, perhaps hundreds of thousands of dollars more. In addition to disposable supplies that need to be purchased for each case, such as applanation plates and suction rings, many lasers incur per-use fees as well. The lasers also require routine maintenance, and there are periodic costs associated with upgrades, as with any technology.

Questions for Assessment

The objectives of this review are to answer the following 3 questions: (1) What are the safety, efficacy, and predictability of femtosecond lasers in creating corneal flaps for LASIK? (2) What are the reported outcomes of LASIK when femtosecond lasers are used to create corneal flaps? and (3) Do available data show differences in outcomes when femtosecond lasers are compared with microkeratomes?

Description of Evidence

Literature searches of the PubMed and Cochrane Library databases were first conducted on May 28, 2009, and re-

Table 1. Femtosecond Lasers with Food and Drug Administration Clearance for Marketing as of May 1, 2012

Laser Device Name	Company	Date Approved	K Number	Indications
FEMTO LDV (formerly Da Vinci Femtosecond Surgical Laser)	Ziemer Ophthalmic Systems AG* (Port, Switzerland)	March 10, 2006	K053511	Creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea
Horus Laser Keratome	Carl Zeiss Meditec AG (Jena, Germany)	December 22, 2006	K062314	Creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea
iFS Laser System	Advanced Medical Optics, Inc.† (Santa Ana, CA)	April 25, 2008 March 8, 2012	K073404 K113151	Creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea; in patients undergoing surgery or other treatment requiring initial lamellar resection of the cornea; patients undergoing surgery or other treatment requiring initial lamellar resection of the cornea to create tunnels for placement of corneal ring segments; in lamellar keratoplasty and corneal harvesting; in the creation of a lamellar cut/resection of the cornea for lamellar keratoplasty and in the creation of a penetrating cut/incision for penetrating keratoplasty; in patients undergoing ophthalmic surgery or other treatment requiring arcuate cuts/incisions, both penetrating and intrastromal
IntraLase Fusion Laser	IntraLase Corp.†	February 9, 2007	K063682	
IntraLase FS Laser, IntraLase FS30 Laser, Models 1,2,3	IntraLase Corp.† (Santa Ana, CA)	August 16, 2006	K060372	
IntraLase FS Laser	IntraLase Corp.†	September 29, 2003	K031960	
Pulsion FS Laser Keratome	IntraLase Corp.†	February 27, 2002	K013941	
Technolas Femtosecond Workstation Custom Flap (formerly FemTec Laser Microkeratome)	Technolas Perfect Vision GmbH‡ (Munich, Germany)	February 18, 2004	K033354	Creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea
VisuMax Laser Keratome	Carl Zeiss Meditec AG	July 8, 2010	K100253	Creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea; in patients undergoing surgery or other treatment requiring initial lamellar resection of the cornea; in the creation of a lamellar cut/resection of the cornea for lamellar keratoplasty; in the creation of a cut/incision for penetrating keratoplasty and corneal harvesting
WaveLight FS200 Laser System	Alcon Laboratories, Inc. (Fort Worth, TX)	October 21, 2010	K101006	Creation of a corneal flap in patients undergoing LASIK surgery or other surgery or treatment requiring initial lamellar resection of the cornea; in patients undergoing surgery or other treatment requiring initial lamellar resection of the cornea to create tunnels for placement of corneal ring segments; in the creation of a lamellar cut/resection of the cornea for lamellar keratoplasty; in the creation of a penetrating cut/incision for penetrating keratoplasty and for corneal harvesting

Source: US Food and Drug Administration. Available at: http://www.fda.gov/. Accessed May 1, 2012.
*Da Vinci application filed by SIE Ltd Surgical Instrument Engineering.
†Advanced Medical Optics, Inc, acquired IntraLase Corp, on April 27, 2007; Abbott Laboratories, Inc, acquired Advanced Medical Optics, Inc, on February 26, 2009, and renamed the company Abbott Medical Optics, Inc.
‡Since 2009, in joint venture with Bausch & Lomb, Inc, Rochester, NY; FemTec application was filed by 20/10 Perfect Vision Optische Gerate GmbH.

peated on March 19, 2010, December 7, 2010, and October 12, 2011, using combinations of the terms *femtosecond, LASIK, surgery, refractive, keratorefractive, microkeratome*, and *complication (truncated)* without language or date limitations. The searches retrieved 636 citations. The first author reviewed these citations and selected 198 articles to review in full text to consider their relevance to the assessment questions. Abstracts of meeting presentations

were not included in the assessment. The publications were divided among the panel members who reviewed them in a standardized fashion and selected 101 as relevant to the assessment questions. Of these, panel members chose 58 articles that they considered to be of medium or high relevance to the questions posed for this assessment. The panel methodologist (A.S.) then assessed the studies according to the strength of evidence. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies.[3]

Four studies[4–7] described well-conducted randomized trials with adequate power and follow-up to draw well-supported conclusions and were rated level I. Fourteen studies[8–21] described randomized trials that were rated level II. These trials provided useful information but had deficiencies that made them lower quality. The most common deficiency was a lack of a priori sample-size calculation or post hoc power calculation. Several were not masked, did not provide numbers of subjects at follow-up points, or failed to describe methods of randomization. The remaining 40 studies were rated level III and described uncontrolled case series or case reports (26), nonrandomized comparative trials (9), laboratory experiments (4), or case-control studies (1).

Published Results

Visual, Optical, and Functional Outcomes of Femtosecond LASIK

Numerous studies have been published on the visual, optical, and functional outcomes of femtosecond lasers used in LASIK procedures.[4–6,9–11,13,15,17,22–37] Most studies focused on IntraLase (Abbott Medical Optics, Inc, Santa Ana, CA) femtosecond lasers. Additional studies provided details of visual results with femtosecond lasers, even though this was not a main study outcome.[12,38–52] The majority of the published visual results with IntraLase femtosecond lasers are from earlier iterations of the technology: the 15-kHz and 30-kHz platforms. Relatively few studies have focused on visual outcomes from the IntraLase FS60 laser, a 60-kHz platform, or later iterations of the device.[11,15,19,22,35]

Studies Involving Only IntraLase Femtosecond Lasers for LASIK

In 1 of the larger case series, a Spanish study of 485 eyes with myopia,[33] all procedures were performed by the same surgeon using an IntraLase femtosecond laser and the excimer photoablation was performed with the Technolas 217C (Technolas Perfect Vision GmbH, Munich, Germany; Bausch & Lomb, Inc, Rochester, NY). Mean spherical refraction before surgery in this group was −3.9 diopters (D) (range, 0 to −11 D; standard deviation, 2.0) with mean cylindrical refraction of −0.9 D (range, 0 to −4.75 D; standard deviation, 0.9). By 3 months after surgery, 414 eyes (85.4%) achieved uncorrected visual acuity (UCVA) of 20/25 or better (level III evidence). Mean spherical refraction after surgery was −0.02, and mean cylindrical refraction was −0.1 D. Thirty-five eyes (7.2%) required enhancement.

