Review Article

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# Femtosecond lasers for eye surgery applications: historical overview and modern low pulse energy concepts

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**Abstract:** This review provides an overview of the historical development and modern applications of femtosecond (fs) lasers in ophthalmology, with a focus on the optical concepts involved. fs-Laser technology is unique because it allows very precise cutting inside the eye through optically transparent tissue, without a need for any mechanical openings. fs-Lasers were historically first used for refractive cornea surgery, later also for therapeutic cornea procedures and lens surgery. Further new areas of ophthalmic application are under development. The latest laser system concept is low pulse energy and high pulse frequency: by using larger numerical aperture focusing optics, the pulse energy required for optical breakdown decreases, and athermal tissue cutting with minimal side effects is enabled.

**Keywords:** ablation of tissue; laser-induced breakdown; laser materials processing; ophthalmic optics and devices; ultrafast lasers; visual optics, refractive surgery.

## 1 Introduction

Medical laser technology over the past 40 years was heavily influenced by ophthalmic surgery applications, and vice versa. The optically transparent structures of the eye, cornea, lens, and vitreous body, make delivery of the laser energy at visible and near infrared (NIR) wavelengths at different focal depths much easier than other tissue types in the body, thereby giving access to surgical interventions without having to open or mechanically enter the eye (Figure 1). Different types of lasers, with various wavelengths, pulse durations and power levels interact with eye tissues in a range of ways. For example, continuous or long-pulse green light is used for local thermal spot coagulation at the retina, while ns-pulses of UV light serve for highly accurate surface ablation of tissue, e.g. for reshaping the cornea surface. A broader overview and more details of these laser–tissue interaction mechanisms are given in excellent quality in several text books [1, 2].

This review article focuses on ultrashort-pulse NIR lasers. It provides an overview of the technology history of femtosecond lasers for ophthalmology as well as associated optical technologies like OCT imaging, and describes modern optical concepts in depth. It also provides a brief overview of medical procedures, particularly in vision correction (refractive) surgery. The medical application history and details of the ophthalmic surgical methods involving fs laser use were already covered in more detail in another recent review paper [3].

## 2 Solid-state laser technology in ophthalmology

### 2.1 Nd:YAG laser with ns pulse durations

The first type of short-pulsed laser successfully used in ophthalmology were the Q-switched Nd:YAG solid-state lasers. They operate at near infrared (1064 nm) or visible (532 nm) wavelengths, where important structures of the eye (cornea, lens, and vitreous body) are highly transparent. Their pulse durations are a few nanoseconds (ns), and for ophthalmic applications pulse energies in the range of 0.3–10 mJ are typically used [4].

When Nd:YAG laser pulses are strongly focused at a location inside the eye, to spot sizes of a few microns, the combination with short pulse durations creates very high intensities at the laser focus, above $10^{11}$ W/cm$^2$. Under these conditions, a phenomenon called ‘optical breakdown’ occurs. In the first step, multi-photon absorption leads to

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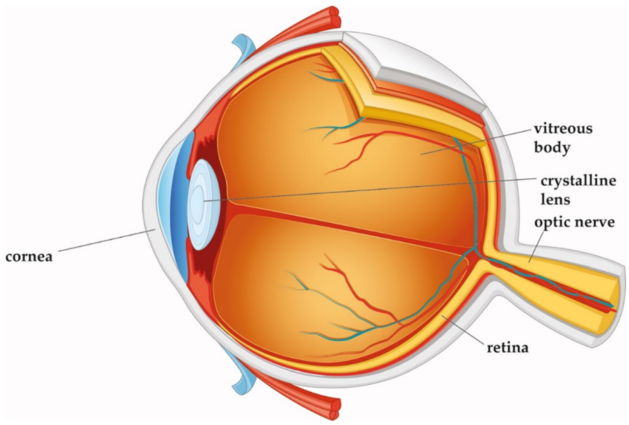



**Figure 1:** Cross-section of the eye. Cornea, crystalline lens, and vitreous body are transparent in the healthy eye. Copyright© Dardenne Clinic.

ionization of some tissue molecules, creating free electrons. In the subsequent second step, these 'seed' electrons absorb photon energy and are thus accelerated. After repeated photon absorptions, electrons reach a sufficiently high kinetic energy to ionize more molecules by impact ionization, creating more free electrons. If the laser irradiation is intense enough to overcome electron losses, an avalanche effect occurs [2].

When the extremely fast rising electron density exceeds values of approximately $10^{20}/cm^3$, a plasma state of matter (cloud of ions and free electrons) is created at the laser focus [2]. This plasma is highly absorbing for photons of all wavelengths. Therefore, the rest of the laser pulse is mostly absorbed by the plasma, increasing its temperature and energy density (Figure 2).

The hot plasma rapidly recombines to a heated gas, with a thermalization time of the energy initially carried by free electrons of a few picoseconds (ps) to tens of ps [5]. This time is much shorter than the acoustic transit time from the center of the focus to the periphery of the plasma volume, leading to confinement of the thermoelastic stresses caused by the temperature rise. Conservation of momentum requires the stress wave emitted in this geometrical configuration to contain both compressive and tensile components [5]. If sufficient pulse energy density is applied, the tensile stress wave becomes strong enough to induce fracture of the tissue, causing the formation of a cavitation bubble [5]. Depending on the pulse energy, the pressure wave can reach supersonic speed (shock wave). The high plasma temperature also leads to almost immediate evaporation of the tissue within the focal volume, generating water vapor and gases like $H_2$, $O_2$, methane, and ethane [6]. The resulting gas pressure pushes the surrounding tissue further away (Figure 2). The maximum volume temporarily achieved by the bubble scales with the pulse energy above the threshold for laser-induced optical breakdown (LIOB). During bubble expansion, the internal pressure ultimately can drop below atmospheric pressure due to the outward moving material's inertia, resulting in the bubble dynamically collapsing. The bubble collapse may create another shock wave [2]. All these effects together are often referred to as "photodisruption" of tissue.

