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The Role of Low-Energy Femtosecond Laser in Lens Surgery

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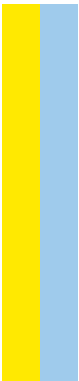


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THE ROLE OF LOW-ENERGY FEMTOSECOND LASER IN LENS SURGERY

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“Uma força menor aplicada persistentemente é igual a uma força maior.”

Gottfried Wilhelm von Leibniz

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List of Abbreviations

AI – arcuate incisions
AK – arcuate keratotomy
AL – axial length
AMD – age-related macular degeneration
BSCVA – best spectacle corrected visual acuity
CDE – cumulative dissipated energy
CDVA – corrected distance visual acuity
CME – cystoid macular edema
CP – conventional phacoemulsification
CPA – chirped pulse amplification
D – diopters
ECL – endothelial cell loss
EDOF – enhanced depth of focus
EPT – effective phacoemulsification time
FLACS – femtosecond laser assisted cataract surgery
FLALS – femtosecond laser assisted lens surgery
FPR – first Purkinje reflex
FS – femtosecond
FSAK – femtosecond laser assisted arcuate keratotomy
FSL – femtosecond laser
HD-OCT – high-definition optical coherence tomography
IOL – intraocular lens
IOP – intraocular pressure
LEC – lens epithelial cells
LOCS – lens opacity classification system
LogMAR – logarithm of the minimal angle of resolution
LRI – limbal relaxing incisions
MAE – mean absolute error
MIOL – multifocal intraocular lens
NA – numerical aperture

Nd: YAG – neodymium-doped yttrium aluminum garnet

NSAID – nonsteroidal anti-inflammatory drug

OCT – optical coherence tomography

PC – pupil center

PCO – posterior capsule opacification

PCR – posterior capsule rupture

PROMs – patient reported outcomes measures

RCT – randomized controlled trials

RK – radial keratotomy

RLE – refractive lens exchange

SE – spherical equivalent

SIA – surgically induced astigmatism

TPV – total pupil variation

UCVA – uncorrected visual acuity

UDVA – uncorrected distance visual acuity

Abstract

Introduction: Phacoemulsification has been the long-established standard technique of lens surgery (whether in the presence of a cataract or a transparent crystalline lens). Femtosecond laser technology emerged as capable of providing competing indexes of reproducibility, precision, efficacy, and customization regarding several steps involved in lens surgery, as compared to conventional phacoemulsification. This aspect is most relevant when refractive error correction is a concern, such as it is the case of premium lens surgery. Furthermore, cataract surgery itself has shifted goals in the direction of the best refractive correction, blurring the pre-established frontiers between purely refractive and cataractous lens removal. Independency of spectacles by means of surgical intervention has concurrently become the desire of an increasingly significant part of the population. With this regard, the advent of intraocular lenses specifically designed for improving refractive autonomy further increased the demand for higher levels of safety and efficacy of the surgical techniques, opening the stage for new actors such as femtosecond laser-based systems. In this quest, the emergence of the low-energy pulse concept aimed to expand the performance of femtosecond laser technology by overcoming some limitations of high-energy femtosecond laser devices. These historical limitations are mainly related to pupil dynamics (laser-induced miosis) and capsular complications (tags or ruptures). It is believed that low-energy systems address these challenges by delivering less laser energy by pulse, thus reducing thermal and mechanical stress during surgery. The present research aims to increase the knowledge on the role of low-energy femtosecond laser in the context of lens surgery. For the matter, the more inclusive expression such as femtosecond laser assisted lens (clear or cataractous) surgery (FLALS) will be preferably used, along the thesis, over the more restrictive femtosecond laser assisted cataract surgery (FLACS).

Purpose: The main objective of this research is to assess the performance of low-energy femtosecond laser assisted lens surgery as compared to manual phacoemulsification, both at the non-refractive level (accuracy, safety and reproducibility of surgical steps) and refractive level (refractive accuracy, efficacy and safety), independently of the existence of lens opacity (cataract).

Material and Methods: The research involved five studies. A retrospective study compared the performance of low-energy femtosecond laser assisted lens surgery (FLALS) versus conventional phacoemulsification (CP) with refractive lens exchange (RLE), in the context of presbyopia correction. The procedure's refractive and non-

refractive results were analysed. This study comprised a total of 56 eyes of 28 patients who had randomly assigned FLALS in one eye and CP in the other, with implantation of a multifocal intraocular lens (MIOL). The clinical outcomes and the results of a level of satisfaction questionnaire were compared between two groups according to the technique employed (FLALS vs CP) for a period of up to four years; accuracy, stability, efficacy, and safety indices were also assessed.

Another study aimed at assessing the role of femtosecond laser-assisted capsulotomy centration in the long-term intraocular positioning of a multifocal intraocular lens (MIOL), and consequent clinical outcomes at the refractive level and quality of vision. This prospective intraindividual comparative study comprised total of 60 eyes of 30 patients submitted to refractive lens exchange (RLE) surgery for presbyopia correction, with femtosecond laser assisted lens surgery (FLALS). For every patient, capsulotomy centration was randomly performed according to pupil center (PC) in one eye and first Purkinje reflex (FPR) in the other. All eyes were implanted with a sinusoidal MIOL. The positioning of the intraocular lens (IOL) was assessed after a period of 3 years and comparison was made between the two groups (PC and FPR). Evaluation of the uncorrected and corrected visual acuities (far, intermediate and near vision), spherical equivalent (SE), internal aberrometry and quality of vision was also performed.

Two retrospective studies contemplated the safety profile, regarding adverse events, of low-energy femtosecond laser assisted cataract surgery. One of the studies, involving the intraindividual comparison of pupil behaviour between low-energy FLACS and CP, entailed a total of 164 eyes of 82 patients that undergone uncomplicated cataract surgery in a single ophthalmology center. The recorded pupil images were evaluated at pre and post laser treatment (after suction release) and at several surgical timepoints for both techniques. Pupil areas were calculated and compared in the same eye undergone FLACS (pre vs post laser treatment), between eyes (CP vs FLACS) in the same patient and between groups. Subgroups were built regarding age and ocular comorbidity. The other retrospective study involved an intraindividual comparison of pupil changes according to cataract grade between low-energy femtosecond laser-assisted cataract surgery (FLACS) and conventional phacoemulsification (CP). This was accomplished by extracting data from surgical records from patients submitted to cataract surgery with CP in one eye and FLACS in the other. Inclusion criteria was both eyes of same patient having the same cataract grade in accordance with Lens Opacity Classification System (LOCS) III. Total pupil variation (TPV) was measured after recorded images, with intraindividual comparison between techniques, according to cataract grade (≤ 3 and > 3), age and cumulative dissipated energy (CDE).

Finally, a literature review was conducted to analyse the state of the art of femtosecond laser assisted lens surgery, adding a novel focus on the technique's indications.

Results: This analysis is based on the research objectives proposed in our research. Upon comparing the visual outcomes of low-energy FLACS and CP in the context of presbyopia lens surgery, it was shown that a higher percentage of patients attained uncorrected and corrected visual acuity of 20/20 and above with the femtosecond laser assisted surgery. Refractive stability was also achieved earlier with FS. These results were clinically, although non-statistically significant, relevant to the scope of the research. Quality of vision was similar between techniques. Femtosecond laser assisted capsulotomy centration on the first Purkinje reflex was associated to a better IOL centration towards the visual axis, as compared to pupil centration. This was also associated to a statistically significant lower level of ocular aberrations. Global comparison of non-refractive outcomes showed some differences between techniques. Comparison of CDE, as a non-refractive outcome, showed superiority of FLACS over CP. The incidence of capsule-related complications and laser-induced pupil constriction with the low-energy FS platform employed in this research was null. Furthermore, our research showed that, regarding pupil status, low-energy FLACS showed better results than CP in softer cataracts' surgery. Total surgical time was similar between low-energy FLACS and CP.

Conclusions: Our research provides strengthened evidence of the role of low-energy femtosecond laser in the context of lens surgical removal. Impacting on all crystalline lens (with or without cataract) surgery, we showed a low incidence of complications, an early and long-term visual and refractive stability, high safety and an enhanced and customized centration of capsulotomy. Our findings are primarily promising in the domain of refractive surgical correction.

Keywords: presbyopia correction, femtosecond laser, low-energy surgery, FLACS, FLALS, phacoemulsification, crystalline lens

Resumo

Introdução: A facoemulsificação tem sido a técnica standard de cirurgia do cristalino (quer na presença de catarata ou cristalino transparente). A tecnologia de laser de femtosegundo emergiu com a expectativa de apresentar índices competitivos de reprodutibilidade, precisão, eficácia e customização relativamente a vários passos da cirurgia de cristalino, quando comparada com a facoemulsificação convencional. Este elevado padrão técnico é crucial quando a correção do erro refrativo é um alvo a atingir, como é o caso da cirurgia premium de cristalino. Entretanto, a própria cirurgia da catarata tem orientado os seus propósitos na direção da melhor correção refrativa, esbatendo a fronteira entre a pura remoção de catarata e a cirurgia refrativa do cristalino. A independência do uso de óculos através de intervenção cirúrgica é também o desejo de uma parte significativa e crescente da população. Nesta perspetiva, o aparecimento de lentes intraoculares especificamente produzidas para aumentar a autonomia refrativa mais tem estimulado a procura de elevados níveis de segurança e eficácia das técnicas cirúrgicas, abrindo palco para novos atores como os sistemas baseados no laser de femtosegundo. Nesta busca, emerge o conceito de pulso de baixa energia como tentativa de expandir a performance da tecnologia do laser de femtosegundo, ultrapassando algumas limitações associadas aos aparelhos de laser de femtosegundo de alta energia. Estas limitações históricas estão essencialmente relacionadas com a dinâmica pupilar (miose induzida pelo laser) e com complicações capsulares. Crê-se que os sistemas de baixa energia podem ultrapassar estas limitações ao diminuir o nível de energia por pulso, reduzindo assim o stress mecânico e térmico durante a cirurgia. A presente tese procurou aumentar o conhecimento do papel do laser de femtosegundo de baixa energia no contexto da cirurgia do cristalino. A este propósito, a expressão, mais inclusiva, de cirurgia do cristalino (com ou sem catarata) assistida a laser de femtosegundo (FLALS), será preferencialmente utilizada ao longo da tese, por comparação com o termo corrente e mais restritivo de cirurgia de catarata assistida a laser de femtosegundo (FLACS).

Objetivos: O principal objetivo desta investigação é avaliar a performance da cirurgia de cristalino assistida a laser de femtosegundo de baixa energia comparativamente à facoemulsificação convencional, quer ao nível não-refrativo (precisão, segurança e reprodutibilidade dos passos cirúrgicos) quer ao nível refrativo (precisão, eficácia e segurança refrativas), independentemente da existência de opacidade lenticular (catarata).

Material e métodos: A investigação envolveu cinco estudos. Um estudo retrospectivo comparou a performance da cirurgia de cristalino assistida a laser de femtosegundo (FLALS) de baixa energia com a facoemulsificação convencional (CP), no contexto de cirurgia de presbiopia com cirurgia refrativa do cristalino (RLE). Os resultados refrativos e não-refrativos foram analisados. Este estudo incluiu um total de 56 olhos de 28 pacientes que foram submetidos a FLALS num olho e CP no outro, com implantação de lente intraocular (LIO) multifocal, de forma randomizada. Os resultados clínicos e o nível de satisfação foram comparados entre grupos de acordo a técnica empregue (FLALS versus CP) por um período de até 4 anos; estabilidade, e índices de segurança e eficácia foram realizados.

Um outro estudo avaliou o papel do centramento da capsulotomia realizada por laser no posicionamento a longo prazo de uma lente intraocular multifocal, e consequentemente os resultados a nível refrativo e de qualidade de visão. Este estudo comparativo intraindividual prospetivo compreendeu um total de 60 olhos de 30 pacientes submetidos a cirurgia refrativa do cristalino (RLE) para correção da presbiopia, com FLALS. Em cada paciente, o centramento da capsulotomia foi realizado, de forma randomizada, em relação ao centro pupilar (PC) num olho e ao primeiro reflexo de Purkinje (FPR) no outro. Em todos os olhos foi implantada uma lente intraocular multifocal sinusoidal. O posicionamento da lente intraocular foi avaliado após um período de 3 anos e comparação foi feita entre os dois grupos (PC e FPR). Foi realizada a avaliação da acuidade visual, corrigida e não corrigida, para longe, intermédio e perto, equivalente esférico (SE), aberrometria interna e qualidade de visão.