Nordan et al[31] reported on 208 eyes with a mean spherical equivalent of −4.30 D (range, −0.13 to −12.40 D) before surgery. All excimer ablations were performed using the Technolas 217 or the VISX STAR2 (formerly VISX, Inc, Santa Clara, CA, now Abbott Medical Optics, Inc, Santa Ana, CA) lasers. Of the 96 eyes that were available for follow-up at 6 months and that were targeted for emmetropia, 98% achieved UCVA of 20/40 or better (level III evidence). All eyes achieved a best-corrected visual acuity (BCVA) of 20/30 or better; 27 eyes gained 1 line, 5 eyes gained 2 or more lines, 4 eyes had a 2-line loss, and 12 eyes had a 1-line loss. Of those with low myopia (<−3.00 D; n = 37), all were within 1.00 D of emmetropia; 35 eyes (95%) were within a half diopter. All of the eyes in this group had a BCVA of 20/30 or better, with 29 eyes (79%) achieving a BCVA of 20/20 or better at 6 months. For those with moderate myopia (<−3.00 to −5.90 D; n = 44), 42 eyes (96%) were within 1.00 D of emmetropia, 26 eyes (59%) achieved 20/20 UCVA, and none were worse than 20/30. For those with high myopia (>−6.00 D; n = 15), none of the eyes attained 20/20 UCVA, and 93% were 20/40 or better. None of the eyes in any of the groups required retreatment by the 6-month follow-up.

Different excimer laser platforms also may affect the visual outcomes, regardless of the flap creation device. Binder and Rosenshein[23] analyzed data on 721 eyes that had conventional or wavefront LASIK using 1 of 3 laser platforms (VISX STAR S4 [formerly VISX, Inc, now Abbott Medical Optics, Inc], LADARVision 4000 [Alcon Laboratories, Inc, Fort Worth, TX], WaveLight Allegretto [formerly WaveLight AG, Erlangen, Germany, now Alcon Laboratories, Inc]). Flaps for all eyes were created using IntraLase femtosecond lasers (both the 15-kHz and 30-kHz versions). Attempted flap thicknesses ranged from 80 to 150 μm, based on corneal thickness before surgery, with the majority (84%) aiming for 90 to 110 μm. Flap diameters were consistently planned for 9.0 mm. Wavefront aberrometry was also assessed at the 2- or 3-month visit, regardless of which ablation treatment the patient had undergone. Mean spherical equivalent before surgery ranged from a low of −3.57 D to a high of −4.75 D; cylinder ranged from a mean of 0.82 D to 1.29 D. In this group of patients, the Star S4 wavefront laser group had better BCVA after surgery, although it was not deemed clinically significantly better than any other laser-platform group (level III evidence). The WaveLight excimer laser produced the highest percentage of eyes with UCVA of 20/20 or better (80%) after surgery.

Studies Involving Other Femtosecond Lasers

There have been limited data published to date on femtosecond lasers other than IntraLase femtosecond lasers, and the majority of the data were published within the past 1 to 2 years.[24,32,36,37] Blum et al[24] reported on visual outcomes with the VisuMax (Carl Zeiss Meditec AG, Jena, Germany) femtosecond laser and the Zeiss MEL 80 excimer laser (Carl Zeiss Meditec AG). In that study of 32 eyes, mean

spherical equivalent before surgery was −4.04 D. All eyes were targeted for emmetropia; 29 flaps were intended for 120 μm and 1 flap each was intended for 110, 140, and 150 μm. All flap diameters were between 7.8 and 9.0 mm. At 3 months after surgery, 25% of the eyes gained 1 line of vision and 16% gained 2 lines (level III evidence). Overall, 3% reached 20/10 UCVA, 9% reached 20/12.5, 47% reached 20/16, 91% reached 20/20, 97% reached 20/30, and 100% reached 20/40 or better.

Reinstein et al[37] treated 12 patients bilaterally with the VisuMax femtosecond laser and MEL 80 excimer laser. In this study, mean spherical equivalent refraction was −3.40 D; all flaps were intended for 110 μm. One eye had a 7.5-mm intended flap, 14 eyes had an 8.0-mm intended flap, and 8 eyes had an 8.5-mm intended flap. At 3 months after surgery, 100% of the eyes achieved 20/20; 54% gained 1 line of vision and 4% lost 1 line of BCVA relative to the baseline (level III evidence). The group noticed a "tendency for slight overcorrection" on the spherical equivalent refraction histogram after surgery.

Two studies[32,36] evaluated the efficacy of the Femto LDV femtosecond laser; both studies used the WaveLight Allegretto laser for the excimer ablation. Pietilä et al[32] designed their study to evaluate flap characteristics and efficacy, but they included visual outcomes. All surgeries included an intended flap thickness of 110 μm; 766 eyes had an intended flap diameter of 9.0 mm, 20 eyes had an intended flap diameter of 9.5 mm, and 1 eye had an intended flap diameter of 8.5 mm. The overall mean spherical equivalent refraction was −4.92 D (n = 698) in the myopic eyes and +2.14 D (n = 89) in the hyperopic eyes. In this large cohort of 787 eyes, visual acuity results at 1 month were provided for 570 myopic eyes and 65 hyperopic eyes (level III evidence). In the myopic eyes, 150 (26.3%) gained 1 line of BCVA relative to the baseline and less than 1% lost 1 line or gained more than 2 lines. In the hyperopic eyes, 6 eyes (9.2%) gained 1 line and 2 eyes (3.1%) gained 2 lines of BCVA relative to the baseline. No change in BCVA relative to the baseline occurred in 417 myopic (73.2%) and 57 hyperopic eyes (87.7%).

Vryghem et al[36] evaluated 111 myopic eyes that had flaps created using the Femto LDV femtosecond laser (level III evidence). All eyes were targeted for emmetropia, and the horizontal flap diameter was targeted at 9.5 mm. The optical zone was 6.5 mm in all cases, and the residual stromal bed after ablation was planned to be at least 250 μm. The horizontal flap diameter was targeted at 9.5 mm. The mean spherical equivalent was −4.56 D before surgery. At 6 months after surgery, UCVA was 20/25 or better in 109 eyes (98.2%) and 20/20 or better in 105 eyes (94.6%). Absolute astigmatic error was reduced to 0.25 D or less in 100 eyes (90.1%) and 0.50 D or less in 110 eyes (99.1%). At 6 months, no eye had a significant loss of BCVA.

Contrast Sensitivity and Higher-Order Aberrations

In a study in which all LASIK flaps were created with an IntraLase femtosecond laser, Binder and Rosenshein[23] found that the excimer laser platform and ablation profile (conventional vs. wavefront) influenced the higher-order aberrations (HOAs) after surgery. By using only an IntraLase femtosecond laser to create all flaps, the authors hoped to eliminate the flap creation technique as a potential cause of HOA variability, leaving the excimer laser platform and treatment type to account for the variability. In their study, the WaveLight Allegretto and VISX STAR S4 wavefront procedures produced a small improvement in mean BCVA, whereas the LADARVision did not. None produced results that were statistically better than levels before surgery. Likewise, the VISX STAR S4 had the lowest mean HOA root mean square increase after surgery and had a statistically significant median percentage decrease (10.7%), but the WaveLight Allegretto had the largest increase in mean and median HOA root mean square. All lasers produced a narrow range in myopic spherical equivalent after surgery. Spherical aberrations were not different across the laser platforms. Higher-order aberration root mean square values ranged from 0.1 to 0.5 μm in 83% before surgery, but only 64.2% after surgery.

Buzzonetti et al[9] compared corneal aberration changes in 47 eyes of 28 myopic patients who underwent conventional LASIK using the Technolas 217 excimer laser. Flaps for 23 eyes of 13 patients were created using the IntraLase femtosecond laser, and flaps for 24 eyes of 15 patients were created using a Hansatome microkeratome. Topography-derived corneal aberrations were calculated with estimated pupil diameters of 3.0 and 5.0 mm. In patients with a 5.0-mm pupil, total and higher-order corneal wavefront aberrations changed significantly, whereas in the 3.0-mm pupil, no significant changes were noted in the IntraLase femtosecond laser group (level II evidence). Total corneal aberrations remained the same between the 3-month and 1-year time points, regardless of pupil size.