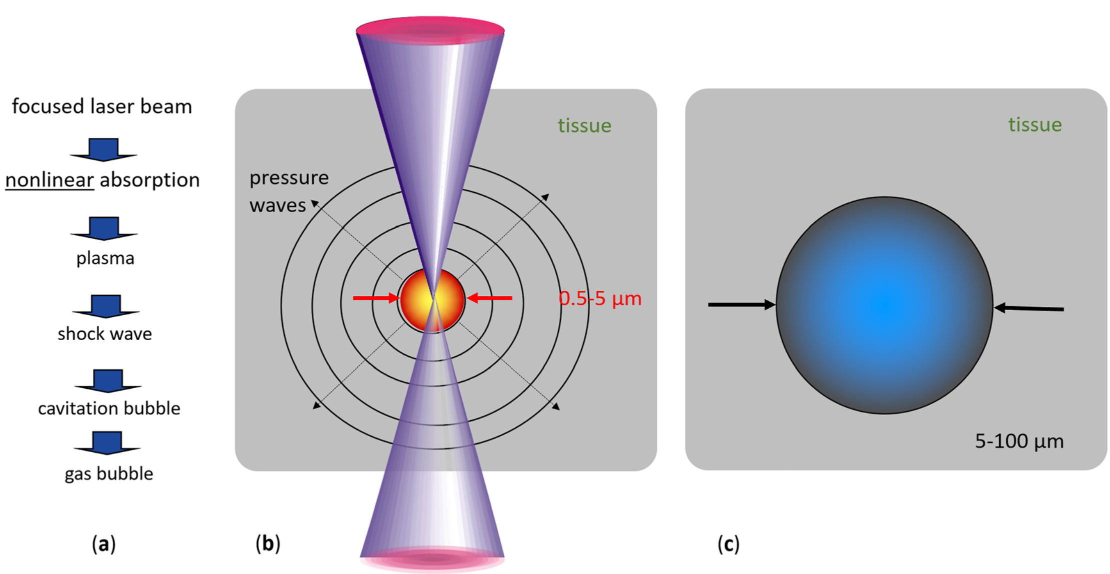



**Figure 2:** fs Pulse laser effects in tissue: (a) sequence of events, (b) plasma diameter range (red) and emitted pressure wave pattern (circles), and (c) range of possible cavitation bubble dimensions (pulse energy dependent) [11].

With typical ophthalmic Nd:YAG laser pulse energies, cavitation bubble radii are in the range of 1000–2000 µm, and shock wave amplitudes at 1 mm distance from the focus reach 100–500 bar [7]. These rather pronounced mechanical side-effects restrict the use of Nd:YAG lasers. When shorter pulse ps ($10^{-12}$ s) lasers became available, their mechanical side-effects proved to be smaller, but still too large for delicate tasks as required for many ophthalmic applications. This limits Nd:YAG laser application in clinical ophthalmology [3].

## 2.2 Femtosecond lasers

Femtosecond (fs: $10^{-15}$ s) lasers are a more recent advance in solid-state laser technology. They operate at near-infrared wavelengths similar to Nd:YAG lasers but at pulse durations of less than 1 ps. As the threshold radiant exposure (J/cm$^2$) for inducing LIOB in tissue is about two orders of magnitude lower in the fs pulse duration regime than at 10 ns [8], much lower pulse energies can be applied to separate tissue. High pulse frequencies from 15 kHz up to even MHz are then used to create continuous cut planes inside the tissue by placing many pulses close to each other with three-dimensional beam scanning systems.

The lower pulse energies lead to a drastic reduction of the mechanical side effects of the LIOB. For 300 fs pulses of 0.75 µJ energy, the generated cavitation bubbles have radii of only 45 µm in water, which is almost two orders of magnitude smaller than for ns pulses with energies in the mJ range [9]. Also, the associated pressure waves are much weaker, 1–5 bar at 1 mm distance [10] (Figure 2). This process is referred to as “plasma-induced ablation”, as the disruptive mechanical side effects of ns pulses described above are absent. Also, the thermal side effects of fs pulses in tissue are almost negligible [2].

## 2.3 Modern low pulse energy high pulse frequency fs lasers

Early fs lasers for ophthalmic surgery used relatively high pulse energies of about 10 µJ [12, 13]. In order to further reduce pulse energies and accompanying side effects at a given wavelength, two process parameters can be optimized:

First, by shortening the pulse duration: the latest fs lasers can achieve pulse durations of 200–300 fs, while earlier models had pulse durations of up to 800 fs.

Second, by reducing the focal spot size: the focal volume of a Gaussian laser beam is dependent on the axial extension, the so-called Rayleigh range ($z_R = \pi w_0{}^2/\lambda$) and the beam waist $w_0 = f\lambda/\pi w_L$, where $f$ is the focal length of the lens, $w_0$ the beam radius at the focus, and $w_L$ the beam radius at the focusing lens. In other words, the focal volume varies inversely with the cube of the numerical aperture NA = $w_L/f$ of the focusing optics (Figure 3). The larger the numerical aperture NA, the smaller the focal spot and finally, the smaller the energy threshold for LIOB [14].

To practically increase the NA, either the lens diameter of the focusing optics can be increased, which quickly leads to bulky and over-proportionally expensive optics at higher NAs, or the focusing optics can be positioned closer to the eye. The first approach was introduced by IntraLase™ in 2003 to the market and is still used by the majority of laser systems. Ziemer Ophthalmic Systems implemented the latter approach, bringing smaller laser focusing optics closer to the eye. This was achieved using a microscope lens with a short focal length as focusing optics. Using this approach pulse energies could be reduced by more than a factor of 10. Guiding the laser beam via an articulated mirror arm to a handpiece containing the focusing optics enabled a compact device design. The handpiece made it possible to use the laser under a surgical microscope without the need to move the patient during the surgery.

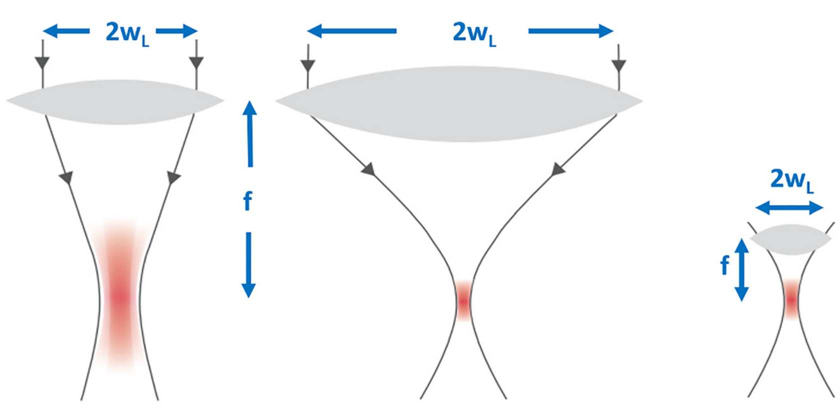



**Figure 3:** The focal volume of a Gaussian laser beam scales inversely to the cube of the numerical aperture NA = $w_L/f$ of the focusing lens. The larger the NA, the smaller the focal spot volume. Copyright© Ziemer Ophthalmic Systems.

First systems designed for corneal surgery were released to the market in 2007. Overall, the system was more compact and lightweight as conventional systems. Integrated wheels enabled mobile use in different buildings and transport between clinics in a small van.