Dois estudos retrospectivos contemplaram o perfil de segurança, relativamente a eventos adversos, da cirurgia de catarata assistida a laser de femtosegundo. Assim, um dos estudos, envolvendo a comparação intraindividual do comportamento da pupila entre FLACS de baixa energia e CP, englobou um total de 164 olhos de 82 pacientes submetidos a cirurgia de catarata não complicada num centro oftalmológico. As imagens gravadas da pupila foram avaliadas antes e após o tratamento com laser (depois da sucção) e ao longo da cirurgia, para ambas as técnicas. As áreas pupilares foram calculadas e comparadas no olho submetido a cirurgia de catarata assistida a laser de femtosegundo (FLACS) antes e após o tratamento laser, entre os olhos (CP versus FLACS) do mesmo paciente e entre grupos. Subgrupos foram criados relativamente à idade e morbilidade ocular. Um outro estudo retrospectivo envolveu uma comparação intraindividual da variação pupilar de acordo com o grau de catarata, entre cirurgia de catarata assistida a laser de femtosegundo (FLACS) de baixa energia e facoemulsificação convencional (CP). Esta avaliação foi realizada através da extração

de dados de registos cirúrgicos de pacientes submetidos a cirurgia de catarata com CP num olho e FLACS no outro. Como critério de inclusão, ambos os olhos do mesmo paciente tinham o mesmo grau de catarata, segundo a classificação do Lens Opacity Classification System (LOCS) III. A variação pupilar total (TPV) foi medida segundo imagens gravadas, com comparação intraindividual entre as técnicas, de acordo com o grau de catarata (≤ 3 e > 3), idade e energia cumulativa dissipada (CED).

Finalmente, uma revisão da literatura foi realizada para analisar o estado da arte da cirurgia de cristalino (catarata) assistida a laser de femtosegundo, adicionando um novo foco sobre as indicações da técnica.

Resultados: Esta análise foi baseada nos objetivos de investigação propostos na tese. A comparação dos resultados visuais entre FLALS E CP no contexto de cirurgia de presbiopia do cristalino mostrou que uma percentagem mais elevada de pacientes atingiu acuidades visuais, corrigida e não corrigida, iguais ou superior a 20/20 com a cirurgia assistida a laser de femtosegundo. A estabilidade refrativa foi também atingida mais cedo com FS. Estes resultados foram clinicamente, embora não estatisticamente, significativos, e relevantes no âmbito desta investigação. Centramento da capsulotomia no primeiro reflexo de Purkinje foi associado a melhor centramento da lente intraocular (LIO) em relação ao eixo visual, quando comparado com o centramento na pupila. Este facto também mostrou associação com um nível inferior de aberrações oculares, estatisticamente significativo. Uma comparação global dos resultados não-refrativos mostrou algumas diferenças entre as técnicas. A comparação de CDE, como um parâmetro não-refrativo, mostrou superioridade do FLALS em relação a CP. A incidência de complicações relacionadas com o saco capsular e de constrição pupilar induzida por laser foi nula neste estudo. Adicionalmente, a nossa investigação mostrou que a cirurgia de cristalino assistida a laser de femtosegundo de baixa energia evidenciou superioridade em relação à facoemulsificação convencional, relativamente ao comportamento pupilar em cataratas menos densas. O tempo cirúrgico total foi semelhante entre FLALS de baixa energia e CP.

Conclusões: Esta investigação reforçou a evidência do papel do laser de femtosegundo de baixa energia, no contexto de remoção cirúrgica do cristalino. Sendo impactante em toda a cirurgia de cristalino (transparente ou opacificado), os nossos achados, de uma baixa incidência de complicações, estabilidade e segurança iniciais e a longo prazo ao nível visual e refrativo, capsulotomia melhorada e customizada, são potencialmente relevantes no domínio da correção cirúrgica da refração.

Palavras-Chave: correção da presbiopia, laser de femtosegundo, cirurgia de baixa energia, FLACS, FLALS, facoemulsificação, cristalino

Publications

Salgado R, Torres P, Marinho A. Femtosecond Laser-assisted Lens Surgery with Low-energy Pulse versus Conventional Phacoemulsification for Presbyopia Correction: An Intraindividual Study. *The Open Ophthalmology Journal* 2021; 15(1): 43-53. doi: 10.2174/1874364102115010043

Salgado R, Torres PF, Marinho A. Pupil Status with Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification: An Intraindividual Comparative Study. *Clinical Ophthalmology*. 2023; 17: 331-339. doi.org/10.2147/OPTH.S399788.

Salgado R, Torres P, Marinho A, Ribeiro FJ. Cataract Grade and Pupil: Comparison Between Conventional Phacoemulsification and Low-Energy Femtosecond Laser Assisted Cataract Surgery. *Clinical Ophthalmology*, 2023; 17: 2193-2200. doi.org/10.2147/OPTH.S420931.

Salgado RMPC, Torres PFAAS, Marinho AAP. Pupil versus 1st Purkinje capsulotomy centration with femtosecond laser: Long term outcomes with a sinusoidal trifocal lens. *J Biophotonics*, 2024; 17(5): e202300446. doi:10.1002/jbio.202300446

Salgado RMPC, Torres PFAAS, Marinho AAP. Update on Femtosecond Laser-Assisted Cataract Surgery: A Review. *Clinical Ophthalmology*, 2024; 18: 459-472. doi:10.2147/OPTH.S453040

Salgado R. O papel do Femto. In: "Presbiopia". Lisboa, Sociedade Portuguesa de Oftalmologia: Filomena Ribeiro (ed), 2019: 167-171. ISBN: 978-989-98118-8-1

Overview of the Thesis

The thesis includes six chapters.

Chapter 1 contemplates a description of femtosecond laser technology and principles of refractive lens surgery.

Chapter 2 reports the current knowledge and state of the art regarding the use of femtosecond laser in lens surgery.

Chapter 3 identifies and structures the objectives of the thesis.

Chapter 4 covers the scientific research undertaken in the pursuit of the objectives of this thesis, focusing on the related published papers.

Chapter 5 is a comprehensive discussion that includes all the research conducted within the dissertation's scope.

Chapter 6 presents the final conclusions drawn from the present thesis and indicates future paths regarding the use of femtosecond laser in lens surgery.

Chapter 7 consists of the list of references.

1. Introduction

1.1. General Introduction

Conventional phacoemulsification has long-established sequential steps, such as initial paracentesis (main and side ports), capsulorhexis, lens fragmentation and aspiration, each of them having paramount importance to the final result and being prone to complications. In 2008, femtosecond laser was introduced in cataract surgery and since then, its application has widened and covered most of the above-mentioned standardized steps. Femtosecond laser, furthermore, has extended towards enhanced and combined refractive procedures. The characteristic short pulses (in the range of 10^{-15} seconds) of small amounts of energy differentiates FS laser from previous lasers in ophthalmology. This is accomplished in the way that a more focused energy, accurate control, and less damage to neighbor tissues are attainable. Thereafter, critical steps, such as capsulorhexis, are more safely, predictably, accurately, and reproducibly performed (regarding capsulotomy position, size, shape and strength), allowing optimized IOL intracapsular positioning; this is critical to “effective lens position” and most relevant to all premium IOLs refractive results. Thus, FS capsulotomy is strongly advised in subluxated and mature cataracts. Furthermore, laser lens segmentation and fragmentation simplify emulsification, with reduction in ultrasound cumulative energy, global manipulation forces and perceived lens hardness, increasing safety in cataract surgery. For this purpose, precise real-time imaging systems (with tri-dimensional), such as optical coherence tomography of the anterior segment, are mandatory and necessarily integrated in currently employed laser devices.

Femtosecond laser intervention was meant to surpass manual phacoemulsification in nearly every aspect of lens surgery. Its high performance in most steps of lens surgery opened a path to optimization of refractive results, a current goal, since nowadays, cataract surgery cannot be perceived outside the refractive universe. In particular, the ageing of patients who have undergone corneal refractive procedures in the past, poses additional refractive challenges regarding predictability in this new presbyopic population. The removal of an eminently refractive structure such as the crystalline lens, independently of the reasons for its removal (with or without cataract), unquestionably implies, with no exceptions, a very concrete refractive concern.

1.2. Femtosecond Laser Technology

1.2.1 Concept

Femtosecond laser technology derives its name from the generated pulse duration: in the order of 10^{-15} seconds^{1,2}. Produced at the near-infrared range (1,053 nm), the extremely short pulse time of this solid-state laser is liable to achieve photodisruption in target tissues, avoiding the undesired effects of previous lasers, such as thermal impact^{3,4,5}. A technique called chirped pulse amplification (CPA) is mostly used to amplify a femtosecond laser pulse and satisfy the intensity requirement for achieving enhanced precision and minimize collateral tissue effects during eye surgery⁶. When in association with other adjustable laser parameters, namely, power, repetition rate and spot size, the laser-tissue interaction can be further customized and optimized. Photodisruption is a sequential three-step event: plasma formation, shock wave generation and cavitation. (Fig. 1)

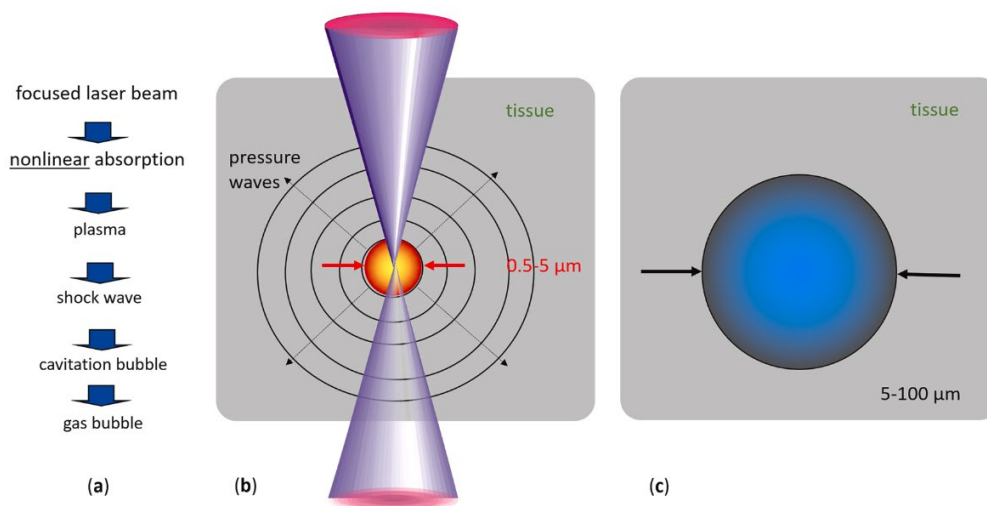


Figure 1.1: Photodisruption with a FS laser. (a) sequence of events, (b) plasma diameter range (red) and emitted pressure wave pattern (circles), and (c) range of possible cavitation bubble dimensions (pulse energy dependent). Adapted from Pepose 2008⁷.

Henceforth, femtosecond (FS) laser separates tissue by ablation and cleaving; the relative weight of each is determined mainly by the pulse energy level⁵. To achieve photodisruption, an energy threshold must be surpassed, depending on the nature of treated tissue and different laser features: numerical aperture (NA) and wavelength. (Fig. 2)

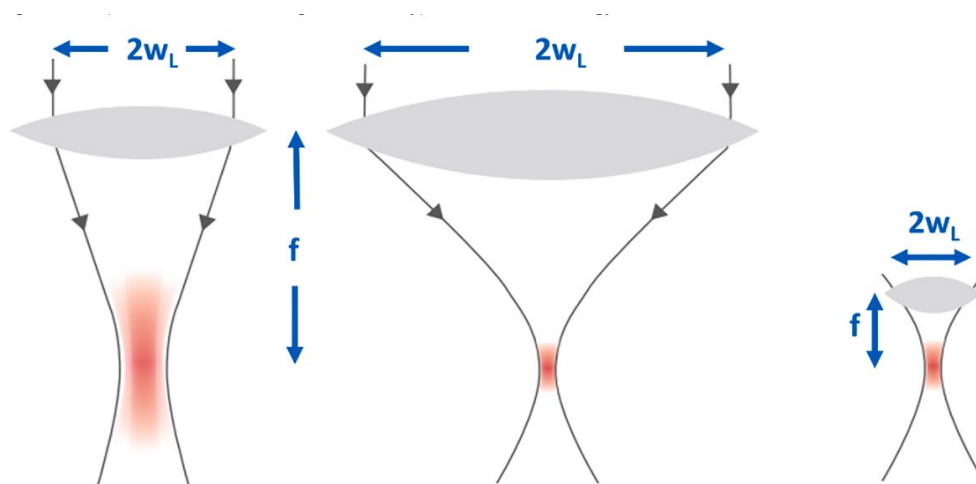


Figure 1.2: The focal volume of a Gaussian laser beam scales inversely to the cube of the numerical aperture $NA = w_L/f$ of the focusing lens. The larger the NA, the smaller the focal spot volume. Adapted from Asshauer 2021⁸.