Schallhorn et al[34] analyzed night-driving performance (linked to night-vision symptoms) and compared outcomes in wavefront-guided LASIK with an IntraLase femtosecond-laser-created flap with conventional LASIK with a microkeratome-created flap in moderate myopes. Performance-based tasks can relate more directly to a patient's perceived impression of his or her vision, perhaps more so than clinical parameters such as UCVA or BCVA, the authors asserted. This retrospective, comparative study evaluated all eyes in 2 LASIK studies; the manifest spherical equivalent before surgery was between −4.50 D and −6.00 D. Main outcomes included the ability to detect and identify distances of road hazards in night-driving simulation with and without a glare source before and 6 months after LASIK. A mean reduction in performance in every parameter occurred with the conventional microkeratome group, and a mean improvement was seen in the wavefront IntraLase femtosecond laser group (level III evidence). The authors noted the impossibility of separating the results to determine whether the outcome was due to the ablation profile, flap-creation technique, or both.

Reinstein et al[37] measured mesopic contrast sensitivity at 3, 6, and 12 cycles per degree in a VisuMax laser–treated group and did not find any statistically significant differences from before surgery to 3 months after surgery at any frequency level (level III evidence). There was an increase in mean HOA root mean square from 0.30 to 0.48 μm after surgery, in coma from a mean of 0.15 to 0.25 μm after surgery, and in spherical aberrations from 0.10 to 0.27 μm

Table 2. Mechanical Microkeratome and Femtosecond

Study (Level of Evidence)	Intended Flap Thickness	Pachymetry Method	Mechanical Microkeratomes			
			Carriazo-Barraquer*	Carriazo-Pendular†	Hansatome‡	Moria LSK 1*
Patel et al,[6] 2007 (I)	120 (IntraLase) 180 (Hansatome)	US			138 (22)	
Alio and Pinero,[8] 2008 (II)	110	VHF US		118 (8.5) 106–139		
Ahn et al,[55] 2011 (III)	110 (femtosecond lasers) 130 (Moria)					
Hamilton et al,[44] 2008 (III)	110–120 (IntraLase) 130 (Moria)	US				
Javaloy et al,[25] 2007 (III)	120 (IntraLase) 130 (Moria)	Confocal microscopy				
Kezirian and Stonecipher,[26] 2004 (III)	130 (IntraLase) 130 (Carrizo-Barraquer) 180 (Hansatome)	US	153 (26) 59–210		156 (29) 25–250	
Rosa et al,[42] 2009 (III)	160 (Hansatome) 120 (Zyoptix and IntraLase)	US			149 (24.9) 102–198	
Salomao et al,[20] 2009 (III)	100–110 (IntraLase) 180 (Hansatome)	US			131 (25)	
Talamo et al,[53] 2006 (III)	110	US				130 (19) 71–186
von Jagow and Kohnen,[54] 2009 (III)	100 (IntraLase) 120 (Zyoptix)	OCT				
Yao et al,[56] 2011 (III)	100 (VisuMax) 110 (Moria)					

OCT = optical coherence tomography; US = ultrasound; VHF = very high frequency.
Note: Average (standard deviation), range where included (μm).
*MORIA S.A., Antony, France.
†SCHWIND eye-tech-solutions (GmbH & Co. KG, Kleinostheim, Germany).
‡Technolas Perfect Vision GmbH, Munich, Germany, and Bausch & Lomb, Rochester, NY.
§Bausch & Lomb, Rochester, NY.
‖Advanced Medical Optics, Inc, acquired IntraLase Corp, on April 27, 2007; Abbott Laboratories, Inc, acquired Advanced Medical Optics, Inc, on
¶Carl Zeiss Meditec AG, Dublin, CA.
#Ziemer Ophthalmic Systems AG, Port, Switzerland.

after surgery. Unfortunately, no explanations were given for the HOA increases because this study was designed more to assess flap thickness than visual outcomes. None of the other studies on non–IntraLase femtosecond lasers evaluated contrast sensitivity or other HOAs.

Flap Creation for Thin-Flap LASIK and Post-Radial Keratotomy

Thin-flap LASIK, sometimes referred to as "sub-Bowman's keratomileusis" in the medical literature, is a variation of LASIK with targeted flap thicknesses generally between 90 and 110 μm. Durrie et al[11] performed thin-flap LASIK with IntraLase femtosecond laser-created flaps in 1 eye and performed photorefractive keratectomy (PRK) in the contralateral eye of 50 patients. Wavefront-guided excimer ablations with the LADARVision 4000 were performed. Visual recovery, including low-contrast acuity, was faster in the thin-flap group, but the 3- and 6-month results were similar between the groups (level II evidence). More eyes in the thin-flap group reached 20/12.5 or better (18% vs. 2% in the PRK group), and that trend held at every follow-up time point, with 88% of the thin-flap eyes reaching 20/20 compared with 48% of the PRK eyes. Ocular Response Analyzer (Reichert, Inc, Depew, NY) results were similar between the 2 groups. In the same cohort, Slade et al[15] reported greater early preference for the thin-flap–treated eye, which generally equalized by the third month after surgery (level II evidence). Hatch et al[19] performed a similar contralateral eye study in 52 patients and found no significant difference in visual outcomes by 3 months after surgery (level II evidence).

Two studies analyzed visual outcomes of patients with residual low myopia or secondary hyperopia after radial keratotomy (RK).[29,30] In both cases, an IntraLase femtosecond laser was safely used to create thin LASIK flaps, but the authors did suggest limiting the femtosecond laser use to eyes with <8 RK incisions because of the potential for complications (see "Safety and Complications"). In general, most eyes had UCVA >20/40, and astigmatism also was improved (level III evidence).

Mechanical Microkeratome Compared with Femtosecond Laser

Eleven studies selected for this review referenced flap thickness in a comparative analysis (Table 2).[6,8,20,25,26,42,44,53–56]

Laser Comparative Studies

Mechanical Microkeratomes			Femtosecond Lasers					
*Moria M2**	*Moria M3**	*Moria One Use**	*Zyoptix XP*[§]	*IntraLase*[‖] *15 kHz*	*IntraLase*[‖] *30 kHz*	*IntraLase*[‖] *60 kHz*	*VisuMax*[¶]	*Femto LDV*[#]
				143 (16)				
118 (7.8) 101–131					116 (6.2) 101–126			
126.0 (19.9)						130.3 (13.2)	133.9 (13.9)	105.8 (8.2)
		117 (16)				120 (13)		
148.0 (16.7)				129 (3.4)				
				114 (14) 78–155				
			125 (23.8) 68–161			143 (18.4) 107–173		
					111 (14)			
142 (24) 84–203					119 (12) 82–149			
			132 (15)			113 (14)		
	112.18 (5.39)						100.16 (7.87)	

February 26, 2009, and renamed the company Abbott Medical Optics, Inc.

Most used subtraction ultrasound as the method of measurement, whereas 1 study used very high-frequency ultrasound,[8] 1 study used confocal microscopy,[25] and 2 studies used optical coherence tomography.[54,55] The standard deviation was generally smaller for the femtosecond lasers than for mechanical microkeratomes. The range of flap thicknesses also was notably different. The mechanical microkeratomes ranged from as thin as 25 μm to as thick as 250 μm,[26] whereas the femtosecond lasers ranged from as thin as 78 μm to as thick as 173 μm.