## 3 Femtosecond laser-tissue interaction

The ultrashort pulse laser-tissue interaction process regime is determined by seven key laser parameters:

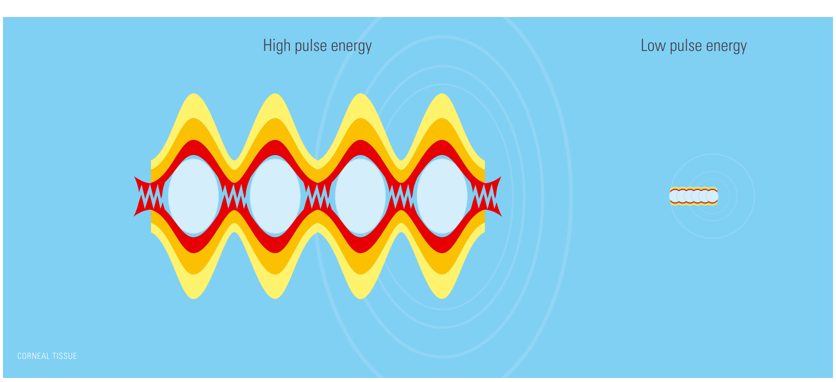
- Pulse energy
- Pulse repetition rate
- Pulse duration
- Wavelength
- Focusing power (NA of the focusing optics)
- Focus spot shape (Gaussian or other, more or less aberration-free)
- Spatial pulse spacing (pulse raster and scan patterns)

Based on the above laser parameters, the nature of the cutting processes of the two groups of fs lasers differs. In the high pulse energy laser group, the cutting process is driven by mechanical forces applied by the expanding bubbles. The bubbles disrupt the tissue at a larger radius than the plasma created at the laser focus (Figure 4a). On the other hand, in the low pulse energy group, spot separations smaller than the spot sizes are used for spatially overlapping plasma interaction regions. Evaporation of the tissue inside the plasma volume effectively separates tissue without a need for secondary mechanical tearing effects (Figure 4b). When in addition high pulse frequencies are applied (MHz range), the effective cutting speeds achieved are similar to the high energy laser group.

The benefit of tissue cuts achieved by overlapping plasma interaction zones with low energy pulses is a uniquely smooth surface, with virtually no damage to the adjacent tissue [15]. This is particularly important for the quality of cuts in the human cornea for refractive eye surgery, such as so-called “flaps” and lenticular cuts (see Chapter 4 below). Also for the cutting of other delicate eye tissues in cataract surgery and therapeutic cornea surgery this regime is beneficial – see [3] for more details. High energy pulses with low pulse frequency, on the other hand, rely partially on mechanical tearing for tissue separation in between the actual laser foci. This tearing is accompanied by more stress or potentially even damage to the adjacent tissue [16], as shown by the levels of stress hormones detected after laser treatments [17].

In general, only the fraction of energy within a laser pulse that is actually absorbed inside the tissue is responsible for interactions with tissue. Using the nomenclature of Vogel et al. [18] and including the terms linear absorbed energy and subthreshold material modification, the following diagram (Figure 5) depicts the energy redistribution of the emitted laser energy of a surgical laser device at the end of the tissue dissection process. Only nonlinear absorbed energy contributes to the tissue dissection process. This portion of the emitted energy is approximately 10–25% for fs pulses, but depends highly on the actual process parameters [18].

As the linear absorption of the IR wavelengths (1030–1060 nm) used in clinical fs lasers in transparent eye tissues is very low, on the order of 0.1 $cm^{-1}$ [8], the initial part of a laser pulse is mostly transmitted until the irradiance threshold for LIOB is reached in the center of the focus. For pulse energies only slightly above the threshold, more than 50% of the incident energy can be transmitted beyond the focus [18], as a divergent beam with rapidly decreasing irradiance (thus dissipating harmlessly). In




(a) (b)

**Figure 4:** a) High pulse energy, low pulse frequency (large spot separation). The color gradings symbolize the strain levels in the tissue surrounding the induced bubbles; b) low pulse energy, high pulse frequency (small spot separation, overlapping plasma interaction zones). Copyright© Ziemer Ophthalmic Systems.

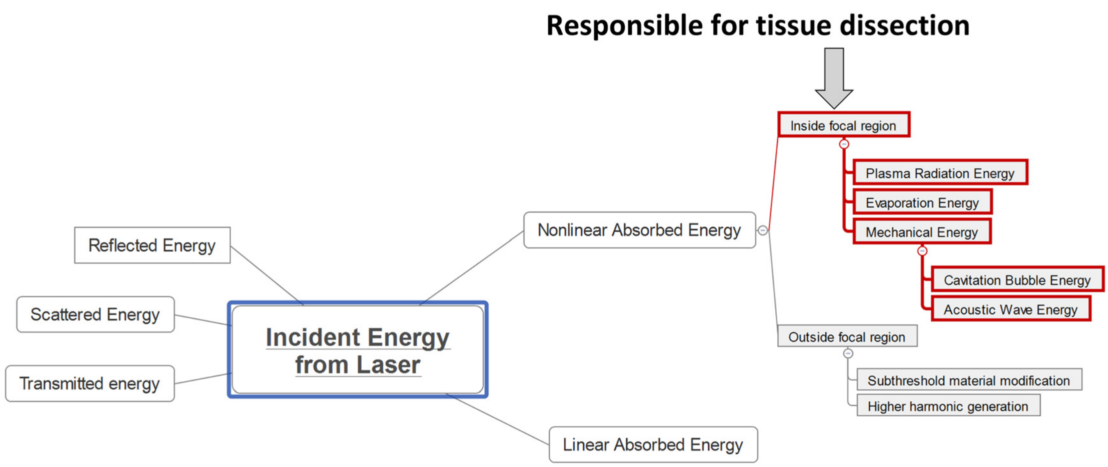



**Figure 5:** Redistribution of energy in a pulsed laser process for tissue dissection. Copyright© Ziemer Ophthalmic Systems.

practical ophthalmic use, scattering and absorption of the laser radiation by somewhat opaque tissue can also reduce the amount of energy reaching the laser focus. For example, laser cutting the cornea at locations with scars requires higher pulse energies than in normal clear cornea. The energy losses depend on the thickness of the scattering material that the laser light is traveling through before reaching the focus. Therefore, the energy loss is more severe when cutting through a several mm thick cataract lens nucleus than through corneal scars, which are only fractions of 1 mm thick, and can reach double-digit percentages of the incident energy.

fs Laser pulses with energies moderately above the LIOB threshold, the generated plasma reaches only a much lower density than with high energy pulses [8]. Thus, the thermal energy transferred to the nearby tissue after each laser pulse is correspondingly very low. This in combination with the low linear absorption leads to an overall process that can be considered as non-thermal. Visible tissue modifications that could be attributed to a thermal interaction are limited to the outermost surface of a cut with an extent of less than one micron (i.e. smaller than a cell) [2]. This is in contrast to other laser-tissue interaction regimes, where thermal effects are either intended or present although unwanted. In those regimes, the applied laser dose can be an appropriate quantity to characterize the laser process. As can be appreciated from Figure 5, the emitted or incident energy in terms of an overall dose insufficiently characterizes fs laser tissue interaction. This holds true for both low and high energy regimes. To the best of our knowledge and after 20 years of clinical use and research, there are no reports of clinically relevant thermal side effects of the use of fs lasers.

More important than an overall dose are process parameters that contribute to mechanical effects. First and predominantly, the part of the pulse energy which directly contributes to cavitation bubble energy and shock waves (which can have effects at some distance away from the laser focus) [18]. In contrast to thermal effects, which are negligible, the fs process regime (i.e. low vs high pulse energies) changes the mechanical impact on tissue layers adjacent to the cut. In a comparative study of nJ and μJ pulse energy fs-laser cutting of cornea [15], it was shown that the lower pulse energy regime avoided cell damage and reduced inflammation reactions in the adjacent stroma tissue.