The interaction process between an ultrashort pulse laser and biological tissue is determined by the following key laser parameters:

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

The nature of the cutting processes of an FS laser varies according to the parameters above. The higher the energy pulse, the greater the ablated tissue through expanding gas bubbles (disrupting the tissue at a larger radius than the plasma created at the laser focus). The lower the energy pulse, the lesser the ablated tissue and separation is dependent on the cleaving occurrence (evaporation of the tissue inside the plasma volume effectively separates tissue without a need for secondary mechanical tearing effects. In the latter case, for effective cutting speed purposes, higher pulse frequencies and tighter spots are applied ⁸. (Fig. 1.3)

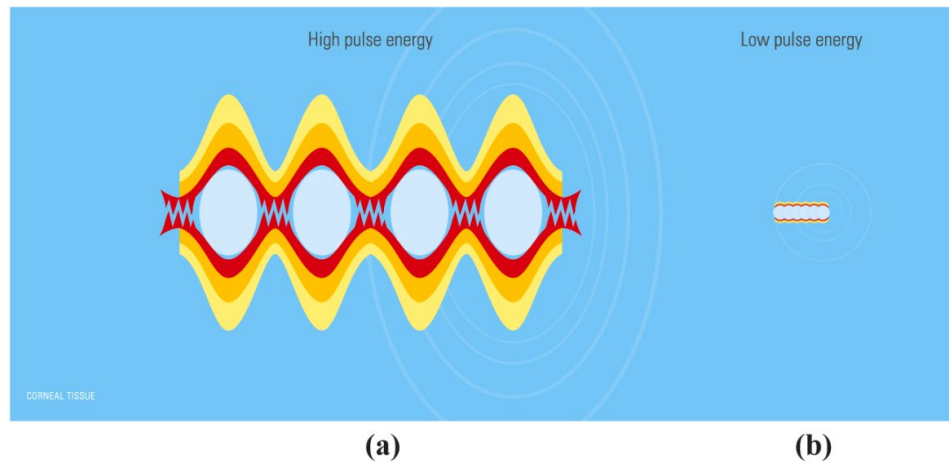


Figure 1.3: Different patterns of FS pulse. (a) High pulse energy, low pulse frequency (large spot separation). The color gradings symbolize the strain levels in the tissue surrounding the induced bubbles; (b) low pulse energy, high pulse frequency (small spot separation, overlapping plasma interaction zones). Adapted from Asshauer 2021⁸.

1.2.2. Patterns of Femtosecond Laser Pulse

Presently, there are two different FS laser pulse patterns, regarding energy level and frequency. On one hand, there are devices (the majority of laser systems available) producing high-energy and low-frequency pulses, in the order of μJ and KHz, respectively. On the other hand, there is a laser platform producing low-energy high-frequency pulses, in the range of nJ and MHz, respectively. The latter pulse pattern (low energy with high repetition rates) offers some advantages: high laser focusing accuracy and cutting precision, accompanied by less gas generation, which reflects on a reduced collateral damage to the surrounding tissue^{8,9}. The mechanical thrust on adjacent tissues is, by this physical evidence, substantially bigger with high-energy pulse FS.

The energy level of a FS laser pulse at a certain wavelength depends on the focal spot size; this focal volume is, in turn, inversely proportional to the numerical aperture (NA) of the focusing optics. The larger the NA, the smaller the focal spot and ultimately, the lower the energy. There are two ways of producing an augmented NA: by increasing the lens diameter of the focusing optics or by positioning the focusing optics closer to the eye. (Fig. 1.4)

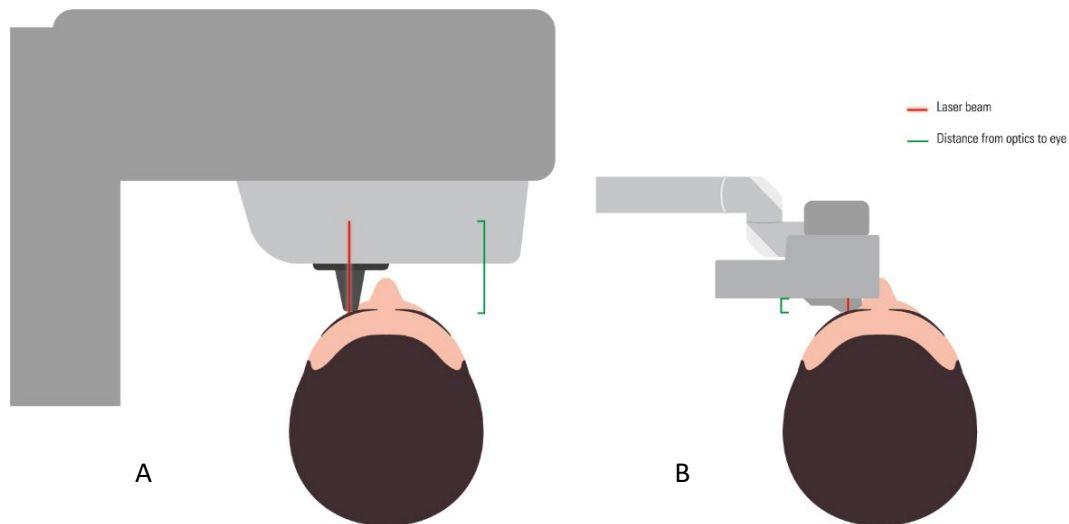


Figure 1.4: FS laser energy delivery methods of fs lasers. A - head under laser gantry, long distance from optics to the eye; B - articulated arm with handpiece placed onto the eye, very short distance from optics to eye; green markings indicate working distance of laser optics. Adapted from Asshauer 2021⁸.

Most of the available laser platforms, such as LenSx (Alcon Laboratories, Fort Worth, Inc.), VICTUS (Bausch & Lomb, Inc.), Catalys (Johnson & Johnson Vision Care, Inc.) and LensAR (LensAR, Inc.) have opted by the first approach, whereas Femto LDV Z8 (Ziemer Ophthalmic Systems AG) has chosen the second approach⁹⁻¹¹. (Fig. 1.5)



Figure 1.5: The different FS laser platforms available. a - VICTUS; b - LenSx; c - Catalys; d - LensAR (LensAR, Inc.); e - Femto LDV Z8.

The former devices have large optics requiring stable and relatively immobile platforms. With the latter device, the laser beam is guided through an articulated mirror arm into a handpiece which contains the focusing optics; this feature allows a reduction of pulse energy by a factor of 10 or more. Furthermore, this design enables the handpiece use under a surgical microscope, rendering the whole platform more portable and compact. Table 1 shows the main features of femtosecond laser platforms available for lens surgery.

	LenSx	LensAR	Catalys	Victus	LDV Z8
Company	Alcon	LensAR	Jonhson& Jonhson	Bausch& Lomb	Ziemer
Room size required (m)	3.4x4.3	4.57x4.57	3.04x3.35	3.4x3.7	No specific needs
Docking	Curved applanation lens	Fluid-fill suction ring	Fluid-fill suction ring	Curved applanation lens	Fluid-fill suction ring
Imaging	HD- OCT	Confocal+ Scheimpflug camera	HD-OCT	HD-OCT	HD-OCT

Table 1. Features of FS platforms. HD-OCT: high-definition optical coherence tomography. Adapted from Bonnet 2020¹².

1.2.3. Delivery Procedure

In order to correctly apply the FS laser to the eye, an adequate, stable and well-tolerated patient interface is of foremost importance. This device-patient engagement, described as docking, is currently achieved by means of two different methods: eye applanation (with a curved lens) or liquid interface^{13,14}. (Fig 1.6)

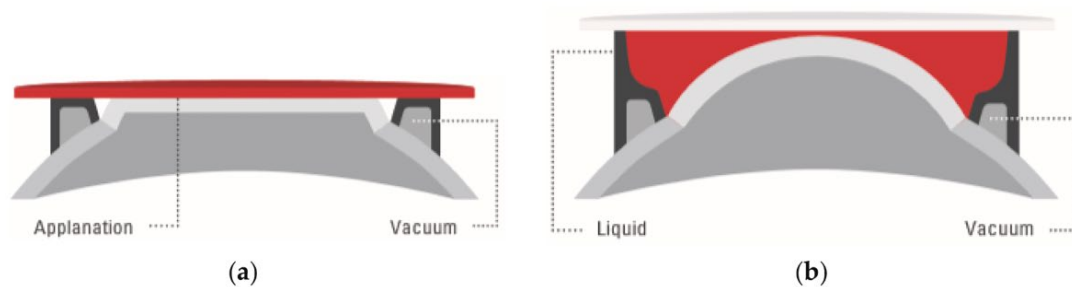


Figure 1.6: Eye docking interface designs: (a) contact interface in direct touch with the cornea (flat); (b) Liquid optics interface, no direct touch on the cornea, no deformation. Adapted from Latz 2021⁹.

While the current literature shows no difference between the two methods regarding capsulotomy regularity, there is some evidence of increased incidence of anterior capsular tears or tags with applanating interfaces, due to the occurrence of corneal folds¹⁵. Amongst the features of non-applanating interfaces (which use a scleral suction ring and a fluid immersion chamber) are a lower induced intraocular pressure, larger treatment area and a more proficient compensation regarding lens tilt¹⁴. (Fig. 1.7)

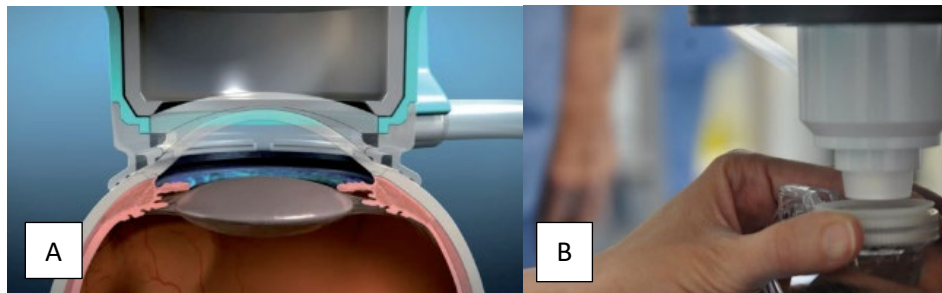


Figure 1.7: Examples of eye docking methods of FS platforms. A - LenSx applanating SoftFit® interface; B - Catalys liquid interface. Adapted from Bonnet 2020¹².

Docking adds an additional, time-consuming, step when compared to conventional phacoemulsification (CP)¹⁶; this is particularly the case of immobile platforms, which require mobilization of the patient between the FSL platform and operating room or set. (Fig. 1.8)

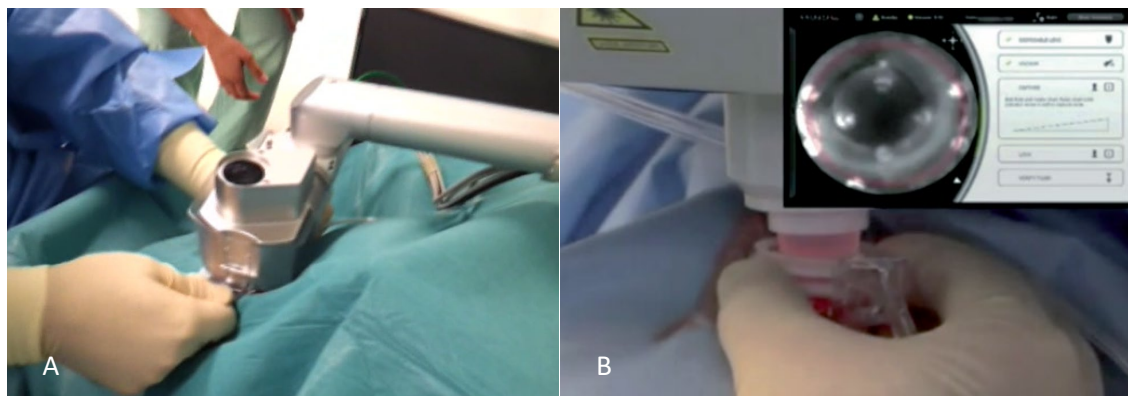


Figure 1.8: Examples of docking settings of FS lasers. A - LDV Z8 presenting a mobile arm, with patient lying in operating bed; B - Catalys immobile platform with a dedicated integrated bed. Panel B was adapted from Bonnet 2020¹².

Docking has, inherently, a rate of possible complications, from a mildly frequent transient conjunctival redness or hemorrhage to a very rare incomplete laser treatment due to suction loss¹⁷⁻²⁰.

1.2.4. Supporting Imaging Technology

In order to perform the proposed laser-assisted surgical steps (capsulotomy, corneal incisions and lens fragmentation), accurate and reliable imaging is paramount. A thorough three-dimensional reconstruction of anterior eye structures is currently provided by either optical coherence tomography (OCT) - most of FS platforms - or 3D confocal structured illumination combined with Scheimpflug imaging (LensAR)^{11,20-22}. (Fig. 1.9)

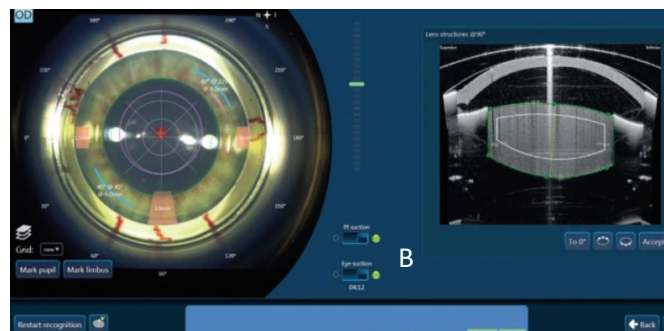


Figure 1.9: 3 D imaging with VICTUS using swept-source OCT. Adapted from Sun 2019²³.