Aberrations

Nine of the articles reviewed[4,5,8–10,13,17,27,28] compared optical aberrations for mechanical microkeratomes with femtosecond lasers. In a study comparing Hansatome (Bausch & Lomb, Rochester, NY) with IntraLase femtosecond laser LASIK, Buzzonetti et al[9] noted a significant induction (described as the increasing factor, defined as the ratio between the postoperative and preoperative mean values of the optical aberration) of spherical-like aberration for both groups, whereas the increasing factor greatly increased for total and coma-like aberrations in the Hansatome group 12 months after LASIK (level II evidence). Chan et al[10] also found differences in induced aberrations based on the microkeratome used, in favor of the femtosecond laser (level II evidence). The 15-kHz IntraLase femtosecond laser group had fewer high-order spherical and coma aberrations and more trefoil aberrations than the Hansatome group. These differences were statistically significant at 3 months but not at 1, 6, or 12 months after LASIK. In a contralateral eye study, Durrie and Kezirian[5] demonstrated significantly more trefoil aberrations in the Hansatome group compared with the IntraLase femtosecond laser group 3 months after LASIK (level I evidence). They concluded that this factor may make an IntraLase femtosecond laser a better option than the Hansatome microkeratome in the treatment and prevention of HOAs after LASIK. Medeiros et al[28] compared an IntraLase femtosecond laser with the Moria M2 (MORIA S.A., Antony, France) and the Hansatome microkeratomes and found significantly less induction of total higher-order and spherical aberration in the femtosecond group but no differences in coma root mean square (level III evidence). Lim et al[27] demonstrated similarities in HOAs between Hansatome microkeratome and IntraLase femto-

second laser outcomes; however, the induction of spherical aberration was significantly greater in the Hansatome group 3 months after LASIK (level III evidence). Montes-Mico et al[13] also demonstrated an advantage in using an IntraLase femtosecond laser over a mechanical microkeratome (in this case the Carriazo-Barraquer [MORIA S.A., Antony, France]) in terms of induced HOAs (level II evidence). At 6 months after LASIK, femtosecond laser LASIK resulted in lower corneal HOAs, compared with mechanical microkeratome LASIK over various pupil sizes. The authors concluded that femtosecond lasers for LASIK surgery may be a better choice for wavefront-guided LASIK than mechanical microkeratomes.

In a randomized contralateral eye study comparing induced aberrations with the IntraLase femtosecond laser and Hansatome microkeratome flap creation in fellow eyes, Tran et al[17] created LASIK flaps without immediately applying the excimer laser. The investigators found a significant hyperopic shift in manifest refraction in the Hansatome microkeratome group after the creation of the corneal flap (level II evidence). No statistically significant changes in manifest refraction were seen in the IntraLase femtosecond laser group. Statistically significant changes in trefoil and quadrafoil aberrations were seen in the Hansatome group. After flap lift and excimer laser application, a significant increase in coma was seen in the Hansatome group. The authors concluded that the creation of the LASIK flap alone can modify the eye's optical characteristics in lower-order aberrations and HOAs (significantly more so in the Hansatome group compared with the IntraLase femtosecond laser group) and theorized that this may have significant clinical implications in wavefront-guided LASIK treatments.

Conversely, Calvo et al[4] did not find any differences in corneal total HOAs, spherical aberration, coma, or trefoil between flaps created with a Hansatome microkeratome and a 15-kHz IntraLase femtosecond laser at any time point during 3 years after LASIK (level II evidence). Likewise, Alio and Pinero[8] found no statistically significant differences in coma-like or spherical-like root mean square corneal aberrometry among the IntraLase femtosecond laser, Moria M2, and Carriazo-Pendular microkeratomes 3 months after LASIK (level III evidence). Munoz et al[14] found similar increases in anterior corneal aberrations after myopic LASIK in 98 eyes of 50 patients, comparing a 15-kHz IntraLase femtosecond laser and Carriazo-Barraquer microkeratome (level II evidence).

Clinical Results (Visual Acuities, Manifest Refractions)

Many of the articles selected for review compared clinical results between the femtosecond laser and the various mechanical microkeratomes. In 6 studies (level I evidence,[4,6] level II evidence,[10] level III evidence[25,27,44]), no significant differences were seen in clinical results between the laser and the mechanical microkeratome at any time points after LASIK (including 1, 3, 6, 12, and 36 months after surgery). However, in 5 other studies, clinical differences were seen, all in favor of IntraLase femtosecond lasers. Durrie and Kezirian[5] noted significantly better mean UCVA at all intervals from 1 day to 3 months after surgery in eyes treated with an IntraLase femtosecond laser, compared with the Hansatome mechanical microkeratome (level I evidence). The mean spherical equivalent at 3 months was closer to emmetropia with the IntraLase femtosecond laser than with the Hansatome (-0.19 D vs. -0.34 D, respectively), and the mean residual astigmatism at 3 months also was significantly higher in the Hansatome group than in the IntraLase femtosecond laser group (0.32 D vs. 0.17 D, respectively). Kezirian and Stonecipher[26] reported a higher accuracy of refractions (91%) after surgery with an IntraLase femtosecond laser compared with the Carriazo-Barraquer and Hansatome mechanical microkeratomes 3 months after LASIK (73% and 74%, respectively; level III evidence). Surgically induced astigmatism in sphere corrections was significantly less with an IntraLase femtosecond laser than with the other devices as well. Montes-Mico et al[13] demonstrated improved BCVA for an IntraLase femtosecond laser compared with the Carriazo-Barraquer mechanical microkeratome in terms of lines of BCVA gained at 6 months post-LASIK. In this study, 24 eyes gained 1 line of BCVA and 18 eyes gained $\geq$2 lines post-LASIK with a femtosecond laser versus 18 eyes that gained 1 line and no eyes that gained $\geq$2 lines post-LASIK with a mechanical microkeratome (level II evidence). Predictability in the femtosecond laser for the LASIK group showed 98% of eyes achieved within $\pm$0.50 D of the attempted correction in spherical equivalent, higher than that of the mechanical microkeratome LASIK group (92%). Tanna et al[35] compared the IntraLase femtosecond laser LASIK with the Moria One Use mechanical microkeratome LASIK. They demonstrated that, at all time points measured, the percentage of eyes that achieved a UCVA of 20/20 or better after surgery was statistically significantly higher in the femtosecond laser group than in the microkeratome group (level III evidence). Also, a higher percentage of eyes in the femtosecond laser group achieved a UCVA of 20/16 at 3 months after surgery than in the microkeratome group. Finally, a lower percentage of eyes in the femtosecond laser group than in the microkeratome group lost 2 or more lines of BCVA at 1 week and 1 month after surgery.

Corneal Biomechanics, Flap Morphology, and Ultrastructure

By using the Ocular Response Analyzer, Hamilton et al[44] compared the changes in biomechanical parameters, corneal hysteresis, and corneal resistance factor in 3 groups of patients with myopia. One group underwent LASIK with flaps created with a Moria One Use mechanical microkeratome. The second group underwent LASIK with flaps created with an IntraLase femtosecond laser, and the third group underwent PRK. The investigators found no differences in the changes in corneal hysteresis or corneal resistance factor among the groups (level III evidence). There was a correlation between ablation depth and the reduction in corneal hysteresis, and this correlation was strongest in the femtosecond laser group and weaker in the PRK and

microkeratome groups. The authors concluded that LASIK using the femtosecond laser caused a significantly more predictable change in corneal biomechanics, which correlated strongly with ablation depth, than the change with PRK and LASIK performed using a mechanical microkeratome to create the flap.