In modern versatile ophthalmic fs-laser systems, a large range of pulse energies is available, so that adapted amounts of pulse energy can be used for each tissue type and geometry. By using just the required amount of pulse energy, not more, the mechanical side effects described above as well as gas production are minimized.

## 4 Supporting technology needed in ophthalmic fs-laser systems

To achieve practical fs-laser systems for clinical use, some critical supporting technologies need to be developed as well. Most notable is the patient interface system that connects the eye via suction to the laser beam delivery system and ensures a stable relative position during treatment. Further laser beam scanning technologies have to be applied, and finally imaging of tissue structures is required in order to place cuts at a desired location.

## 4.1 Patient interface systems

For some laser systems, the patient's head is placed under a gantry containing focusing optics. A sufficiently long working distance is required to allow the patient's head to move in and out. Either the gantry has to move for docking, or the patient support device. In other systems, an articulated arm with a handpiece with focusing optics at its end is used. Due to the flexible arm, the optics can be moved very close to the eye (Figure 6). The patient is kept stationary during docking.

The actual eye contact is established via sterile, single-use parts, called "patient interfaces". Two different types are in use: applanating interfaces with a curved or flat interface directly contacting the cornea or so-called liquid-optics interfaces, where a vacuum ring creates contact to the sclera or the outer cornea, and the center is filled with liquid. The liquid-optics interfaces allow laser energy transmission while leaving the cornea in its natural shape (Figure 7) [19]. They are mainly used in cataract surgery applications (see Chapter 6 below). Applanating interfaces very effectively stabilize the cornea position during surgery through mechanical contact. They are slightly more invasive, and used mostly in refractive surgery applications, where maximum precision of intracorneal cut positions is of key importance (see Chapter 4).

The stability of the docking contact during laser emission is of primordial importance. Loss of contact harbors the risk of cutting in wrong planes. Therefore, all lasers are designed to automatically monitor vacuum levels, sometimes complemented with imaging of the eye position (eye tracking), and to immediately stop laser emission

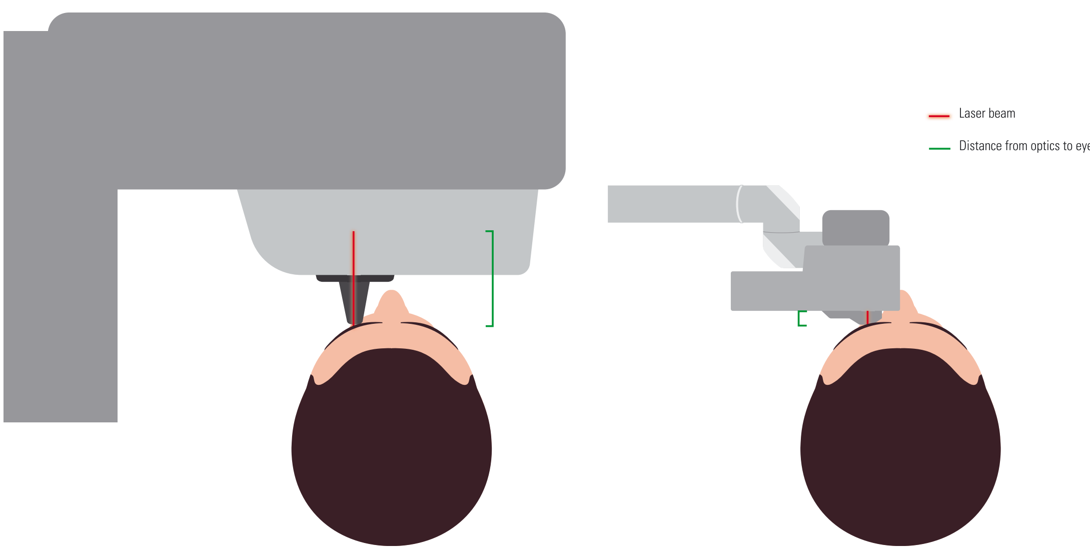



**Figure 6:** Typical eye docking methods of fs lasers (a) head under laser gantry, long distance from optics to (b) articulated arm with handpiece placed onto the eye, very short distance from optics to eye; green markings indicate working distance of laser optics. Copyright© Ziemer Ophthalmic Systems.

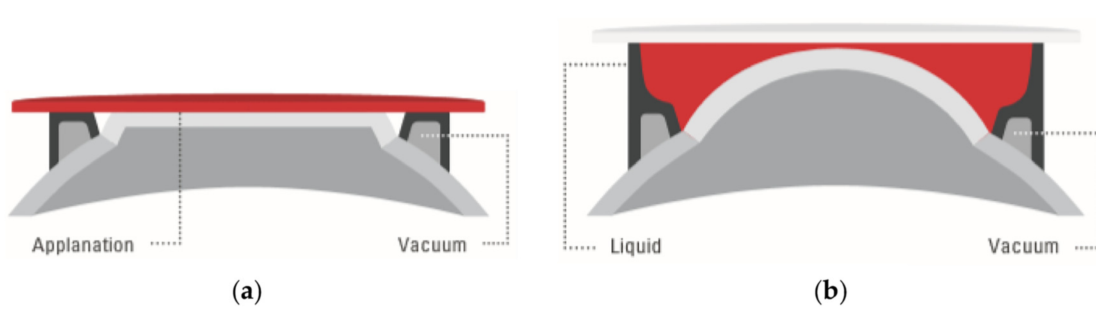



**Figure 7:** Typical patient interface designs: (a) contact interface in direct touch with the cornea (flat). (b) Liquid optics interface, no direct touch on the cornea, no deformation. Copyright© Ziemer Ophthalmic Systems.

upon loss of contact. Of course, the eye surgeons also monitor their patients during the procedure. In case of laser systems with an articulated arm, the surgeons can also use their manual skills to actively stabilize the laser handpiece while in contact with the eye. This can prevent vacuum loss when patients move unintentionally during surgery. In any case, after a vacuum loss the treatment can usually be resumed immediately after a new docking.

## 4.2 OCT and alternative imaging technology

In addition to integrated camera systems that provide a frontal view of the eye, some laser systems provide depth ranging. Optical coherence tomography (OCT) is an optical technology allowing to image structures inside tissues, similar to ultrasound, but with a near microscopic resolution of 5–20 μm [20, 21].

The first application of OCT for biological purposes was described by Adolf Fercher et al. for the *in vitro* measurement of the eye's axial length in 1988 [22]. The early clinical OCT systems used time domain (TD) OCT technology, where the length of the reference arm of an interferometer is mechanically changed. Due to speed limits of this process, these early devices were limited to 1D scans (A-scans), or later small 2D scans consuming a lot of time. The frequency-domain OCT (FD-OCT, also known as "Fourier domain") technology meant a technological breakthrough: it used a fixed reference arm length but a spectrometer with a linear detector array instead of a single detector. Optical path length differences between the interferometer arms in this case produce a periodic modulation in the interference spectrum. By Fourier transformation, entire A-scans can be retrieved from the measured spectrum at the frame rate of the detector array [2]. FD-OCT enabled much higher scan speeds, making 2D- and even 3D-imaging feasible in routine clinical use. The first ophthalmic application of FD-OCT was published in 2002 [23].