Some of these platforms integrate swept source OCT (such as VICTUS) with automatic structures recognition and others provide augmented reality to enhance structures' borders and densities (LensAR). Also, most of the FS devices present an integrated camera system that allows a frontal view of the eye. (Fig. 1.10)

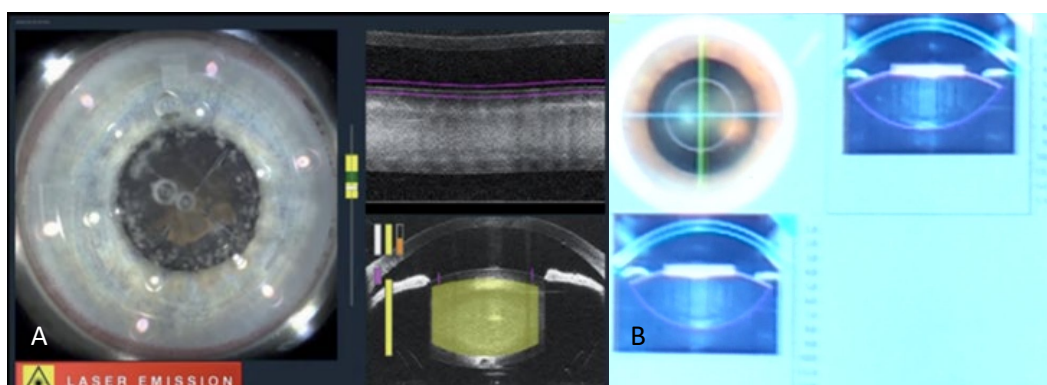


Figure 1.10: Display with a front view image of two FSL platforms. A - LenSx; B - Femto LDV Z8. Panel A was adapted from Bonnet 2020¹².

2. Clinical Applications of Femtosecond Laser in Lens Surgery

2.1. Capsulotomy

Dimensions (shape and size) of capsulotomy are determinant variables affecting effective lens position, which impacts on postoperative refractive results. Inadequate sizing of the capsulotomy may result in IOL tilt, decentration, and increased posterior lens capsule opacification²⁴⁻²⁷. Furthermore, for premium IOLs (toric, enhanced-depth-of-focus, or multifocal), which have more demanding optical designs, capsulotomy centration is most relevant for achieving optimal results²⁸⁻³⁰.

Circularity, precision, predictability, and reproducibility of FSL capsulotomy are the features that have been demonstrated to be superior to CP^{26,30,31}.

The capsulotomy incision starts below the surface of the anterior capsule and continues through the capsule cutting in a cylindrical or spiral fashion, depending on the FS device. (Fig. 1.11)

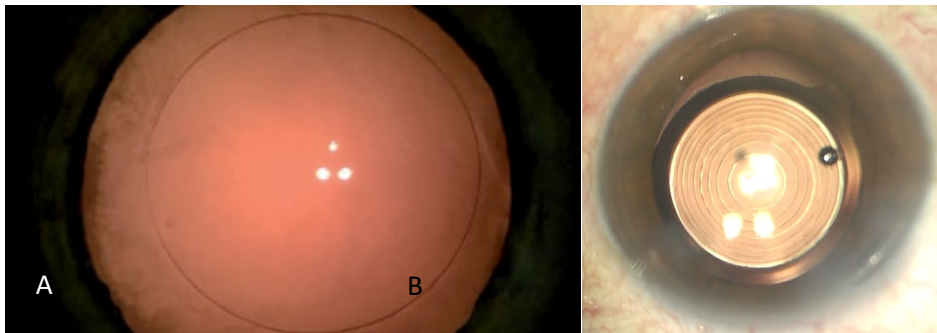


Figure 1.11: FS laser capsulotomies, with remarkable circularity in A and B; also, IOL edge overlap in B. A - LenSx; B – LDV Z8. Panel A was adapted from Bonnet¹².

The surgical step sequence also differs according to the platforms available. Thus, most of the FS devices perform capsulotomy before lens fragmentation, whereas one of them (Ziemer's) executes capsulotomy afterwards. This feature does have clinical impact, since, for white cataracts (generally a contraindication for FLALS with most platforms) it is liable for performance with the latter device (Ziemer), as nucleus fragmentation equalizes the gradient pressure inside the capsular bag before capsular opening, preventing radial capsular tear extensions, also known as "Argentinean Flag Sign"³².

Femtosecond laser platforms enables customization of the diameter and centration of the capsulotomy, adequately set via OCT (or equivalent, such as Sheimpflug) imaging upon docking; safety margins (from iris) are usually adjustable, as well.

A six-fold better IOL centration with FSL capsulotomy compared to manual capsulorhexis was found in some studies^{26, 33, 27, 28}, anticipating better clinical results. Capsulotomy can be centered on several landmarks or reference points: pupil, optical (corneal) or capsule center or custom placement (such as the lens apex or the first Purkinje reflex)³⁴; the available FS platforms share at least two of the aforementioned referential possibilities. A better overlap between the lens edge and the capsulotomy may reduce the incidence of posterior capsular opacification (PCO) postoperatively³⁵. Schultz *et al*³⁶ published more favorable results, regarding a capsule-IOL overlap of 360 degrees on the IOL anterior surface, with capsular bag-centered capsulotomy as opposed to pupil-centered capsulotomy. Also, femtosecond laser can be used to perform anterior capsular markings for toric IOLs alignment³⁷.

Regarding preoperative pupil size, normally a diameter not inferior to 4 mm, is compatible with the FS devices available³⁸. As to pupil size after the laser pretreatment, constriction (miosis) has been commonly reported for femtosecond laser-assisted surgery, casting this shadow on FLACS, in general, and presenting it as a feature of this technique in the published literature. However, the vast majority of the publications available refer to high-energy FLACS or, seldom include low-energy pulse devices, but without data results differentiation^{17,34,39}. In fact, recent literature on low-energy FLACS does not show evidence of miosis with this technique, demonstrating comparable results with CP, regarding pupil behavior. The explanation for this may be related to the lower level of pulse energy, causing less impact on the surrounding tissue and prostaglandins release. Also, it has been described that applanation can decrease pupil size, by means of transient ischemia to the iris sphincter induced by applanation docking³⁹.

Several strategies have been adopted to resolve this laser-induced miosis with high-energy pulse devices. The reinforced preoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a demand in this case. Intraoperative measures, such as intracameral viscoelastic, epinephrine (injection or perfusion), or mechanical dilation have been used, generating a profuse literature on this particular drawback⁴⁰⁻⁴².

Anterior capsule strength is related to the amount of energy applied during capsulotomy. The higher the energy pulse, the more irregular the edges; the lower the energy pulse, the smoother the capsulotomy edges^{29,43,44}. Accordingly, recently published works do

show a lower incidence of capsular complications (tears, tags) with low-energy pulse as compared to high-energy pulse FLALS^{10, 45-46}.

Although capsulotomy sizing can be adjusted with FS platforms, an average diameter of 5 to 5.25mm is generally chosen for most cases^{47,48}. However, this reference value may be limited by pupillary dilation and laser-specific pupil safety margins.

To summarize, in favor of femtosecond laser assisted lens surgery: circularity is better than with conventional phacoemulsification; capsulotomies are more precise (in size and shape), reproducible and better centered compared to manual capsulorhexis^{25,49-50}. However, against this technique are two limitations: maintenance of pupil dilation and the considerable rate of capsule-related complications, after laser treatment with high-energy pulse devices.

The present research was conducted with a low-energy FS device.

2.2. Lens Fragmentation

Femtosecond laser allows lens nucleus fragmentation, substituting for this surgical step conventionally performed by ultrasound with CP technique. The different platforms allow fragmentation customization according to the available patterns on the laser system⁵¹, beyond ensuring anterior and posterior safety margins as displayed upon imaging of the capsular bag^{12,40}; these margins are adjustable within each FS device's program range. (Fig 1.12)

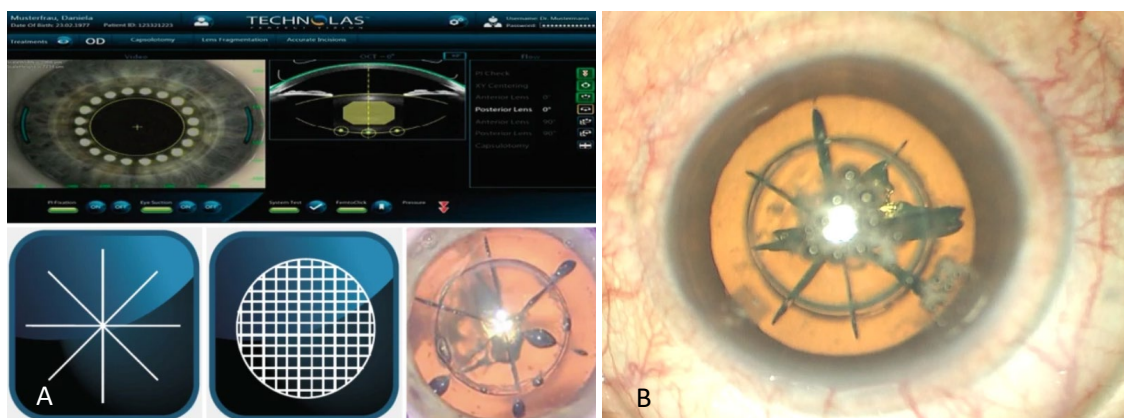


Figure 1.12: Examples of lens fragmentation patterns. A - VICTUS; B - LDV Z8. Panel A was adapted from Sun 2019²³.

Laser pre-cutting of the nucleus precludes oxidative stress, heat, inflammation, and tissue damage associated with ultrasound, as it shortens the phacoemulsification time

and cumulative dissipated energy (CDE)^{52,53}; with a reduction of 33%-70% of delivered energy, by softening the crystalline lens^{49,50}.

Roberts *et al*⁵⁴ reported a capsular block syndrome with subsequent posterior capsule rupture, occurring when an excessive pressure is produced inside the capsular bag during lens laser fragmentation. This extremely rare phenomenon is caused by the expanding gas bubbles, a feature of the tissue ablation produced with high-energy pulse systems.

In synthesis: FLALS has proven to be advantageous over CP as it reduces the amount of phacoemulsification energy. Nevertheless, FS requires adequate pupillary dilation to safe completion. High-energy FLALS is contraindicated in white cataracts.

2.3. Clear Corneal Incisions

Femtosecond laser technology enables customized, precise and predictable sizing (width, length, and depth), shaping and location of full-thickness corneal incisions⁵⁵. (Fig. 1.13)

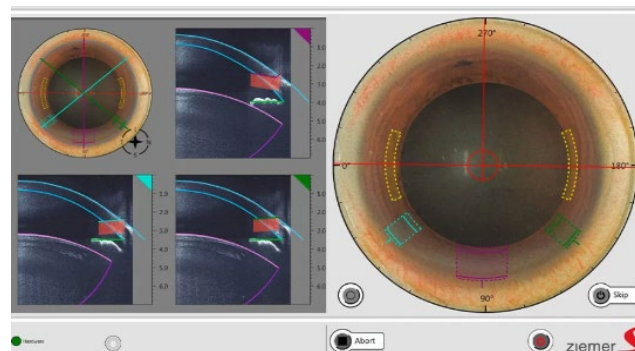


Figure 1.13: Example of FS laser assisted clear corneal incisions, with LDV Z8.

Corneal incisions constructed with FS have been proven stable, repeatable, and safe as compared with CP in numerous studies⁵⁶⁻⁵⁸. Mastropasqua *et al*⁵⁹ found that there is less wound gape and decreased wound edema, with laser created incisions compared to manual incisions.

The main corneal incision and paracentesis are accomplished by FS platforms customizable settings, generally upon imaging of the eye. Laser allows the construction of a more complex wound shape (like biplanar or triplanar), with higher consistency regarding reproducibility as compared to CP. Likewise, the incidence of Descemet's

membrane detachment, endothelial misalignment and posterior wound contraction are low with FLALS^{58,59}.

Instrumental manipulation time (e.g., with phaco probe), to our point of view, may constitute an important variable in wound recovery; this time duration is longer with CP.

Regarding surgically induced astigmatism (SIA), recent literature points to a similarity between FS and CP, in terms of results⁴⁵.

As a FS handicap, peripheral vascularization of the cornea prevents completion of the laser cut (forcing to manual aid), due to the suction-driven blanching of the limbic vasculature. Therefore, less vascularized areas should be looked for (if possible) when adjusting the laser cuts parameters upon imaging⁶⁰.

In favor of FLALS, is the fact that incisions are more reproducible, less prone to wound gape and leakage^{50,56,58}. The limitations are location and completion of FSL created wound in some cases.

2.4. Arcuate/Astigmatic Keratotomies

Corneal partial-thickness incisions are included in the armamentarium of corneal astigmatism surgical correction. Classically performed in a manual (blade) manner, keratotomy with FS technology shows higher predictability and repeatability, adding the possibility of completely intrastromal incisions beyond the standard anterior penetration^{61, 62}.

These designated arcuate incisions (AIs) can be performed by the FS laser at the surgeon's predetermined depth, length, location, and treatment axis; additionally, anterior penetrating AIs can be opened manually intraoperatively or post-operatively to enhance the effect^{63,64}. (Fig. 1.14)



Figure 1.14: Example of FS laser assisted arcuate keratotomies (AKs), with LDV Z8.