Kim et al[57] quantified and compared late adhesion strength after surgery in corneal flaps made with a femtosecond laser with flaps made using a mechanical microkeratome in rabbits. The grams of force needed to detach the flaps in the femtosecond laser group were significantly higher than in the mechanical microkeratome group 3 months after LASIK. The investigators theorized that because the femtosecond laser produces greater corneal stromal inflammation early after surgery, this is likely to increase flap adhesion strength later. Knorz and Vossmerbaeumer[58] replicated these findings in a rabbit model, comparing adhesion strength of flaps created using an Amadeus II (Ziemer Ophthalmic Systems AG) mechanical microkeratome and the 150-kHz IntraLase femtosecond laser with varying side cuts. The investigators found significantly stronger flap adhesion with an IntraLase femtosecond laser compared with the Amadeus II. For IntraLase femtosecond flaps, an inverted (150-degree) side-cut increased flap adhesion significantly compared with a standard (70-degree) side-cut.

Ortiz et al[45] compared the change in corneal curvature from the predicted surgical radius (sculpted in the corneal stroma) and the measured radius after surgery of the first surface of the cornea after LASIK for myopia using the Moria M2 mechanical microkeratome and an IntraLase femtosecond laser. The refractive change in corneal curvature was lower after femtosecond laser LASIK than microkeratome LASIK because of the planar versus meniscus nature of the flaps, as described previously. Refractive data in this study showed a mean difference between the intended and achieved spherical equivalent of 0.9 D in the mechanical microkeratome group and 0.5 D in the femtosecond LASIK group (level III evidence). The authors recommend that estimations of refractive changes induced by the creation of the flap be taken into consideration in surgery design.

Patel et al[40] evaluated the changes in refractive index of the human corneal stroma during LASIK, measuring the effects of exposure time and the method used to create the flap, comparing the Moria M2 mechanical microkeratome with an IntraLase femtosecond laser. After lifting the LASIK flap, the refractive index of the stroma was measured using a customized manual Abbe refractometer. This measurement was repeated immediately after photoablation. The mean refractive index increased for both groups and was directly correlated to treatment time (level III evidence). Before photoablation, the refractive index was significantly lower in the microkeratome group. Photoablation increased the refractive index of the stroma in both groups. Hydration of the stroma also was significantly greater in the microkeratome group than in the femtosecond laser group. The investigators concluded that the hydration state directly influences the refractive index of the cornea during LASIK and that this information can be used to better understand the changes in outcomes observed in LASIK when using various methods.

A comparison of goblet-cell density after femtosecond laser versus mechanical microkeratome LASIK was carried out by Rodriguez et al.[59] They used impression cytology to show a greater reduction in goblet-cell populations after a 15-kHz IntraLase femtosecond laser LASIK than after Moria M2 mechanical microkeratome LASIK (level III evidence). The investigators theorized that the change in goblet-cell density is due to the length of time that the suction ring exerted pressure on the conjunctiva and that these changes may contribute to the development of an ocular surface syndrome after LASIK procedures. However, no other objective markers of dry eye or any subjective appraisal of dry eye syndrome were included in this report.

In a series of studies, Sarayba et al[60,61] evaluated the stromal-bed quality of LASIK procedures after mechanical microkeratomes compared with femtosecond lasers. Qualitative surface roughness was assessed by electron microscopy after LASIK performed on human donor eyes using a Hansatome microkeratome, Zyoptix XP (Bausch & Lomb and Technolas Perfect Vision GmbH) microkeratome, and 15-, 30-, and 60-kHz IntraLase femtosecond lasers. The 30- and 60-kHz IntraLase femtosecond lasers created a smoother stromal bed than either of the mechanical microkeratomes. The investigators theorized that this was due to the tighter spot/line separation and lower energy per pulse of the faster femtosecond lasers.

Comparative corneal sensitivity was evaluated in 3 studies.[5,7,27] Patel et al[7] found no difference in corneal sub-basal nerve regeneration when comparing a 15-kHz IntraLase femtosecond laser with a Hansatome microkeratome, and there was no difference in corneal sensitivity measured by gas esthesiometry (level I evidence). They also did not find a relationship between corneal subbasal nerve density and corneal sensitivity. Lim et al[27] assessed return of corneal sensation after LASIK performed with the Hansatome mechanical microkeratome compared with an IntraLase femtosecond laser. They found a faster corneal sensitivity recovery in the IntraLase femtosecond laser group compared with the Hansatome group, with corneal sensitivity in the peripheral area nearly normalized at 3 months after surgery in the IntraLase femtosecond laser group (level III evidence). Conversely, Durrie and Kezirian[5] also evaluated recovery of corneal sensation between a Hansatome mechanical microkeratome group and an IntraLase femtosecond laser group; they found no significant difference in the rate of recovery of corneal sensation between the 2 groups (level I evidence).

Alio and Pinero[8] used very high-frequency ultrasound (Artemis 2, Ultralink LLC, St. Petersburg, FL) to evaluate flap thicknesses at different locations on the cornea 1 month after LASIK with flap creation by the Moria M2, Carriazo-Pendular, and IntraLase femtosecond laser devices. No differences were found in central flap thickness among the 3 devices; however, statistically significant differences were noted among the peripheral flap thickness values depending on the device used (level II evidence). The nasal and temporal flap thicknesses were significantly larger for the Moria M2 group. The Carriazo-Pendular and IntraLase femtosec-

ond laser flaps were more homogeneous, showing a planar or near-planar morphology profile in all cases.

Javaloy et al[25] used tandem scanning confocal microscopy (model 165A; Advanced Scanning Ltd, New Orleans, LA) to assess flap morphology and inflammation in eyes treated with a Moria M2 microkeratome and compared the results with eyes treated with an IntraLase femtosecond laser. Although the difference between the desired and the actual flap thickness was not significant when medians of both groups were compared, the confocal microscope measurements yielded a positive correlation between corneal and flap thickness before surgery for the mechanical microkeratome, but not for the femtosecond laser (level III evidence). The authors theorized that femtosecond laser's lack of correlation could be explained by the nonprogressive compression that the femtosecond laser produces over the cornea when cutting. Likewise, Sonigo et al[62] used the in vivo Heidelberg Retina Tomograph II/Rostock Cornea Module (HRT II/RCM; Heidelberg Engineering GmbH, Heidelberg, Germany) confocal microscope to evaluate the flaps of subjects undergoing LASIK with the Hansatome microkeratome or an IntraLase femtosecond laser. Evaluation of both groups on day 7 showed keratocyte transformation, most likely related to cellular activation beneath the interface (level III evidence). After using an IntraLase femtosecond laser, the flap margin appeared microscopically as a clear-cut edge that included the epithelial plug. At 2 months after surgery, secondary fibrosis was observed, adjacent to the still well-defined IntraLase femtosecond laser flap edge. This reaction diminished with time, leaving a fibrotic scar adjacent to a wound constriction originating from the surrounding stroma. The flap margin of the mechanical microkeratome had the appearance of a less clearly identified fibrotic scar with no epithelial plug. No clinical correlations were provided in this study.

von Jagow and Kohnen[54] used anterior segment optical coherence tomography to assess the corneal architecture of flaps created by a Zyoptix XP mechanical microkeratome and an IntraLase femtosecond laser. They observed the morphology of the flaps created by the femtosecond laser to be a regular planar shape with a maximum difference of the mean thickness at different measurement points of 13 μm. By comparison, the general morphology of the microkeratome flaps was meniscus shaped, with a maximum difference in mean values of 45 μm. The authors concluded that the flap architecture created with the femtosecond laser was more regular and accurate than the flap architecture created with the microkeratome (level III evidence). Ahn et al[55] found differences between femtosecond lasers and a Moria M2 microkeratome and between the femtosecond lasers themselves (level III evidence). These findings were postulated to be due to the different mechanisms of action of each laser (e.g., a flat versus curved contact surface).