Later, a variation of frequency-domain OCT technology was developed, "swept-source" (SS) OCT. In this case, a tunable light source with a frequency sweep indicated by a saw-tooth frequency profile over time is used in combination with a fast single-pixel detector instead of a spectrometer. As FD-OCT, SS-OCT can achieve shot-noise limited resolution with the advantage of larger measurement ranges. Further details of OCT technology, and advantages and limitations of its different versions, exceed the scope of this review, but can be found in Chapter 7.3 of the textbook by Kaschke et al. [2].

The initial ophthalmic use of OCT was exclusively for retinal imaging. Starting in 1994, the technology was also developed for imaging the anterior segment of the eye [24]. The possibility of quickly creating high-resolution cross-section images of the cornea, anterior chamber, and lens was a prerequisite for practical cataract surgery laser systems. Imaging and OCT guided surgery was first envisioned by Zeiss and first demonstrated for imaging guided femtosecond laser surgery by H. Lubatschowski et al. [25].

In most modern cataract fs-laser systems, 3D OCT scans are performed after docking the laser interface to the eye. The LENSAR™ system uses a different technology, a 3D confocal structured illumination combined with Scheimpflug imaging [26, 27].

Scheimpflug imaging uses a tilted arrangement of object and image planes, with the imaging lens positioned in between at an appropriate angle. Combined with a slit illumination, it allows the simultaneous sharp imaging of a section of tissue at different depths of the anterior segment of the eye, i.e. imaging of cornea and lens simultaneously. With rotation of this imaging setup around the optical axis of the eye and software processing of the resulting images, a 3D image of the entire anterior segment can be achieved [2]. This principle was first described by Theodor Scheimpflug in 1904. The first commercial medical Scheimpflug camera was the Topcon SL-45, the first rotating video version with electronic image analysis was the Zeiss SLC [2]. Today the principle is routinely used in many diagnostic eye imaging

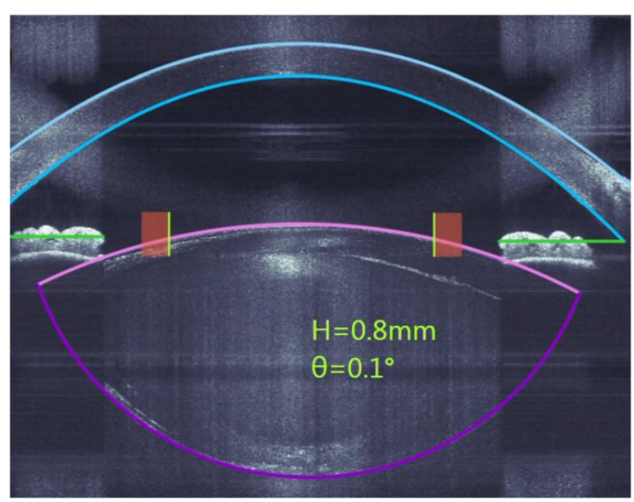



**Figure 8:** Example of the OCT-guided placement of an fs laser cut pattern for cataract surgery: blue: corneal anterior and posterior surface, pink and purple: lens anterior and posterior surface, green: iris plane, yellow: capsulotomy cut, brown: safety margins to iris. Copyright© Ziemer Ophthalmic Systems.

devices, such as cornea topographers, as well. Scheimpflug technology has limitations in accuracy, in particular with respect to visualization of tissue boundaries in the context of decreased transparency (i.e. corneal scars). However, it is possible to estimate the density of the lens based on measured local light scattering and to adapt the lens fragmentation pattern accordingly [28].

Independent of Scheimpflug or OCT technology, the resulting images are then analyzed by image processing software, identifying the tissue boundaries of interest [29]. These are notably the anterior and posterior sides of the cornea, the anterior and posterior surfaces of the lens, and the iris. This information is used to automatically propose the suitable positions inside the eye for the planned laser cuts, which are also displayed on screen for checking and confirmation by the eye surgeon (Figure 8).

### 4.3 Scanning technology

In order to achieve a medically desired cut pattern inside the eye, the individual laser spots need to be arranged in suitable geometrical patterns. The calculation of such patterns is achieved by software, which also controls the scanning systems to position the laser foci in lines, planes, or even 3D geometries. Optical scanning of the laser focus in two dimensions can be achieved by galvanometer-driven scanning mirrors, combined with another mechanism to change focus position along the beam axis. Alternatively, 3D positioning of the focus by mechanical displacement of focusing optics with a reduced field diameter, combined with a fast micro-scanning technology, is also used.

An example of a cut pattern used for cornea flap cutting (see Chapter 4.1 below) is shown in Figure 9.

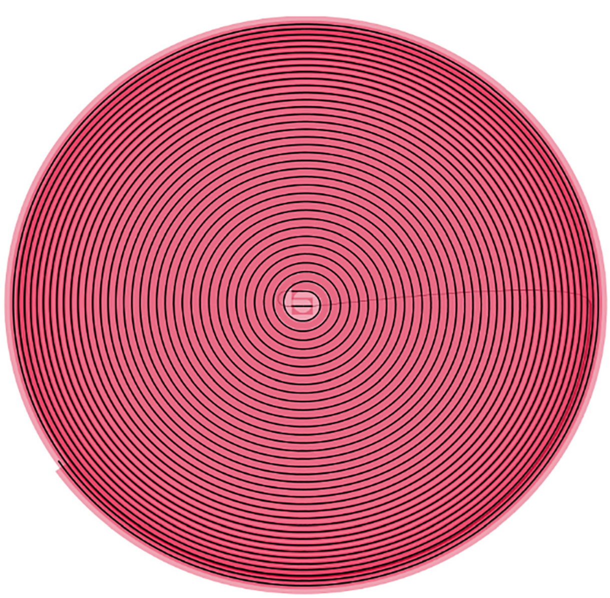


**Figure 9:** Laser focus scan pattern used for cornea "flap" cutting during refractive LASIK surgery. Copyright© Ziemer Ophthalmic Systems.

## 5 Clinical applications history

The first reported ophthalmic use of short pulse lasers at near-IR wavelengths was in 1979 by Aron-Rosa, who treated posterior capsule opacification (PCO) after cataract surgery [30]. In 1989, Stern et al. demonstrated that by decreasing pulse width of ultrashort-pulsed lasers from nano- to femtoseconds, ablation profiles showed higher precision and less collateral damage [31]. At the same time, optical coherence tomography developed and provided non-invasive 3D *in vivo* imaging with fine resolution in both lateral and axial dimensions at a micrometer level [32]. These developments offered ophthalmic surgeons a tool for high precision cutting and visual control through imaging and ultimately allowed a gamut of treatment applications for such lasers within the field of ophthalmology. Improvements of the laser focusing optics with higher numerical apertures and higher pulse frequencies of the laser sources have further decreased collateral damage while increasing precision.