Femtosecond laser-assisted arcuate keratotomy (FSAK) is associated to less irritation, epithelial ingrowth, or loss of corneal sensation, beyond diminishing the risk of infection for patients⁶⁵; thus, it can be safely used in patients with ocular surface disease or after keratoplasty. Nevertheless, it is believed that intrastromal AIs may have a reduced astigmatic effect when compared to anterior penetrating AIs, due to the fact that the former do not involve Bowman's membrane.

Intrastromal incisions are also used for non-refractive marking of the implantation axis of toric IOLs⁶⁶.

Several studies point out to comparable results between FS laser-assisted corneal incision and toric IOLs implantation, in correcting mild (<1.25 D), central, and with-the-rule astigmatism, regarding safety, efficacy and stability⁶⁷⁻⁷¹.

However, most of the available studies show some superiority of toric IOLs implantation compared to FSAK, in moderate-to-high (>1.25 D), against-the-rule, or limbus-to-limbus astigmatism correction^{70, 72, 73}.

Regarding the nomograms for femtosecond laser-created AIs, the literature is scarce. Wortz & Gupta developed a nomogram for correction of low levels of astigmatism⁷⁴. Baharozian *et al*'s FSL anterior penetrating AI nomogram was designed for patients with <1.25 D of astigmatism and it is a modification of Donnenfeld's manual limbal relaxing incisions (LRI) nomogram; it accounts for the influence of posterior corneal astigmatism relative to the type of astigmatism being treated and uses a 9.0 mm optical zone⁷⁵. Hence, there are notable advantages with FLALS as compared to CP. Firstly, treatment of astigmatism is much more accurate with FSAK than manual keratotomy, given the ability to control depth and location⁵⁰. Secondly, the ability to perform intrastromal incisions is unique to FSL. Finally, postoperative tuning of astigmatic correction is feasible with opening of laser-assisted incisions (at the slit-lamp).

Nevertheless, FLALS' range of correction is limited to low levels of corneal astigmatism, with improved and FSAK-specific nomograms yet to be developed.

2.5. Clinical Outcomes

There have been some contradictory published reports concerning comparison of corrected, uncorrected distance visual acuities, and refractive outcomes, between FLALS and CP. On one hand, no statistically significant differences between FLALS and CP were found regarding those outcomes in the long-term in some cohort studies and

randomized controlled trials (RCTs)⁷⁶⁻⁷⁹. On the other hand, the few systematic reviews and meta-analyses comparing FLALS and CP show better uncorrected and corrected visual acuities with FLALS as compared to CP^{45,80}. While Kolb *et al.* report better medium-term uncorrected and corrected visual acuities (representing a clinical difference inferior to 0.05 LogMAR) with FLALS⁴⁵, a very recent systematic review and metanalysis by Song *et al.* comprising 41 RCTs, show evidence of an early and long term superiority of FLACS over CP regarding uncorrected and corrected visual acuities, together with a better IOL centration⁸⁰.

Visual acuity can be affected in the long-term by capsular bag-IOL interaction, such as tilt, decentration or posterior capsule opacification. These events are reported to occur less frequently after FLALS⁷⁹⁻⁸¹. Long-term IOL positioning relates to several factors, with capsular bag shrinkage standing out as a major factor for tilt and decentration; this phenomenon is known to be more prominent in CP⁸¹.

Anterior opening diameters have been shown to vary differently (with shrinkage) early in the postoperative period with high energy FLACS, according to the implanted IOL's anterior edge design⁸² and the type of material, with higher anterior capsule contraction induced by hydrophobic IOLs than that induced by hydrophilic IOLs⁸³. The extent of this finding is uncertain but may relate to the tensile strength of the laser-produced capsular margin.

IOL positioning affects effective lens position, which is essential to achieve the best IOL power calculations' results. Furthermore, such positioning impacts decisively on the performance of premium IOLs, such as toric, enhanced depth of focus (EDOF) and multifocal lenses. Kranitz *et al.* identified significantly higher levels of IOL decentration and worse corrected distance visual acuity (CDVA) in the CP group²⁸. Donmez *et al.* reported better uncorrected distance visual acuity (UDVA) at 3 months after toric multifocal IOL implantation with FLACS than with CP⁸⁴. Other authors registered a higher IOL tilt and decentration with CP when compared to FLALS^{85, 86}.

Regarding posterior capsule opacification, some studies show an earlier onset with FLALS^{19,87}, probably related to adjacent laser treatment, which may induce a lens epithelial cells' (LEC) mesenchymal transformation. This impact is generally assumed to override the expected benefits of a laser driven LEC apoptosis close to the capsulotomy edge, interestingly described by some authors⁸⁸⁻⁹⁰; again, laser pulse energy and duration are relevant features regarding this impact. Subgroup analysis of posterior capsule opacification (PCO) with different pulse energy (high vs low) FLALS is almost

inexistent with a few exceptions. Furthermore, evidence is lacking based on subgroup analysis regarding different types of IOLs.

However, Nd: YAG laser capsulotomy rates in FLALS are reportedly lower with respect to CP^{91, 92}. This may be accounted for by a lower PCO grade and, consequently, minor impact on visual acuity.

Another measure of refractive predictability is the mean absolute error (MAE). Depending on the number and study design of the included trials, review and meta-analyses reports are not clear on FLALS superiority over CP regarding postoperative spherical equivalent (SE). Hence, large randomized controlled trials (RCT) based reviews point to a higher predictability of FLALS in the short-term but not in the long-term⁹³, whereas reviews based on a short number of RCT⁷⁹, report an advantage in favor of FLALS' MAE at 12 months follow-up. Other systematic reviews, which included both prospective and retrospective trials, found a clinically important difference of MAE only in the mid-term (1 month to 3 months follow-up)⁴⁵.

The very rare studies approaching the comparison of refractive outcome prediction accuracy between CP and FLACS (using optimized lens constants for modern intraocular lens formulas), point to no statistically significant difference between the two techniques⁹⁴.

Surgically induced astigmatism (SIA) is caused by the wound healing process after corneal incision⁹⁵. This form of astigmatism is caused by the processes at the place where the corneal incision took place, and it is most relevant to toric IOLs implantation. Temporal clear corneal incisions with FS have been reported to be astigmatically neutral⁹⁶, and statistically similar to CP's^{97,98}. Differences between FLALS and CP, regarding SIA, only seem to be clinically significant at the reproducibility and predictability (achieved vs attempted) levels, without statistically significant difference with respect to overall magnitude of SIA⁹⁸⁻¹⁰¹.

Non-refractive, commonly assessed, surgical endpoints are effective phacoemulsification time (EPT), cumulative dissipated energy (CDE) and circularity of capsulotomy. EPT represents the value of phacoemulsification time length at 100% power in continuous mode, while CDE is the EPT in seconds divided by 6000 or the EPT in minutes divided by 100⁴⁵. There is enough evidence that FLALS is superior to CP in every and each of the aforementioned parameters^{24,49,60,102-108}. A more precise and reproducible capsulotomy circularity is registered with FLACS, which allows for better lens centration and a lower risk for lens mispositioning¹⁰⁸⁻¹¹⁰; this, in turn, is liable to translate into a better optical performance^{110,111}.

2.6. Complications

Complications associated with FLALS can be either intraoperative or postoperative. Intraoperative complications usually described are docking suction loss, subconjunctival hemorrhage and capsule or pupil related^{18,54}.

Docking suction loss is consequent to interface defects, patient eye movement, and anatomic particularities such as conjunctivochalasis, pinguecula, pterygia or bleb filtration surgery. Some FS platforms have different diameter suction rings to improve fitting of the docking piece. In the event of suction loss, laser treatment is to be suspended immediately to avoid mistreatment.

Subconjunctival hemorrhage is caused by the vacuum applied, total treatment time, and the specific docking interface; this complication is frequently reported with appplanation docking, rather than with a liquid-interface¹⁰.

Posterior capsule rupture (PCR) has been reported to be less frequent with FLACS than with CP^{45, 78, 112-114}. Regarding anterior capsule complications (tears or tags), the reported evidence of higher incidence with FLALS is two-fold: firstly, it is described to be variable, from 0.1% to as high as 4%^{17,115-118}, secondly, this complication is mostly related to high-energy pulse FS platforms^{18,28,45,106,119,120}. These findings can be explained by the microscopically different capsulotomy edges, as produced by the different laser settings. Commonly, high-energy FLALS produces less smooth and notched capsulotomy edges, when compared to low-energy pulse FS^{9,121-123}. This microscopic difference may account for the very low incidence of anterior capsule complications of low-energy FLALS, comparable to CP.

Either way, overall implications of all capsule related complications (such as need for vitreoretinal surgery or affecting visual outcomes), seem to be not statistically significant in a global comparison between FLALS and CP^{45,114,124}. Nevertheless, the impact of such events should not be underestimated in the context of premium IOL implantation as it irrevocably compromises the surgical success, as capsular integrity and further optimal centration are capital in the final result. Unfortunately, literature comparing low-energy FLALS and CP that contemplates this niche or subgroup of refractive cataract surgery is scarce, although not absent^{46,125}.

Pupil constriction is a commonly reported feature of FLALS^{18,39,114,122,126}, associated to prostaglandin release during laser treatment of the anterior capsule¹²⁷⁻¹²⁹. Pupil miosis is a severe and undesirable event as it affects the feasibility of lens surgery. Therefore, a multitude of actions, either single or in combination, have arisen to address this issue¹²⁹⁻

¹³¹. Also, it is recommended to observe specific laser-related conditions, as the distance from intended capsulotomy edge and pupillary margin (>1 mm recommended) and duration of laser treatment^{132,133}.

However, most of the published literature reports this complication without differentiating between types of FS pulse, i.e., high or low energy (or even excluding the latter type). Current publications show evidence of an absence of laser-induced miosis with low-energy FLALS^{10,123,134,135}. Also, in the few systematic reviews and meta-analyses that include low-energy FLALS and subgroups analysis, the reported incidence of laser-induced pupil miosis is virtually null and comparable to CP⁹. On the contrary, high-pulse energy FLALS is associated with pupil constriction almost universally^{45,78,113,121}. The impact of such evidence should not be ignored and is still to be integrated in the common knowledge of femtosecond laser-assisted lens surgery.

Concerning postoperative complications, corneal and retinal statuses have been the object of several studies. Published literature, based on randomized controlled trials (RCTs) englobing the two types of femtosecond pulses (mostly high-energy) does not present evidence of a statistically significant difference between the techniques in normal eyes¹³⁶⁻¹⁴⁰. Endothelial cell loss (ECL) is reported to be lower with FLACS as compared to CP in several reviews and meta-analyses^{45,85,93,100,141-143}; this advantage is also reported in the few intraindividual RCT studies comparing low-energy FLACS and CP¹⁴⁴. Laser-assisted lens fragmentation reduces effective phacoemulsification time with less volume irrigation and CDE, especially in harder cataracts^{100,138}, leading to less ECL. Moreover, some studies enhance the evidence of this protective effect in corneal dystrophies (such as Fuchs'), by means of the above cited mechanisms¹⁴⁵⁻¹⁴⁷.

Regarding the incidence of cystoid macular edema (CME), most systematic reviews and meta-analyses showed no significant differences between FLACS and CP^{93,100,141,148}. Similarly, measurement of most retinal parameters (total macular volume, foveal thickness, and outer macular ring) had comparable results in both techniques¹⁴⁹⁻¹⁵¹. However, a short-term postoperative lower central macular volume with FLALS was registered in some studies involving patients with age-related macular degeneration (AMD)¹⁵². Also, in diabetic patients with absent or mild retinopathy, central macular thickness is reported to return to preoperative values after surgery with FLACS when compared to CP¹⁵³. Hence, FLACS may be advantageous in patients with macular vulnerability⁴⁵; this indication being further supported by the evidence of the higher impact of ultrasound energy on the inflammatory response of the posterior segment as compared to FLACS^{57,150,154}.

In a prospective cohort study, Ciona *et al.* reported higher expression of cytokines in the aqueous humor of diabetic patients who underwent FLACS (with a high energy pulse platform) as compared to CP¹⁵⁵. However, no difference was registered between clinical inflammatory biomarkers (such as macular volume or central retinal thickness MCT) between FLACS and CP. On the other hand, a randomized controlled trial by Schwarzenberger *et al.* did not show any differences in cytokines between low-energy FLACS and CP¹⁵⁶.

A considerable learning curve is in demand for FLALS, depending on the surgeons' experience; above these numbers, a significant decrease in intraoperative complications is registered in most studies^{16,17,37,124,125,157-159}.

2.7. Indications and Contraindications

2.7.1. Indications

FLALS has been advocated in refractive lens (with or without opacification) surgery with premium IOL implantation^{160,161}, due to the ability to produce a highly precise, reproducible, and customizable capsulotomy (regarding width and centration), surpassing CP standards. This fact is paramount for achieving an optimized IOL centration, essential to a premium IOL's performance.

New IOLs models, capsulotomy fixated, have consequently emerged, with the aim of providing better stability on the long term^{162,163}.

Furthermore, low to moderate amounts of astigmatism can be addressed to by FS arcuate keratotomies (FSAKs)¹⁶⁴.