Intraocular Pressure

In a study involving a porcine eye model, comparisons of IOP were made between eyes in which mechanical and femtosecond laser microkeratomes were used.[63] Intraocular pressure was recorded via a transducer connected to the anterior chamber of the model eye by direct cannulation. The Moria M2 was compared with an IntraLase femtosecond laser. The IOP increased during the suction phase, reaching a mean of 122.5±30.4 mm Hg and 160.5±22.7 mm Hg during the cutting phase of the Moria M2 group (average total time, 36.4±7.5 seconds). For the IntraLase femtosecond laser group, the IOP increased to 89.2±24.3 mm Hg during the suction phase and 119.3±15.9 mm Hg during the laser application phase (average total time, 92.9±13.5 seconds). The authors concluded that the IOP increased significantly in both groups but to a lesser extent with IntraLase femtosecond laser treatment, albeit for a longer time interval in the IntraLase femtosecond laser group. Similar findings were noted in another study.[64] In a comparison among 4 femtosecond lasers, Vetter et al[65] found significant variability in the IOPs during flap preparation also using a porcine model.

Quality of Vision (Contrast Sensitivity/Acuity, Visual Experience)

Low-contrast sensitivity/acuity was assessed by several investigators.[6,10,13,27] Chan et al[10] used Early Treatment Diabetic Retinopathy Study mesopic, 25% low-contrast acuity charts to evaluate differences between subjects treated with a Hansatome mechanical microkeratome and an IntraLase femtosecond laser. At 1 and 6 months after LASIK, the femtosecond group had statistically significant gains in low-contrast visual acuity compared with the mechanical microkeratome group (level II evidence). By 12 months, the differences were not statistically significant, although the IntraLase femtosecond laser group continued to demonstrate gains in low-contrast acuity compared with the baseline. Lim et al[27] used Vision Contrast Test System plates (Vistech Consultants, Inc, Dayton, OH) under photopic and mesopic conditions to test contrast sensitivity of LASIK subjects treated with the Hansatome mechanical microkeratome compared with an IntraLase femtosecond laser. In the IntraLase femtosecond laser group, the contrast sensitivity value at 12 and 18 cycles per degree under mesopic conditions was significantly improved at 3 months after LASIK compared with the Hansatome group (level III evidence). By using the Functional Acuity Contrast Test (FACT; Stereo Optical Co, Inc, Chicago, IL), Montes-Mico et al[13] (level II evidence) also demonstrated improvement in contrast sensitivity in the IntraLase femtosecond laser group 6 months after LASIK compared with a group treated with a Carriazo-Barraquer mechanical microkeratome at the highest spatial frequency (18 cycles per degree). In contrast, Patel et al[6] also used the FACT to assess low-contrast acuity. They found no significant differences when comparing the IntraLase femtosecond laser group with the Hansatome group at any time point through 6 months after LASIK (level I evidence).

In a study designed to describe the visual experiences encountered during different stages of LASIK and to compare patients' experiences between LASIK performed with the Zyoptix XP mechanical microkeratome and an IntraLase

femtosecond laser, Tan et al[16] interviewed 41 subjects who had microkeratome LASIK in 1 eye and femtosecond LASIK in the fellow eye. These subjects were interviewed by the surgeon 30 to 60 minutes after LASIK using a standardized questionnaire about their visual experiences during surgery, including light perception and ability to see the red fixation light. During both vacuum suction and corneal flap fashioning, a significantly higher proportion of eyes assigned to the Zyoptix XP microkeratome lost light perception than did the IntraLase femtosecond laser group. There were no other significant differences in visual or overall perception between the groups (level II evidence). Overall, 19.5% of patients were frightened by their visual experiences. There was no statistically significant difference in the mean grade of fear for patients in the mechanical microkeratome group compared with the femtosecond laser group, nor was there a significant association between the gender of the patient or any specific type of visual sensation experienced and a frightening visual experience.

Likewise, in another contralateral eye study comparing the Hansatome microkeratome with an IntraLase femtosecond laser, Patel et al[6] inquired about patient preference 3 months after LASIK. Five patients preferred the vision in the eye that received the femtosecond laser flap, 7 patients preferred the mechanical microkeratome flap, and 9 patients had no preference (level I evidence). In the 12 patients who had a preference, the preferred eye was the dominant eye in 5 cases and was the eye with better uncorrected vision in 4 cases.

Safety and Complications

LASIK complications can be subdivided into intraoperative and postoperative categories on the basis of their temporal occurrence. Of these, complications related to the creation of a LASIK flap have traditionally been those of most concern to surgeons. The incidence of flap complications related to the use of mechanical microkeratomes has been reported to be approximately 5%, especially with the use of early-generation microkeratomes. Furthermore, some serious complications, such as inadvertent entry into the anterior chamber, have resulted in debilitating visual consequences, leading to design modifications of microkeratomes. A theoretic advantage of laser-flap creation should be a reduced incidence of severe complications, and the literature supports this claim. However, there are several newly reported and femtosecond-specific complications that have been described. Studies in this section are level III evidence unless otherwise noted.

Several reports of large case series of femtosecond laser flaps using IntraLase have been published. Chang[46] reported his experience in 3009 consecutive cases of femtosecond laser-assisted sub-Bowman's keratomileusis. The total complication rate was 19 of 3009 eyes (0.63%). Of these, 10 were flap complications (0.33%) during surgery and the remaining 9 cases were diffuse lamellar keratitis (DLK) and epithelial ingrowth. Davison and Johnson[47] reported results in 3009 consecutive cases. There were 11 flap complications (0.37%), including 8 suction breaks, 1 incomplete flap, and 2 adherent flaps. Haft et al[38] described 4772 eyes in which an IntraLase femtosecond laser was used and noted an overall complication rate of 44 eyes (0.92%). Flap complications during surgery accounted for 12 eyes (0.25%), and the remaining 32 eyes developed DLK. Seider et al[66] described 4 cases of epithelial gas breakthrough in 2922 consecutive cases (0.13%). Sutton and Hodge[43] reported 3 cases of epithelial trauma in 1000 consecutive eyes (0.3%). Binder[67] reported 103 consecutive flaps created with an IntraLase femtosecond laser. Of those, there was 1 case of suction loss that occurred at 60% of the way through the laser ablation. This case was aborted, and there was no evidence of a vertical cut through the visual axis. On the first day after surgery, the eye appeared to be clinically normal with no visible evidence of laser treatment. Nordan et al[31] reported early experience with an IntraLase femtosecond laser in 208 eyes, of which 4 (1.9%) experienced suction loss; all eyes were successfully retreated within 5 to 45 minutes. Talamo et al[53] reported 2 cases of suction loss in 99 femtosecond cases (2.02%); both were retreated successfully.

Results using other femtosecond lasers included a report by Pietilä et al[32] in 787 consecutive eyes using the LDV femtosecond laser. In this series, there were 21 free caps (i.e., no hinge was created), 10 pseudo-buttonholes, 2 split flaps, 16 decentered flaps, 8 adhesions, and 5 cases of epithelial trauma. There were more complications in the early experience of this group, indicating that there was a learning curve to overcome. Another group that reported an early increased rate of complications with the LDV system thought that this was due to inexperience with the laser or to problems associated with the design of an early prototype. Vryghem et al[36] reported 111 cases, of which 12 developed epithelial sloughing (10.4%), 5 had decentered flaps (4.5%), and 6 each had microstriae, flap adhesions, and irregular borders (5.4%). Reinstein et al[37] reported on the first 24 consecutive flaps created using the VisuMax laser and reported 1 loss of suction. The flap was successfully created by reapplanating the cornea.