The first FDA approved clinical fs-laser system for ophthalmology, the IntraLase™ FS, was launched in 2003 [12]. It was used for corneal cuts in laser *in situ* keratomileusis (LASIK), a refractive surgery (see Chapter 4.1 below), and replaced mechanical cutting devices called microkeratomes. Its first commercial version operated at a 15-kHz pulse frequency and pulse energies of several µJ [13]. Further fs-laser systems for corneal surgeries were launched by multiple manufacturers in the following years. In 2007, the Ziemer FEMTO LDV™ first introduced a new low pulse energy and high pulse frequencies approach.

In 2009, the LensX™ system was introduced, the first commercial fs-laser designed for cataract surgery, thus opening another sector of ophthalmic fs-laser application [33]. Initial versions operated at 33 kHz pulse frequency and pulse energies of 6–15 µJ [34]. LensX became part of Alcon, and again, in the following years, multiple other manufacturers launched similar products. In 2014, the first low pulse energy fs laser system for cataract and cornea surgery, the Ziemer FEMTO LDV Z8™, was introduced to the market. See Latz et al. [3] for more detailed history.

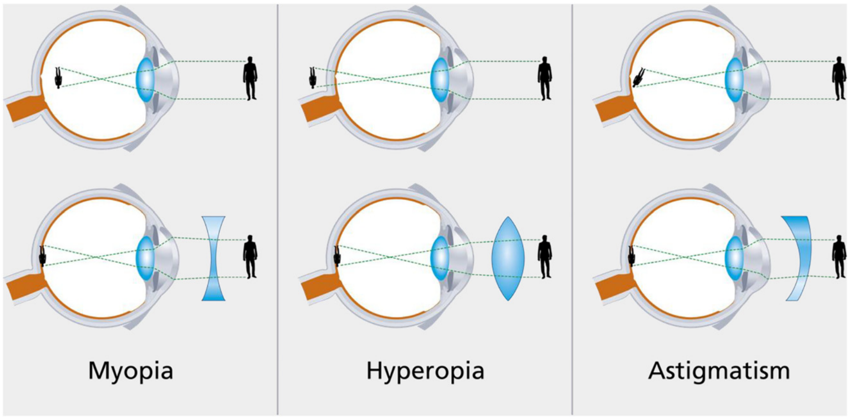



**Figure 10:** Illustration of different types of refractive error and their correction with lenses. Corneal refractive surgery changes the shape of the cornea according to the corrective lenses. Copyright© Dardenne Clinic.

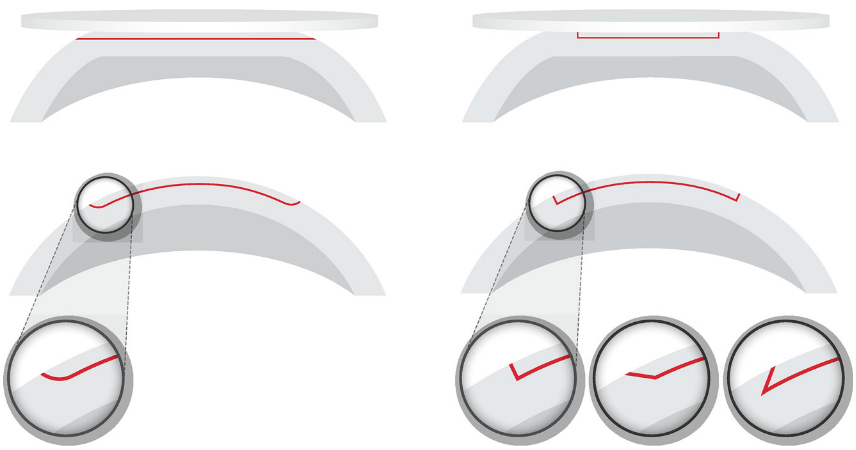


**Figure 11:** Corneal flaps cut by fs-laser: (a) straight plane (red) with continuously curved sides cut during vacuum docking to a flat interface and (b) angulated side cut options (3D cutting geometry). Copyright© Ziemer Ophthalmic Systems.

# 6 Refractive surgery

The human eye functions like the lens of a camera. Images are focused on the retina through a converging system composed mainly of the cornea. If the corneal curvature and thus its refractive power do not precisely match the axial length of the eye, refractive problems like near-sightedness (myopia) or far-sightedness (hyperopia) ensue (Figure 10). Refractive surgery consists of either reducing the refractive power of the cornea (by flattening) or increasing its power (by steepening) or modifying its curvature on a determined meridian to correct astigmatism (cylindrical correction).

## 6.1 fs Flap creation for refractive surgery

In the laser *in situ* keratomileusis (LASIK) procedure, a corneal flap is created. The flap is lifted and then excimer- or solid-state UV-laser energy is used to change the cornea's refractive power by flattening or steepening the stromal bed. Later, the flap is repositioned. Before the advent of fs-laser technology, the flap was created using mechanical devices called microkeratomes. With fs-laser technology, the flap can be completed in various patterns (Figure 11). Kezirian et al. compared fs-(IntraLase™) created flaps to those with two different microkeratomes: they found more predictable flap thickness, better astigmatic neutrality, and decreased epithelial injury in the fs group [35]. Chen et al. confirmed the superiority of fs-laser-created flaps over those cut by microkeratomes. Therefore, in recent years, fs-technology has superseded microkeratomes in preparing flaps for LASIK [36].

## 6.2 Corneal intrastromal pockets and lenticule extraction

Multiple refractive surgery methods use fs-laser cuts to create "pocket"-shaped openings in the cornea, from which material can be either removed or implanted. In both cases, the refractive power of the cornea changes.

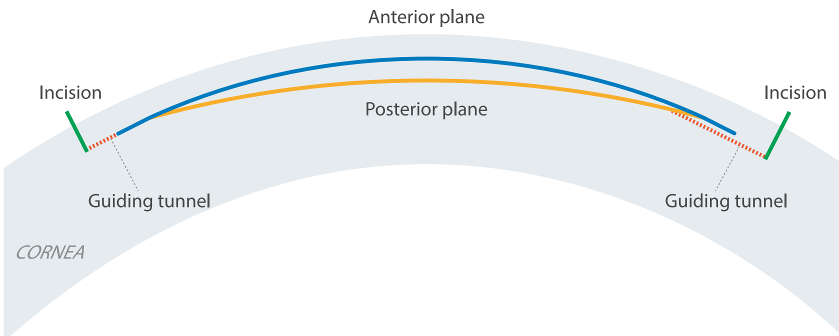



**Figure 12:** Schematic view of intrastromal lenticule cuts performed by fs-laser. The lenticule created between the anterior (blue) and posterior (yellow line) cut planes is extracted by the surgeon via an incision (green line). Optionally, there is a second incision created to help mobilize the lenticule. Copyright© Ziemer Ophthalmic Systems.