Beyond the elective nature of most of the presbyopia lens surgery, hard cataracts can be an indication for FLALS, as laser fragmentation of the lens nucleus reduces total and effective phacoemulsification time and CDE, lowering the risk of corneal endothelial cell loss¹⁶⁵. Also, by means of increasing spot density, Han *et al.* have reported no additional oxidative stress when performing cataract surgery with a low energy femtosecond laser platform¹⁶⁶.

Femtosecond laser assisted lens surgery may be indicated in complex cases with challenging capsulotomies, such as traumatic subluxated cataracts or with zonular instability¹⁶⁷⁻¹⁶⁹, intumescent cataracts and pseudoexfoliation syndrome, by reducing the stress on the zonular fibers and posterior capsule, consequently lowering the rate of postoperative complications. Posterior polar cataracts may be an indication for FLACS,

since OCT imaging and subsequent laser parameters increasing the posterior offset (distance between the posterior extent of nucleotomy and the posterior capsule) have been proven to help avoiding intraoperative posterior ruptures¹⁷⁰. Cataract grade can help determining the choice of FLACS over CP, as the lower EPT or CDE associated to the technique can be beneficial in hard cataracts¹⁷¹. Simultaneously, a faster visual recovery is noted with FLACS^{80,172,173}. In the same manner, eyes with particular conditions, such as shallow anterior chambers, can benefit from such approach¹⁷⁴.

The reported lower impact of FLALS on endothelial cell count when compared to CP, may indicate the former technique in cases of Fuchs' dystrophy and other endothelial degeneration¹⁷⁵.

The lower incidence of posterior capsular opacification (PCO) requiring Nd:YAG capsulotomy with FLACS when compared to CP, has been reported in various publications, contemplating both kinds of femtosecond laser pulse¹⁷⁶.

Femtosecond laser technique can also be used in cases of capsular contraction to enlarge the anterior capsulotomy to the desired size¹⁷⁷. Likewise, regarding pupil status, recent literature shows strong evidence that pupil constriction after FS laser delivery, classically attributed to this technique, is not a feature of low-energy pulse FLALS. This difference is not to be taken lightly as it has a relevant impact on the performance of the several surgical steps onwards.

2.7.2. Contraindications

Patients with several conditions may not be ideal for FLALS.

Docking feasibility may be affected by anatomic particularities such as deep-set eye globe, narrow palpebral fissure, prominent nose and or brow or inability to lay supine, present themselves as contraindications for FLALS^{178,179}. Other conditions can pose an increased challenge to FS laser-assisted cataract surgery and can be considered relative contraindications. Amongst them are some poor pupillary dilation (<6 mm diameter), corneal surgeries (such as keratoplasty), or glaucoma surgery, white cataract, mild corneal scarring or edema.

Also, any condition affecting OCT (or equivalent) imaging of the anterior segment, namely, previous corneal additive surgery (such as intrastromal rings or inlay implants), severe corneal opacity or edema, are main contraindications for FLALS^{23,179}. Previous

radial keratotomy (RK) with thickened incisional scars may pose additional risk of incomplete laser penetrance, leading to anterior capsule tears^{180,181}.

Preoperative pupillary dilation has been addressed to by multiple approaches: several preoperative administration schemes contemplating topical medications such as phenylephrine, cyclopentolate, atropine and/or nonsteroidal anti-inflammatory drugs (NSAIDs)^{182,183}. Additional intraoperative measures have been advocated such as intracameral epinephrine or phenylephrine, viscomydriasis with viscoelastic or placement of iris expansion devices. It should be stressed that deficient pupil dilation poses a different challenge depending on the type of pulse energy level of the FLALS platform. As extensively described, laser-induced miosis with high-energy FLALS adds extra difficulty to a preoperative narrow pupil. This fact gave birth to a vast literature covering multiple strategies to address pupil constriction with high-energy FS platforms^{97,77,184,185}. On the contrary, low-energy pulse FLALS is reportedly not associated to pupil narrowing and therefore poses no additional dilation strategies as compared to conventional phacoemulsification¹³⁴.

Lens fragmentation patterns have been shown to reflect on the level of EPT; this measure had lower values with the grid pattern although the segmentation pattern is recommended for eyes with high lens density¹⁸⁶. Lens fragmentation is to be cautiously employed in white cataracts, due to the low feasibility of adequate imaging of opaque tissue^{23,187}. In particular, laser nuclear fragmentation should be avoided in Morgagnian cataracts due to the possibility of overlap between the anterior capsulotomy and lens fragmentation plan^{187,188}. Laser energy absorption is also conditioned by the variations in water content, as is the case of white or brunescient cataracts. For FS platforms performing lens fragmentation after the capsulotomy step, intumescent cataracts pose an additional risk of capsule rupture, caused by a capsule depth change after capsulotomy decompression^{189,190}. The incidence of anterior capsule complications (tears or incomplete capsulotomy) has been reported to be as high as 33%^{118,191}. This feature is not shared by other FS platforms which perform a different step sequence, accomplishing capsulotomy after lens fragmentation^{9,125}.

Although completeness of capsulotomy and fragmentation may be jeopardized in the presence of corneal opacities (scar or edema), there are isolated case reports of successful FLALS¹⁹². Undoubtedly, the magnitude of such opacities is a relevant parameter in this context.

Distortions in normal anatomy, either natural (pterygium or pinguecula) or iatrogenic (filtering blebs or tubes, as in glaucoma surgery), present themselves as challenging

cases, but should not constitute absolute contraindications, rather demanding additional care; with this regard, success has been reported in such cases¹⁹³. Another concern is the impact of docking on intraocular pressure, due to suction and type of docking; applanating systems are associated to higher pressure upon docking than liquid interfaces^{13,34}. So far there is no evidence of disease progression with well-controlled glaucoma or other optical neuropathies, for such matter^{93,141}. Shorter eyes (lower axial length) have been associated to a higher rise of ocular pressure rise during docking, in particular in patients with glaucoma, although with no associated progression of the disease¹⁹⁴.

3. Objectives

3.1. General objective

The objective of this research is to assess the role of low energy femtosecond laser in the context of lens surgery.

3.2. Specific objectives

3.2.1 To compare low energy femtosecond laser assisted lens surgery with conventional phacoemulsification, at the refractive level (refractive accuracy, efficacy, and safety).

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3.2.2. To compare low energy femtosecond laser assisted lens surgery with conventional phacoemulsification, at the non-refractive level (accuracy, safety, and reproducibility of surgical steps).

4. Research Results

4.1. Femtosecond Laser-assisted Lens Surgery with Low-energy Pulse versus Conventional Phacoemulsification for Presbyopia Correction: An Intraindividual Study.

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RESEARCH ARTICLE

Femtosecond Laser-assisted Lens Surgery with Low-energy Pulse versus Conventional Phacoemulsification for Presbyopia Correction: An Intraindividual Study

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Abstract:

Background:

Lens surgery with multifocal IOL implantation for presbyopia correction is performed by femtosecond laser-assisted lens surgery or conventional phacoemulsification.

Objective:

To compare the clinical results of femtosecond laser-assisted with low-energy pulse conventional phacoemulsification lens surgery for presbyopia correction intraindividually.

Methods:

Charts from patients who underwent Refractive Lens Exchange (RLE) for presbyopia correction in a single center, with Femtosecond Laser-Assisted Lens Surgery (FLALS) in one eye and Conventional Phacoemulsification (CP) in the other, were retrospectively reviewed. All eyes had the same multifocal Intraocular Lens (IOL) implanted. The clinical outcomes and the results of the level of satisfaction questionnaire were compared between the two groups according to the technique employed (FLALS vs. CP) for a period of up to four years. Stability, efficacy and safety indices were also assessed.

Results:

This study comprised a total of 56 eyes of 28 patients randomly assigned FLALS in one eye and CP in the other. No statistically significant difference was observed between the two techniques regarding postoperative visual acuities, duration of surgical procedure, efficacy or safety indexes ($p > 0.05$). Refraction was stable in all FLALS eyes, whereas a change occurred in 2 eyes (7.1%) operated with CP upon 6 months postoperatively, but without statistical significance ($p > 0.05$). Satisfaction was slightly better with FLALS but not statistically significant ($p = 0.134$). No immediate myopia or other adverse events after the femtosecond laser were registered.

Conclusion:

The parameters assessed showed no significant differences between the two techniques, in spite of a difference of refraction stability upon 6 months postoperatively.

Keywords: Femtosecond, Presbyopia, Multifocal IOL, Phacoemulsification, FLACS, Intraindividual, Low-energy pulse.

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1. INTRODUCTION

Presently, presbyopia surgical correction is mostly addressed by Refractive Lens Exchange (RLE) with multifocal IOLs

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implantation. The quality of visual performance after a multifocal IOL implantation is largely determined by common aspects such as decreased contrast sensitivity and photic phenomena [1], which are dependent on the IOL design, residual refractive errors, wavefront abnormalities, and IOL tilt and decentration [2]. Femtosecond Laser-assisted Cataract Surgery (FLACS) has been implemented since 2009 (Nagy *et al.*) [3]. This technology relies on the use of ultrashort pulses

(in the femtosecond range, i.e., 10^{-15} s), its use being advocated in several steps of modern cataract surgery. Femtosecond laser technology enables a higher accuracy level of centration, circularity and adjustability in capsulotomy, when compared to Conventional Phacoemulsification (CP), besides producing customised multiplanar self-sealing corneal incisions, arcuate keratotomy and lens nucleus fragmentation [4 - 6]. Regarding capsulotomy, more accurate centration and more precise shaping and sizing of capsulotomy are associated with a reduction in the incidence of IOL movement, tilt, and decentration, consequently improving refractive stability and predictability [7, 8]. Decentered or tilted IOLs have been associated with an increase in Higher-Order Aberrations (HOAs) [9 - 11]. A considerable amount of literature comparing the clinical outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification has been produced, mostly involving toric and/or monofocal IOLs implantation. Few studies have been published comparing FLACS versus CP accompanied by multifocal IOL implantation [12].

Furthermore, the majority of publications do not differentiate femtosecond lasers on the basis of the pulse pattern, in spite of the physical evidence that devices differ according to the energy level and frequency of the femtosecond pulses, as outlined by Wu *et al.* [13]. Most devices produce pulses in the order of μ J and KHz, in terms of energy and frequency, respectively. To achieve this type of femtosecond emission, the common mechanism employed by the aforementioned group of devices is Chirped Pulse Amplification (CPA), whereas another type of device produces femtosecond pulses of energy and frequency in the order of nJ and MHz, respectively, through another, non-disclosed mechanism.

The goal of this study was to evaluate and compare the outcomes, including efficacy, safety, stability, quality of vision and adverse events rate, of femtosecond laser-assisted lens (clear or cataractous) surgery (FLALS, or FS) employing a low energy (on the order of nJ) and high frequency (in the order of MHz) pulse against Conventional Phacoemulsification (CP) for presbyopia correction with a multifocal IOL implantation.

2. MATERIALS AND METHODS

2.1. Study Design

A retrospective chart review was performed to identify all patients who randomly underwent presbyopic RLE with panoptix panfocal IOL (Alcon Laboratories, Inc.) implantation in both eyes, with conventional phacoemulsification surgery in one eye and femtosecond laser-assisted surgery in the other, between September 1, 2015, and February 1, 2019, at Hospital da Luz Arrabida (HLA). All surgeries were performed at HLA by two comprehensive cataract and refractive attending physicians using the Centurion Vision (Alcon Laboratories, Inc.) phacoemulsification system and the LDV Z8 femtosecond laser platform (Ziemer, Inc.).

2.2. Inclusion and Exclusion Criteria

Preoperative corneal astigmatism less than 0.75D, measured with a Placido - dual Scheimpflug tomographer (Ziemer

Ophthalmic systems AG), was required as an inclusion criteria for the study. Patients were excluded from the study if they had previous ocular surgery other than cataract surgery or RLE, corneal astigmatism more than 0.75D, ocular pathology, corneal abnormalities, and an endothelial cell count less than 2000 cells/mm².

2.3. Chart Review and Data Collection

A total of 28 patients (56 eyes) were identified in the chart retrospective review, following the inclusion and exclusion criteria. The collection was made of demographic and clinical data such as age, sex, date, lens opacity assessment, type of surgery (conventional versus femtosecond laser-assisted), procedure duration, preoperative and postoperative visual acuities and refractive errors, the stability of refraction, adverse events and quality of vision. All charts were reviewed for the preoperative assessment, at the day of surgery, the day after surgery and the postoperative visits scheduled at 1, 3, 6, 12 months and every year thereafter. Biometry, performed using optical interferometer Galilei G6 (Ziemer Ophthalmic systems AG) and every subsidiary examination (such as OCT, corneal topography, specular microscopy, etc.) were conducted by a technician, unaware of the type of surgical technique employed. Visual acuities, uncorrected and corrected, at a distance (UDVA and DCVA) of 6 m, intermediate (UIVA and DCIVA) at 60 cm and near (UNVA and DCNVA) at 40 cm were assessed, under the same photopic conditions (85 candelas/m²), with Snellen chart (for distance) and reading Jaeger chart (for near and for intermediate, with conversion to Snellen notation); ultimately, for analyses purposes, a conversion was also performed to LogMAR notation. Participants' manifested refractions were collected (sphere, cylinder and spherical equivalent), with objective refractive errors assessed by an autorefractor (Topcon Co. Ltd.). Stability of refraction was defined as a manifested refraction change of ≤ 0.5 D between last visit and 1st month visit, giving attention to the expected full recovering from the inflammatory state during the immediate postoperative period, i.e., up to 1 month after surgery. Safety index was defined as the ratio postoperative CDVA/preoperative CDVA (mean value), and efficacy index as the ratio postoperative UCVA/preoperative CDVA (mean value). Accuracy of spherical equivalent (SE) to the intended target (presented as the percentage of eyes within ± 0.13 D, ± 0.50 D, ± 1.00 and ± 1.25 D) was also measured.