Corneal haze may become a more common complication as flaps become increasingly thinner.[68] Rocha et al[41] compared the incidence of haze in femtosecond flaps when stratified by intended flap thickness. Of 199 eyes treated, 32 developed haze. Multivariable analysis demonstrated that younger age and thinner flap were independent factors associated with the development of haze. The authors surmised that disruption of Bowman's membrane by the thin flap might initiate an inflammatory cascade, resulting in increased myofibroblast proliferation and clinical haze. However, another study[18] found no differences in outcomes for intended flap thicknesses of 90 and 120 μm using a 60-kHz IntraLase femtosecond laser (level II evidence).

Microstriae were generally rare, but there was a 15% incidence[24] in a series of 32 eyes of 17 patients when the VisuMax laser was used. This was attributed to difficulty in lifting the flaps during surgery, because the femtosecond flap may require different lifting techniques than a microkeratome flap.

There was 1 reported case[69] of unilateral macular hemorrhage in a 36-year-old patient with preoperative myopia of −6.00 D spherical equivalent. Lifting of the flap also can

be difficult in the setting of previous RK. Two small series[29,30] reported that the femtosecond laser can be used to create flaps after previous RK, but the incidence of splaying of the RK incisions is high, particularly in cases with more than 8 incisions. This may occur as a result of gas breakthrough or during mechanical flap lift. No eyes experienced epithelial ingrowth, buttonholes, or incomplete/free caps, but there were 4 cases of DLK (30.8%).

Complications Specific to Femtosecond Lasers

Because femtosecond lasers use gas bubbles for flap creation, the displacement of gas bubbles from the stroma to other parts of the eye has been observed. Epithelial gas breakthrough may result from suction loss and has been described in this article. However, there have been reports of gas bubbles in the anterior chamber of the eye.[39] When present in the anterior chamber, the gas bubbles did not appear to have any long-term effect on vision and typically were self-limiting. However, there is concern that the bubbles may interfere with the excimer laser eye-tracking systems, and many surgeons wait for the bubbles to reabsorb before proceeding with treatment. The exact pathway that the bubbles might have taken is unknown; optical coherence tomography evidence does not support the theory of migration through the trabecular meshwork. It is possible that the bubbles represent cavitation forces from stray femtosecond laser pulses directly on the aqueous.[70] Conversely, if gas bubbles are not allowed to pass uniformly through the intended flap area, areas of flap adhesion may develop. Minor adhesions can be carefully broken, but attempts to break larger or more coalescent adhesions may result in flap tears.[71] A variation of this is called "opaque bubble layer,"[72] and resulting transient opacities may limit the performance of eye trackers or iris-registration technologies. The impact of opaque bubble layer on the excimer treatment itself is unclear.

Transient light-sensitivity syndrome (TLSS) is a condition that generally occurs in the first few weeks after femtosecond laser LASIK and is characterized by photophobia of varying severity with an apparent absence of inflammation. Munoz et al[48] reported a series of 765 eyes using the 15-kHz IntraLase femtosecond laser; 10 eyes developed TLSS (1.3%) between 6 and 8 weeks after surgery. However, if aggressive steroids were used in the immediate period after surgery, the incidence decreased from 2.8% to 0.4%. All eyes had 20/25 or better vision at the final visit and only 1 eye lost 1 line of BCVA. Of note, in this series, DLK was more likely in the eyes with TLSS (3 of 10 [30%] vs. 23 of 755 [3%] in the eyes without TLSS). Stonecipher et al[49] described a 1.1% incidence of TLSS (63 of 5667 eyes) with an onset of 2 to 6 weeks after surgery. They reported that the incidence decreased after a downward adjustment of the laser energy settings, and they postulated that shock-wave exposure of the keratocytes or corneal nerves may have been a causative factor. Anecdotal support for this hypothesis is provided by the reduced occurrence of reports of TLSS as the frequency rate of the lasers has increased, which allows for less overall energy required to create the LASIK flap.

Rainbow glare is another potential complication that occurs after femtosecond flap creation. Rainbow glare may be caused by diffraction of light from the grating pattern created on the back surface of the flap. It was first reported by Krueger et al[50] in 2008. Bamba et al[22] retrospectively identified 260 consecutive patients who underwent femtosecond flap creation using a 60-kHz IntraLase femtosecond laser with an attempted flap thickness of 90 to 100 μm (98.5% were contacted). The incidence of rainbow glare was 5.8% (15 patients). Most reported seeing between 4 and 12 bands of color, and the symptoms occurred within the first 3 months after LASIK. There was no association of rainbow glare with age, gender, or refractive error before surgery. However, there was a positive correlation with increased raster energy (1.0–1.1 μJ vs. 0.8 μJ). Newer lasers with higher frequencies (i.e., 60 kHz or greater) create closer spacing of the pulses, requiring less energy, and this may reduce the incidence of rainbow glare. Nevertheless, it was suggested that proper maintenance of the optics is mandatory to maintain the quality of the focused beam and the numeric aperture of the focusing optics.

Complications with Femtosecond Lasers versus Microkeratomes

Complications after surgery include certain outcomes that may or may not be related to the method of flap creation, but are reported in this assessment nonetheless. Epithelial trauma seems to be less likely with femtosecond lasers than mechanical microkeratomes. Kezirian and Stonecipher[26] assessed complications in a comparison between an IntraLase femtosecond laser and 2 mechanical microkeratomes, the Carriazo-Barraquer and Hansatome. They reported an incidence of loose epithelium of 9.6% in the Carriazo-Barraquer group and 7.7% in the Hansatome group. Loose epithelium was not seen in any patient treated with an IntraLase femtosecond laser. Moshirfar et al[51] also found significantly more epithelial defects after using a Hansatome microkeratome (2.6%) than after using a 60-kHz IntraLase femtosecond laser to create the flap (0.6%).

Displaced flaps and epithelial ingrowth have been reported with both mechanical microkeratomes and femtosecond lasers. The incidence of both of these complications with femtosecond lasers should theoretically be due less to the architecture of the side-cut angle. In a study of 41 845 consecutive adults (81 238 eyes total; 23 997 treated with Moria ONE microkeratome and 57 241 treated with 60-kHz IntraLase femtosecond laser), Clare et al[73] found 8 eyes (0.033%) with flap displacement occurring within 48 hours of the procedure in the microkeratome group and 2 eyes (0.003%) in the femtosecond laser group. The odds ratio of developing a displaced flap in the microkeratome group was 10.53 times higher than in the femtosecond laser group ($P < 0.005$). Binder[67] reported 2 cases of flap displacement in 103 consecutive eyes. Chang[46] reported 1 case of flap displacement and 4 cases of ingrowth in 3009 eyes. Sutton and Hodge[43] reported no cases of ingrowth in 1000 consecutive

eyes, but reported 4 displaced flaps. Sanchez-Pina et al[33] reported 1 case of epithelial ingrowth in 485 eyes. Letko et al[74] retrospectively compared the incidence of epithelial ingrowth in IntraLase femtosecond laser flaps with a mechanical microkeratome. In the mechanical microkeratome group, 11 of 132 eyes developed ingrowth, compared with 2 of 140 in the IntraLase femtosecond laser group. Kamburoglu and Ertan[75] compared the incidence of epithelial ingrowth in primary IntraLase femtosecond laser cases with IntraLase femtosecond laser enhancement cases. In the primary group, 2 eyes of 6415 developed ingrowth compared with 2 eyes of 108 in the enhancement group.