While many fs-associated surgical interventions in ophthalmology are merely improvements of pre-existing techniques, corneal stromal lenticule extraction is unique to fs-laser technology: in 1994, C. Swinger and T. Shui described for the first time the concept of a corneal lamellar disc isolated by means of a scanned beam of focused ultra-short laser pulses in a patent application [37]. The first physical implementations of this innovative procedure were developed independently and simultaneously by several groups of scientists in Germany and in the USA, and demonstrated in laboratory experiments and animal studies in 1999 by T. Juhasz' group [38] and by L. Lubatschowsky's group [6, 10, 39].

Clinical trials in partially sighted human eyes were first reported in 2003 [40]. The first clinical version of a lenticule extraction procedure, which used a flap cut like in LASIK which was opened to extract the lenticule from above, was introduced in clinical treatment of refractive surgery patients in 2007 [41] and dubbed "FLEx" (Femtosecond Lenticule Extraction).

A refined version, which uses only a small access tunnel incision instead of opening a flap, was first reported clinically in 2010 [42]. It became known under the brand name 'SMILE' (small incision lenticule extraction) of the Carl Zeiss Meditec AG, and largely replaced FLEx in clinical use. It was initially used to treat myopia only, and after some further development also myopic astigmatism [43]. Later, other companies introduced their own laser systems for similar lenticule procedures under different brand names, including 'SmartSight' by Schwind and 'CLEAR' (corneal lenticule extraction for advanced refractive correction) by Ziemer Ophthalmic Systems AG.

The procedure is a laser refractive technique that uses only a single femtosecond laser system to create a pocket and to dissect a lenticule-shaped piece of tissue inside the corneal stroma. The content of the pocket – the lenticule – is removed via a small access tunnel incision. As a result, the cornea is flattened (see Figure 12). Instead of a side cut of approximately 270 arcuate degrees, as in LASIK, lenticule extraction requires only a small arcuate cut of about 90°. Thereby more of the corneal nerves and Bowman layer remain untouched. In addition, sculpting the lenticule instead of ablating the same amount of tissue requires less laser energy. Therefore, the potential advantages of the lenticule technique over traditional LASIK include reduced iatrogenic dry eye, a biomechanically stronger post-operative cornea with a smaller incision, and reduced laser energy required for refractive corrections [44–49].

However, the lenticule procedures have a steeper learning curve for surgeons. In a study by Titiyal of 100 consecutive cases, lenticule dissection and extraction was the most difficult step with 16% complication incidence in the first 50 cases with the potential for severe complications [50]. Izquierdo recently published a study of five eyes of five patients, who were treated with guided lenticule extraction, where two separate incisions were cut with a low-energy femtosecond laser – one for the anterior plane of the lenticule and one for the posterior plane. This separation allowed for safer identification of the dissection plane and reduced complications [51]. One disadvantage of lenticule extraction is the difficulty of correcting hyperopia, since added curvature and not a flattening procedure is required. Current research is experimenting with decellularizing and preserving extracted lenticules for implantation into corneas that are too thin or not stable enough [52]. In a prospective, randomized paired-eye study, SMILE demonstrated good refractive outcomes in terms of predictability, efficacy, and safety. Since LASIK is reportedly an extremely safe and predictable procedure, it is unlikely to prove superiority of alternative methods [53].

# 7 Corneal surgery – keratoplasty

## 7.1 Full thickness keratoplasty

In keratoplasty (cornea transplantation), a corneal button from a deceased donor is sutured into the recipient cornea, either full thickness ("penetrating keratoplasty") or only anterior or posterior layers of the cornea ("lamellar keratoplasty").

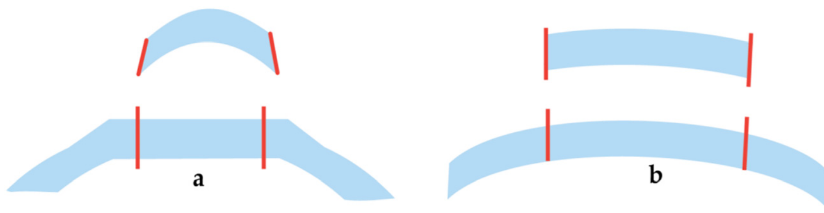



**Figure 13:** Comparison of donor and recipient trephination profiles. (a) Applanation and (b) liquid optic interface. Copyright© Dardenne Clinic.

The leading cause of poor visual outcomes after keratoplasty is induced astigmatism. The better the trephination (cut to separate the corneal button from the cornea) of donor and recipient, the better the fit between the transplant and the recipient, and the lower the astigmatism.

### 7.1.1 Trephination

A perfect trephination system produces a congruent recipient bed and donor buttons and thereby allows well centered tension-free fitting, and efficiently waterproof adapting incision edges [54]. Different trephination systems are currently available: handheld, motor-trephine, excimer- or fs-laser based. Comparison of motor-trephine and excimer-based trephination has shown better alignment of the graft in the recipient bed after excimer laser trephination [55].

It is often problematic to ensure proper centration with trephination in the recipient eye. fs Technology allows for perfect limbal oriented centration through OCT-visualization.

Another problem with trephination is the mechanism by which the recipient eye and donor button are fixated and stabilized: any mechanical impact on the tissue during trephination causes compression and distortion and will decrease the fit of recipient and donor (Figure 13). Common fixation mechanisms include vacuum, applanation, and a combination of both (vacuum suction with applanation). While fs-technology avoids some of the pitfalls of mechanical trephination, comparison of fs- and excimer-assisted trephination showed, nevertheless, superiority of alignment in all sutures-out keratoplasty patients in the excimer group [56].

Different stabilization systems could explain this superiority: while excimer laser-assisted keratoplasty does not require applanation of the cornea, it is needed for the fs-laser used in the cited studies. A new liquid optics interface assisted fs-keratoplasty method developed by Ziemer could solve this problem: here, cutting both recipient and donor is achieved within a liquid interface, which leaves the curvature of the cornea undisturbed. This reduces shear- and compression artifacts in the tissue and improves congruent fitting of the recipient and donor [57]. It will, therefore, be interesting to compare liquid optics interface fs-trephinations with excimer laser-assisted trephinations in the future.

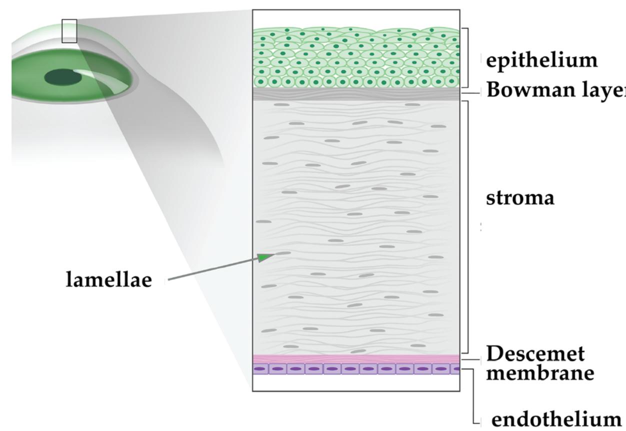



**Figure 14:** Illustration of corneal layers. Copyright© Dardenne Clinic.

### 7.1.2 Sidecuts

In femtolaser assisted keratoplasty (FLAK), different sidecut profiles can be chosen. Theoretical advantages include increased wound surface and thereby accelerated healing and wound stability, better vertical and horizontal alignment of the recipient and donor [58], preservation of healthy recipient corneal endothelium, or transplantation of proportionally more endothelial cells with a top hat profile [59, 60]. It remains to be seen if other factors, such as suture techniques, have to be modified to transmit these theoretical advantages into true clinical benefits [60].