Patient reported outcomes were assessed at the 6 months' visit, using a 5-point Likert scale questionnaire regarding the level of overall satisfaction (graded from 1 - very dissatisfied; 2 - dissatisfied; 3 - neither satisfied nor dissatisfied; 4 - satisfied; 5 - very satisfied) [14], whereas the quality of vision was determined by a 4-point likert scale questionnaire comprising the existence of visual disturbance or photic phenomena, graded from 0 (none) to 4 (very high).

Lens transparency was assessed by slit-lamp examination and assigned a grade according to the Lens Opacities Classification System (LOCS) III. Corneal topography and tomography were determined using a Placido - dual Scheimpflug device (Galilei G6). Macular spectral-domain optical coherence tomography was performed with a modular ophthalmic imaging platform (Carl Zeiss).

The femtosecond laser-assisted lens surgery was performed using a femtosecond laser (LDV Z8, Ziemer, Inc.). Two surgeons (R.S., A.M.) had received training and full accreditation on the device in anticipation of this trial and had performed at least 20 laser applications each before the study began. The femtosecond laser was used to perform capsulotomy, lens fragmentation and corneal incisions, and a phacoemulsification machine was used for further emulsification, irrigation and aspiration of lens material. Due to the portability of the femtosecond device employed (LDV Z8), the surgery was fully performed in sequence (femtosecond laser followed by the phacoemulsification) in the same operating theater, with the patient on the same operating bed. Phacoemulsification was performed using the Active Fluidics™ torsional phacoemulsification machine (Centurion Vision, Alcon Laboratories, Inc.). All operations were unilateral (one eye at a time) and performed under sedation. Both surgeons followed the same surgical protocol.

Preparation of patients was the same for both groups, *i.e.* tropicamide 0.28 mg in association with phenylephrine hydrochloride 5.4 mg contained in an ophthalmic insert (Mydrasert), placed in the lower conjunctival sac and oxybuprocaine hydrochloride 4 mg/l eyedrops before the procedure, with no specific medication for mydriasis prevention required in the femtosecond group. Injection of intracameral cefuroxime (Aprokam) was performed in every patient at the end of each surgery.

All patients were administered prednisolone (Frisolona Forte), ibuprofen (Edolfene) and ofloxacin (Floxedol) eyedrops for 3 weeks postoperatively.

2.4. Intraocular Lens

The Acrysof IQ TNFT00 Panoptix panfocal (Alcon Laboratories, Inc.) is a diffractive aspheric hydrophobic acrylic IOL with a blue light-filtering multifocal design. It is a modified L-haptic lens (0-degree angle), with a 13.0 mm overall diameter, a 6.0 mm optic, and a refractive index of 1.55 at a wavelength of 550 nm. The optical zone of the IOL is composed of a diffractive structure in the central 4.5 mm portion consisting of 15 diffractive zones and an outer refractive annulus. The quadrifocal design was modified so as to provide trifocal functionality for the patient at far (6 m), 60 cm (+2.17 D), and 40 cm (+3.25 D) distance [15]. The

Enlighten Optical Technology employed claims an optimization of light distribution as follows: 50% for far distance with 25% each for near focus and intermediate focus, with 88.0% light transmittance to the retina (for a simulated 3.0 mm pupil) [16, 17].

2.5. Statistical Analysis

Snellen and Jaeger visual acuities were converted to logarithm of the minimum angle of resolution (logMAR) for analysis. Comparisons were based on Student t-test, or non-parametric Mann-Whitney test when the equality of variances was not observed. The efficacy, in terms of UDVA, UIVA and UNVA at 4 weeks and last visit was designated as the primary outcome, with safety, stability, intraoperative and postoperative complications, refraction and patient-reported quality of vision selected as secondary outcomes. The sample size was determined for a significance level of $\alpha = 0.05$ and a power of 90%, considering different standardized effects ranging from 0.9 to 1.25; the resulting sample size ranged from 15 to 27 subjects in each group.

3. RESULTS

3.1. Preoperative Patient Data

The mean age of the 20 women (76.5%) and 8 men (23.5%) was 58.75 ± 5.941 years (range 47 to 73 years). Cataract removal was performed in 4 eyes (7.1%), whilst clear lens extraction was performed in 52 eyes (92.9%). Mean follow-up was 27.59 ± 10.146 months (ranging from 8 to 48 months). The mean IOL power was $+24.38 \pm 3.651$ D (ranging from 13.5.0 to 33 D).

All 28 patients had both eyes operated, with a total of 56 eyes operated. Femtosecond laser-assisted surgery was performed in 28 eyes (50%), whereas conventional phacoemulsification was performed in 28 eyes (50%).

Table 1 shows the patients' preoperative characteristics by technique group. There was no statistically significant difference between the 2 groups preoperatively. Regarding CDVA, each group had 26 eyes (92.8%) with 20/30 or better (Snellen notation), whereas 2 eyes (7.2%) in each group had CDVA worse than 20/30 ($p > 0.50$). The cases were distributed evenly between the 2 surgeons and between the 2 treatment techniques ($p = 0.987$) (Table 2).

Table 1. Patient demographic and clinical characteristics.

Parameter	Monocular		
	Mean value ± SD		P value
	FS	CP	
UDVA (logMAR)	0.36 ± 0.302	0.36 ± 0.294	0.986
CDVA (logMAR)	0.03±0.080	0.04±0.077	0.865
Spherical Equivalent (D)	1.35±2.140	1.75±2.333	0.505
Total corneal astigmatism (D)	0.540±0.227	0.654±0.128	0.188
Nuclear sclerosis†	0.18±0.669	0.14±0.525	0.825
Average keratometry (D)	43.98±1.430	44.02±1.595	0.915
Axial length (mm)	21.87±1.600	21.75±1.644	0.776
Anterior chamber depth (mm)	3.17±0.218	3.19±0.255	0.831

(Table 1) cont....

Parameter	Monocular		
	Mean value $\pm$ SD		P value
	FS	CP	
White-to-white (mm)	11.77 $\pm$ 0.293	11.77 $\pm$ 0.289	0.999

CDVA = corrected distance visual acuity (6 m); CP = conventional phaco; D = diopters; LogMAR = logarithm of the minimum angle of resolution; FS = femtosecond; SD = Standard Deviation; UDVA = uncorrected distance visual acuity (6 m)

†Lens Opacities Classification System III grade

Table 2. Case distribution between the 2 surgeons and between the 2 treatment techniques (p = 0.987).*

Parameter	Surgeon 1	Surgeon 2	Total
Conventional	15	13	28
Phacoemulsification			
Surgery			
Femtosecond	15	13	28
Laser-assisted			
Surgery			
Total	30	26	56

*Chi-square test.

3.2. Refraction and Visual Acuity

Femtosecond laser treatment was delivered successfully in all cases in the FS group, with no adverse events registered (including the presence of myosis or significant bubbles); similarly, conventional phacoemulsification was performed without any adverse events.

Mean postop UDVA was 0.01 ± 0.0661 logMAR (range -0.1 to 0.18) for all operated eyes (both techniques), while mean postop CDVA was -0.01 ± 0.0412 logMAR (range -0.1 to 0). The mean duration of surgical procedures was 14.80 ± 2.733 min for the femtosecond laser-assisted surgery (FLALS or FS) and 14.69 ± 2.121 min for Conventional Phacoemulsification (CP) ($p > 0.05$).

As shown in Table 3, mean postop visual acuity data did not differ significantly between techniques (p values > 0.05) at 6 months postoperatively. Cumulative snellen visual acuity is shown in Fig. (1), comparing uncorrected and corrected postoperative values for far, intermediate and near for the two techniques. Twenty-six eyes (92.8%) in the FS group and 25 eyes (89.3%) in the CP group had a monocular UDVA of 20/25 or better; all eyes in both groups had a minimum UDVA of

20/32 at 6 months postoperatively. Twenty-seven eyes (96.4%), both in FS and CP groups, had a CDVA of at least 20/20, and all eyes in both groups had a CDVA of 20/25 (Fig. 1A).

CDVA = corrected distance visual acuity (6 m); D = diopters; DCIVA = distance-corrected intermediate visual acuity (at 60 cm); DCNVA = distance-corrected near visual acuity (40 cm); LogMAR = logarithm of the minimum angle of resolution; UDVA = uncorrected distance visual acuity (6 m); UIVA = uncorrected intermediate visual acuity (at 60 cm); UNVA = uncorrected near visual acuity (40 cm)

Regarding postop UIVA, the CP group presented with 20/20 in 85.7% of the eyes against 78.6% in the FS group ($p = 0.494$), with closer results for DCIVA of 20/20 (78.6% vs 75%, respectively for CP and FS) ($p = 0.955$) (Fig. 1B). Concerning UNVA and DCNVA, mean values did not differ significantly ($p = 0.803$ and $p = 0.968$, respectively); for DCNVA, 92.8% in the FS group and 85.7% in the CP group achieved 20/25 or better (Fig. 1C). Considering safety in the context of the best measured visual acuity, histograms for far, intermediate and near are shown in Fig. (2), with similar results for both techniques.

Table 3. Postoperative visual and refractive outcomes.

Parameter	Monocular		
	Mean value±SD		P value
	FS	CP	
UDVA (LogMAR)	0.01±0.068	0.02±0.065	0.337
CDVA (LogMAR)	-0.01±0.044	-0.01±0.038	0.522
UIVA (LogMAR)	0.02±0.042	0.01±0.036	0.494
DCIVA (LogMAR)	0.03±0.044	0.02±0.049	0.955
UNVA (LogMAR)	0.04±0.054	0.04±0.059	0.851
DCNVA (LogMAR)	0.05±0.060	0.04±0.070	0.968
Spherical Equivalent (D)	0.009±0.259	-0.054±0.574	0.575

CDVA = corrected distance visual acuity (6 m); D = diopters; DCIVA = distance-corrected intermediate visual acuity (at 60 cm); DCNVA = distance-corrected near visual acuity (40 cm); LogMAR = logarithm of the minimum angle of resolution; UDVA = uncorrected distance visual acuity (6 m); UIVA = uncorrected intermediate visual acuity (at 60 cm); UNVA = uncorrected near visual acuity (40 cm).

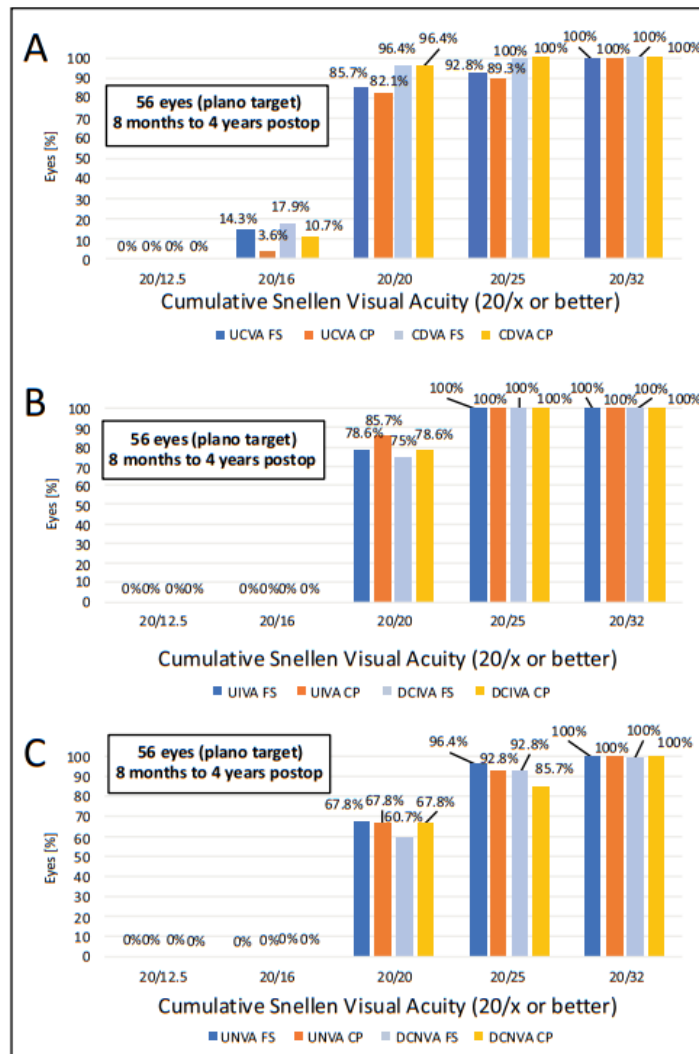


Fig. (1). (A, B and C) Cumulative postoperative monocular visual acuity at last visit (28 eyes in each group) (CDVA = corrected distance visual acuity (6 m); CP = conventional phacoemulsification group; DCIVA = distance-corrected intermediate visual acuity (at 60 cm); DCNVA = distance-corrected near visual acuity (40 cm); FS = femtosecond group; UDVA = uncorrected distance visual acuity (6 m); UIVA = uncorrected intermediate visual acuity (at 60 cm); UNVA = uncorrected near visual acuity (40 cm).