Development of DLK remains an important complication after LASIK procedures.[25,26,57,76] Although DLK may be multifactorial, femtosecond lasers may play a causative role because of the increased energy delivered to the corneal stroma. Kim et al[57] noted a greater incidence of inflammatory cell infiltration in the corneas of the femtosecond laser–treated group than the group treated with a mechanical microkeratome in a rabbit population at 4 and 24 hours after LASIK. Three articles specifically reference a higher incidence of DLK/inflammation with the femtosecond laser compared with a mechanical microkeratome. Gil-Cazorla et al[76] compared the incidence of DLK in 1000 eyes that underwent LASIK with the Moria microkeratome or the 15-kHz IntraLase femtosecond laser. In the Moria group, 1 eye of 1000 developed stage 2 DLK, compared with 5 eyes of 1000 in the IntraLase femtosecond laser group. Of the latter, 1 eye was identified at stage 2 and 4 eyes were identified at stage 3. Clinical relevance and visual acuities were not discussed. Haft et al[38] reported 32 cases of DLK in 4722 eyes, the majority of which were at stages 1 and 2. Chang[46] reported 5 cases of DLK in 3009 eyes, of which 1 developed central necrosis and eventual BCVA of 20/25. Chan et al[10] reported a contralateral eye study of 43 patients who underwent LASIK with Hansatome in 1 eye and IntraLase femtosecond laser in the fellow eye. Three patients developed DLK bilaterally, and 7 patients developed DLK in the IntraLase femtosecond laser–treated eye. The DLK was regarded as "trace," and all cases resolved by the 1-week visit without further intervention and without any effect on visual acuity (level II evidence).

Javaloy et al[25] used confocal microscopy to conduct a quantitative analysis of flaps made by a Moria M2 mechanical microkeratome compared with flaps made by a 15-kHz IntraLase femtosecond laser. The investigators found a higher wound-healing opacity index for the femtosecond laser group and attributed this to 2 factors: (1) thinner flaps created with the IntraLase femtosecond laser versus M2 microkeratome and (2) a greater degree of inflammation observed in the IntraLase femtosecond laser group as demonstrated by a higher incidence of DLK, which produced a greater activation of the anterior keratocyte population. Despite the higher keratocyte activation in the IntraLase femtosecond laser group, the clinical results were statistically better in the femtosecond laser–treated eyes than in the M2 group at 1 and 3 months after LASIK in terms of UCVA and BCVA. Patel et al[6] also used confocal microscopy to assess activation of keratocytes after LASIK performed with a Hansatome mechanical microkeratome compared with an IntraLase femtosecond laser. With the use of the ConfoScan 3 or ConfoScan 4 confocal microscope (Nidek Technologies Srl, Vigonza, Italy) or the tandem scanning confocal microscope, confocal microscopy qualitatively showed more activated keratocytes in images centered at the interface early after bladeless LASIK than after LASIK with microkeratomes (level I evidence). McCulley and Petroll[77] found similar activation of keratocytes in 15-, 30-, and 60-kHz generations of IntraLase femtosecond lasers. Choe et al[52] found rates of DLK (10%–14%) in these generations of IntraLase femtosecond lasers. The DLK was mostly milder stage 1 or 2, but visual acuity data were reported only up to 1 week after surgery.

Two studies (level II evidence) selected for this review focused on dry eye as a comparative outcome measure. Golas and Manche[21] randomized 51 patients to wavefront-guided microkeratome-based LASIK in 1 eye and a femtosecond-based flap in the fellow eye. According to a dry eye questionnaire, there was no statistically significant difference between the groups noted. Salomao et al[20] compared the incidence of LASIK-associated dry eyes after flap creation with a Hansatome mechanical microkeratome and an IntraLase femtosecond laser at 1 month after surgery. As an inclusion criterion, no patient had signs, symptoms, or treatment for dry eye before surgery. The investigators found the incidence of LASIK-associated dry eye to be statistically significantly higher in the microkeratome group (46%) than in the femtosecond group (8%), as was the need for cyclosporine A treatment (24% vs. 7%, respectively) after surgery. The authors postulated that, in addition to neurotrophic effects from corneal nerve cutting, other factors may be important, because no correlation was found between flap thickness (or ablation depth) and the incidence of LASIK-induced dry eye. This may include increased goblet-cell injury with mechanical keratomes, although the suction time was generally less than that for femtosecond laser flaps.

Patel et al[7] found no difference in corneal sensitivity measured by gas esthesiometry when comparing a 15-kHz IntraLase femtosecond laser with a Hansatome microkeratome. Sensation was normalized by 3 months after surgery (level I evidence). Mian et al[12] reported that after using a 30- or 60-kHz IntraLase femtosecond laser, dry eye syndrome and reduced corneal sensation (as measured by Cochet-Bonnet esthesiometry, Luneau SAS, Chartres, France) presented at mild levels and improved at 3 months after surgery, with no effect on flap-hinge position, hinge angle, or thickness (level II evidence). Most patients had mild dry eye symptoms overall, possibly representing an initial selection bias, and by 6 months all parameters measured (tear-breakup time, corneal/conjunctival staining, Schirmer score, and the Ocular Surface Disease Index questionnaire) had reached or neared the levels before surgery.

Conclusions and Future Research

The preponderance of evidence to date suggests that femtosecond lasers create LASIK flaps at least as well as, if not better than, mechanical microkeratomes and that accompanying LASIK procedures have generally good outcomes.

This is not to suggest that mechanical microkeratome–based LASIK is unsafe or needs be abandoned because multiple studies, including reviews by this panel,[78,79] have concluded that those devices provide acceptable outcomes for LASIK. This review is not intended to assess the cost-effectiveness of femtosecond lasers for LASIK because that is a decision best left to individual surgeons, centers, and market forces.

Inevitably, as femtosecond laser devices evolve, there will be further refinements and changes to techniques. Current generations of these instruments are being used to perform the complete refractive procedure by extracting a lenticule of tissue, obviating the need for the excimer laser.[80] Alternatively, modulation of the corneal shape or index of refraction may ultimately be possible with no removal of tissue.[81] Finally, femtosecond lasers are now moving beyond corneal applications and are being applied to intraocular surgery.

As with many assessments of new devices, available evidence spans multiple generations of the technology in question, including several devices from different manufacturers. The literature instills a publication bias into this assessment because the majority of studies were performed with a single femtosecond laser platform, and after-market surveillance of other femtosecond laser platforms is needed. It may be inappropriate to conclude that all femtosecond lasers are equally efficacious, particularly with those laser platforms that have minimal or no reported clinical experience. Also, multiple excimer-laser platforms were used in the studies reviewed, and this may be an important variable that could have influenced the outcomes reported. Grouping of these data, although convenient for assessments such as this, is thus not necessarily appropriate, and further long-term studies are needed on visual acuity, dry eye syndrome, enhancement rates, contrast sensitivity, patient satisfaction, complication rates, and differences in outcomes between the devices.

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[1] Brighton Vision Center, Brighton, Michigan.

[2] Ophthalmology and Visual Sciences, W.K. Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan.

[3] University of California, San Francisco, California; Global Medical Director Optical Express; Gordon-Weiss-Schanzlin Vision Institute, San Diego, California.

[4] Chicago Cornea Consultants Ltd., Chicago, Illinois.

[5] Gordon-Weiss-Schanzlin Vision Institute, San Diego, California.

[6] Center for Excellence in Eye Care, Miami, Florida.

[7] Ophthalmology Clinic, Naval Medical Center, San Diego, California.

[8] Bascom Palmer Eye Institute of Plantation, Plantation, Florida.

[9] Institute of Vision and Optics (IVO), Faculty of Medicine, University of Crete, Heraklion, Crete, Greece.

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Correspondence:
Nancy Collins, American Academy of Ophthalmology, Quality Care and Knowledge Base Development, PO Box 7424, San Francisco, CA 94120-7424. E-mail: ncollins@aao.org.