## 7.2 Lamellar keratoplasty

The cornea is structured in five parallel layers (Figure 14). Often, not all layers of the cornea are diseased. Scars from trauma or infection commonly involve the anterior layers. In contrast, some inherited corneal diseases affect only the inner most layers. Selectively transplanting the pathological layers has several advantages: less tissue is being transplanted, and thereby rejection is limited. With the scarcity of donor material, a donor button can theoretically be divided between two recipients. The integrity of the eye is less constrained. Since there is little adhesion between the interfaces of the corneal layers, manipulation at these levels is possible and visual results are excellent.

In deep anterior lamellar keratoplasty (DALK), approximately 95% of the anterior corneal layers are removed, and only the innermost layers, Descemet membrane and endothelial cell layer stay behind [61]. In contrast, in posterior lamellar keratoplasty the old, non-functioning innermost layer of the cornea is removed and replaced with the same layer of a donor. In both surgeries, fs laser systems help to separate corneal layers at an individually chosen depth and allow for perfect centration, shape, and size of various cuts.

This short overview of corneal surgery underlines the immense versatility and breadth of applications fs-laser technology provides in corneal surgery. A more in depth description of surgical methods in fs-laser assisted corneal surgery is given in a recently published review [3].

# 8 Cataract surgery

In cataract surgery, the natural lens, which has lost its transparency with age, is replaced by an artificial intraocular lens (IOL). Nagy was the first reporting on the use of fs-laser for cataract surgery in 2009 [33]. There has been a quick evolution of the technology and platform ability since then by several manufacturers. Currently, modern and commercially available fs systems allow the following steps to be taken over by the machine:

a) Imaging and measurement of the anterior segment of the eye (incl. cornea, anterior chamber, iris, lens).
b) Planning of fs laser cut application to the tissue (incl. location depth, pattern, and size).
c) Corneal incisions (full-thickness for the introduction of instruments to the eye or partial thickness for treatment of corneal astigmatism).
d) Circular incision to the anterior lens capsule (capsulotomy).
e) Fragmentation of the cataractuous lens nucleus.

For all of the above-mentioned purposes, the eye must be fixed to laser optics by vacuum docking for precise laser application to the intended area and depth, using the technology described above. A recent comprehensive comparison table of the main technical parameters of fs laser systems for cataract surgery, as well as their coverage of other applications, can be found in another review paper by Latz et al. [3].

The main advantages of fs-assisted cataract surgeries are the precision and repeatability of laser incisions to the tissue, reduction in ultrasound energy used for emulsification (liquification) of the lens nucleus by pre-cutting it into small pieces, perfect sizing of corneal incisions with regard to position, length, and depth, and predictability in capsulotomy size and position. Despite the aforementioned obvious advantages and numerous studies showing superiority in performing the single surgical steps over the ones manually performed by surgeons, meta-analysis studies could not prove overall outcome advantages of fs-laser assisted surgery versus the conventional phacoemulsification manual operation [62, 63]. Nevertheless, review articles emphasize usefulness of fs-assisted cataract surgery in some patient groups, i.e. those with low corneal endothelial cell counts, but a clear advantage of the fs method over manual phacoemulsification is not reported in routine cases [64, 65]. Some problems of first generation fs-lasers (e.g. intraoperative pupil narrowing) have been solved by the introduction of low-energy laser concepts [66].

In the following chapter, we briefly describe the main steps of the cataract surgery taken over by the fs-laser machine.

## 8.1 Capsulotomy

Traditionally, cataract surgeons access the cataractuous lens by manually opening the anterior lens capsule by pulling in a continuous curvilinear manner, using a needle or forceps. Size, position, and shape of the capsule opening are related to the effective lens position, a determinant of the IOL power. The IOL power determines the postoperative refractive error of the eye. Inappropriate sizing of the capsular opening may result in IOL tilt, decentration, and increased posterior lens capsule opacification [67–69]. Perfect lens position is of particular importance to IOLs with complex optical properties, e.g. multifocal and toric lenses (for astigmatism correction), or those with an extended depth of focus [70, 71].

fs-Lasers provide precise, predictable, repeatable, well-centered capsular openings, called laser capsulotomy, even in challenging cases [3]. Machine superiority has been demonstrated in several studies [69, 72]. Innovative IOLs are available that are dependent on perfect capsulotomy sizing at a submillimeter level. Those designs allow IOL centration based on the capsulotomy rather than on the capsular bag [73].

### 8.2 Lens nucleus fragmentation

The human lens loses transparency and flexibility throughout life, thus a cataractuous lens cannot be removed through a small incision by suction alone. Femtosecond laser technology allows pre-cutting the nucleus in almost any imaginable shape and reduces the ultrasound energy needed for conventional phaco-emulsification. This is an advantage as the ultrasound energy is a cause of oxidative stress, heat, inflammation, and damage to the tissue [74].

### 8.3 Corneal incisions

Full-thickness incisions through the cornea are necessary for the introduction of instruments into the eye. Traditionally a metal scalpel or diamond blades are used for creating them in different sizes. fs Technology allows predictable sizing (width, length, and depth) of full-thickness corneal incisions. Incorrect positioning of the incision wound induces astigmatism and can provoke prolapse of the iris during the surgery. Studies have shown increased repeatability and safety of wound construction using fs technology resulting in higher stability and water tightness [75–77].

Partial-thickness incisions into the cornea help to reduce preoperatively existing corneal astigmatism. fs Technology allows higher predictability and repeatability of partial thickness incisions, or even completely intrastromal corneal incisions [78]. fs-Laser-assisted corneal incision could be as safe and effective as toric IOLs to reduce astigmatism [79].

## 9 Future applications

Probably the most important evolutionary trends in ophthalmic fs-laser devices are miniaturization, mobility, and versatility. Tools available soon are fs laser-assisted primary posterior capsulotomy and lens capsule marking for positioning of toric IOLs. On the horizon, another technology involves changing the IOL power postoperatively through fs laser energy to achieve emmetropia in all eyes [80].

## 10 Summary

In summary, fs laser technology has evolved over the past decades into a precise, reliable, and versatile tool in ophthalmic surgery. Combined with supporting technologies like sterile eye docking systems, OCT imaging, fast laser scanning, and advanced software, ergonomic and robust systems have become established tools in modern eye surgery operating rooms. fs-Laser-assisted cataract and corneal surgery have reached highly standardized levels worldwide. For these surgeries, fs laser technology has improved patient safety and clinical outcomes and enabled new surgical approaches. Research and development of even more applications is still evolving.

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