The assessment of efficacy and safety outcomes from an essentially refractive point of view (comparing preop CDVA vs. postop UDVA and CDVA, respectively) is also shown in the histograms in Fig. (3). The efficacy index was high for both techniques, with 1.08 ± 0.149 for the FS group and $1.05 \pm$

0.244 for the CP group ($p=0.893$). With regard to the safety index, the FS group of eyes achieved a value of 1.13 ± 0.244 , whereas the CP group had a similar value of 1.12 ± 0.236 ($p=0.888$). Regarding efficacy and safety indexes, there was no clinical difference between the techniques ($p>0.5$).

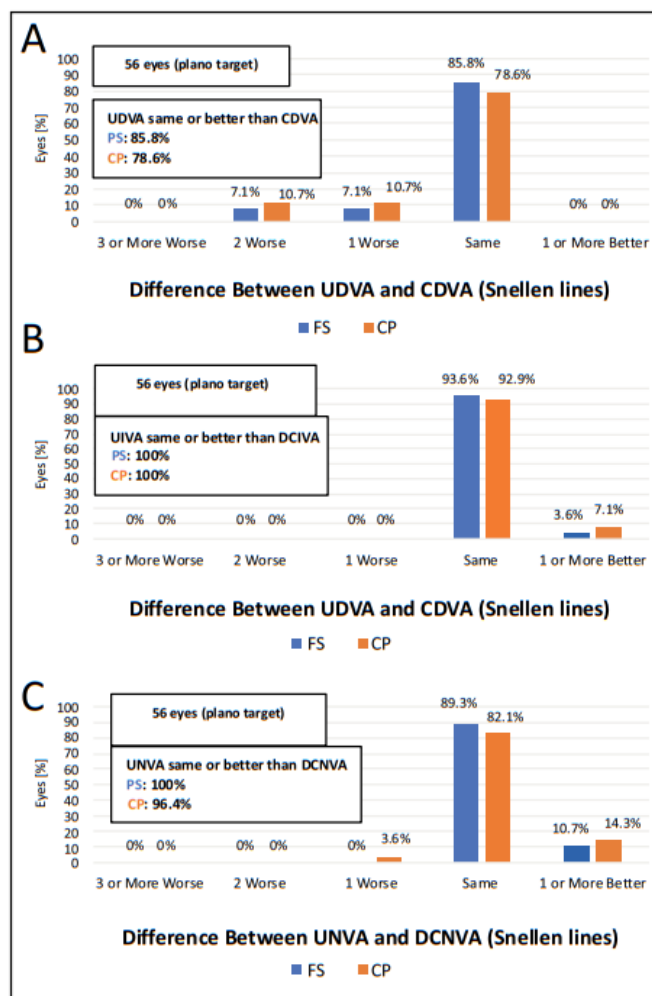


Fig. (2). (A, B and C) Difference between postoperative uncorrected and corrected monocular visual acuity at last visit (28 eyes in each group) (CDVA = corrected distance visual acuity (6 m); CP = conventional phacoemulsification group; DCIVA = distance-corrected intermediate visual acuity (60 cm); DCNVA = distance-corrected near visual acuity (40 cm); FS = femtosecond group; UDVA = uncorrected distance visual acuity (6 m); UIVA = uncorrected intermediate visual acuity (at 60 cm); UNVA = uncorrected near visual acuity (40 cm).

The accuracy of both techniques, regarding postoperative spherical equivalent, is shown in Fig. (4A). In the FS group, 96.4% of the eyes fell in ± 0.50 D range, compared to 84% of the eyes in the CP group. Four eyes (14.2%) in the CP presented with a negative postoperative spherical equivalent in the range of -0.51 to -1.25 D. Postoperative refractive cylinder assessment showed no differences between the two groups (Fig. 4B). Evaluation of the achieved *versus* attempted spherical equivalent refraction was conducted (Fig. 4C and D), with regression analysis showing the determination coefficients

for both groups; the value of R^2 was similar for the FS group ($R^2 = 0.9859$) and CP group ($R^2 = 0.9687$), thus not validating lower predictability of the CP procedure as compared to FS technique for this study population.

Stability of refraction was defined as a change of manifest refraction inferior to 0.5D between the 1st month visit and the last visit. Refraction was stable in all FS eyes, whereas a change occurred in 2 of the 28 eyes (7.1%) operated with CP between 1st month and 6th month visits (Fig. 5). There was a myopic change of 0.50D towards "plano" (0.0D) refraction.

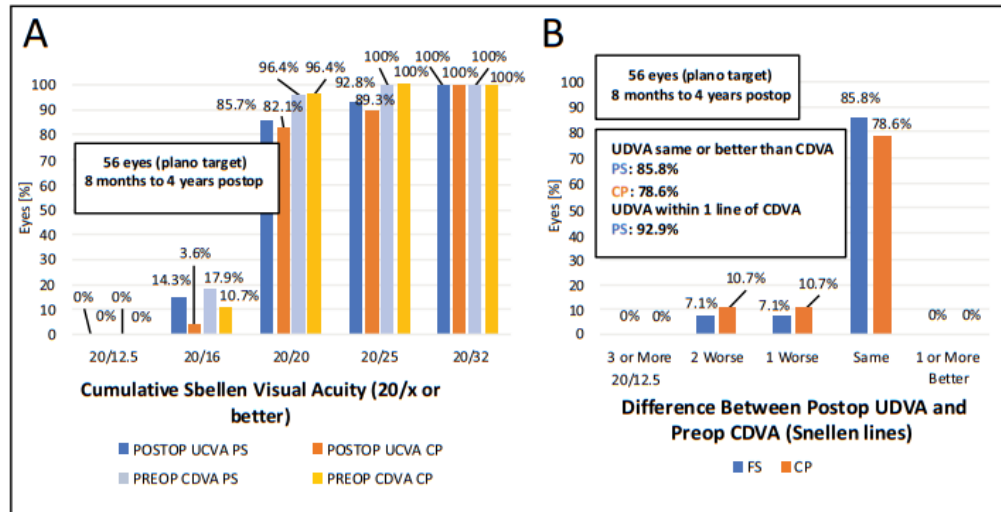


Fig. (3). (A) Cumulative monocular postop UDVA vs. preop CDVA at last visit (28 eyes in each group). (B) Difference between postop monocular CDVA and preop CDVA at last visit (28 eyes in each group) (CDVA = corrected distance visual acuity; FS = femtosecond group; CP = conventional phacoemulsification group; UDVA = uncorrected distance visual acuity).

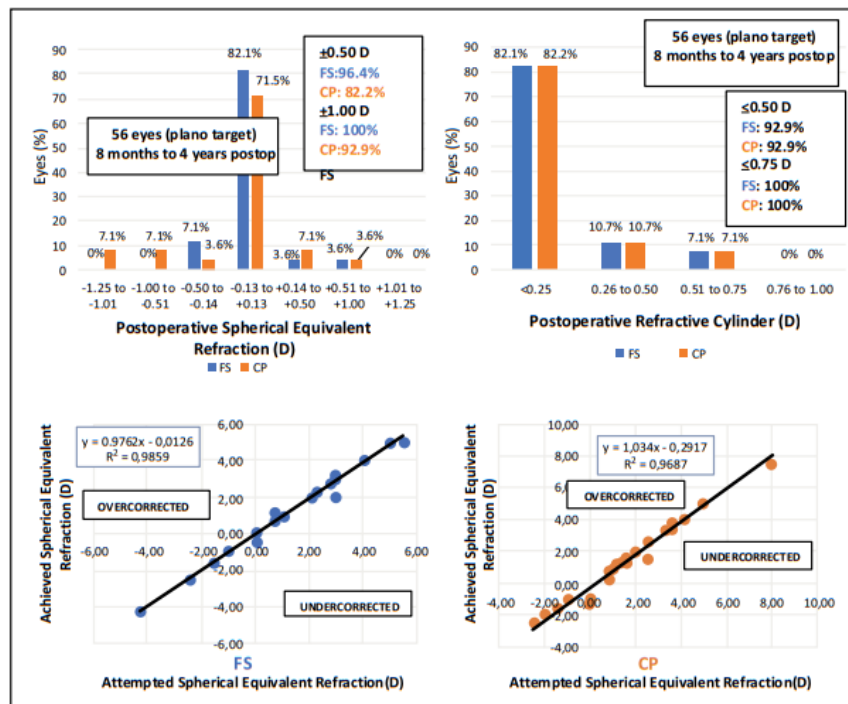


Fig. (4). (A) Accuracy of postoperative refractive spherical equivalent (n=28 eyes in each group). (B) Postoperative Refractive Cylinder (D). (C and D) Achieved versus Attempted Spherical Equivalent Refraction (CP = conventional phacoemulsification group; D = diopters; FS = femtosecond group).

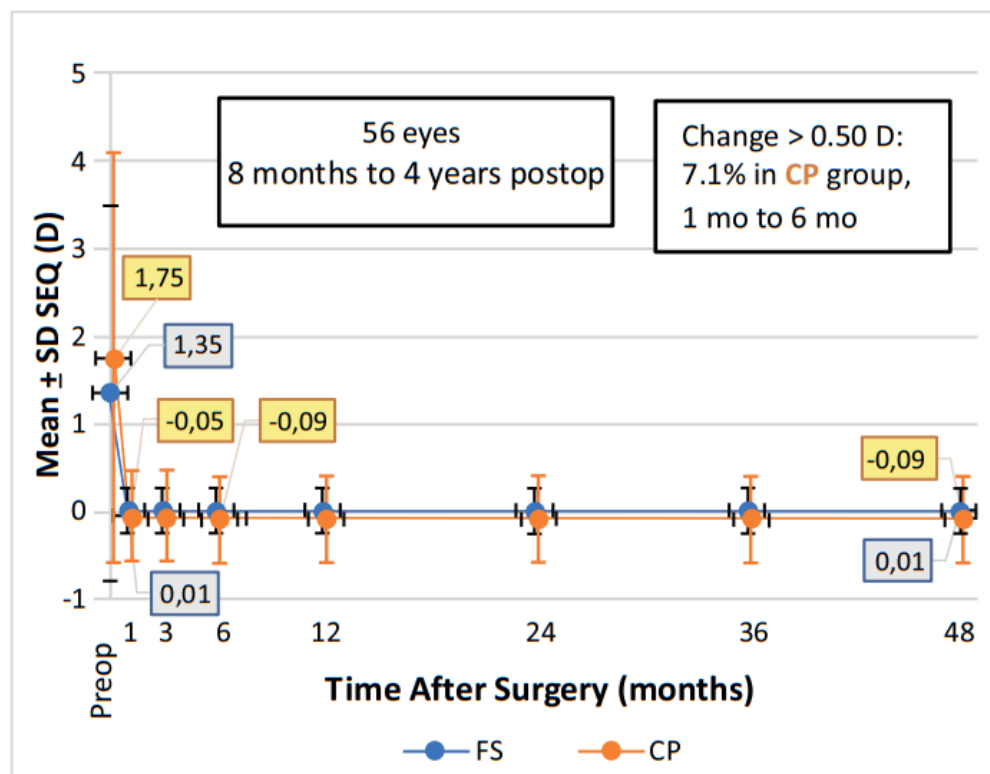


Fig. (5). Stability of spherical equivalent refraction (CP = conventional phacoemulsification group; D = diopters; FS = femtosecond group).

Table 4. Postoperative visual and refractive outcomes.

Parameter	Monocular		
	FS	CP	p value
QoV	1.14±0.650	1.29±0.713	0.103
Satisfaction Index	4.54±0.508	4.34±0.488	0.134

No statistically significant difference between the two techniques was obtained regarding refraction assessment, in spite of a difference between techniques regarding the accuracy of spherical equivalent (SE), with 96.4% of eyes in the FS group presenting postoperative manifest refraction in the ± 0.50 D range, as compared to 84% of the CP group eyes. At 6 months' timepoint, we found no significant difference in the postoperative visual acuity or postoperative spherical equivalent between the two groups.

Quality of vision and satisfaction, assessed at 6 months' visit, were slightly better with FLALS, but still not statistically significant ($p=0.103$ and $p=0.134$, respectively) (Table 4).

4. DISCUSSION

To this point, no other study involving presbyopia correction has assessed the visual outcomes intra-individually

with this follow-up line of time (4 years). In the current study, we chose to evaluate patients' charts at 4 weeks and beyond when the majority of postoperative oedema and inflammation had settled. At the 6 months' timepoint, we found no difference in the postoperative visual acuity between the two groups, with no changes thereafter in subsequent visits. The stability of refraction for both techniques was high, notwithstanding the registered changes in the CP group and pointing to some earlier stabilization of refraction in the FS group, thereby being in agreement with other studies [18, 19].

The high values of efficacy and safety indexes in both groups enlighten the good performance of the PanOptix IOL in what concerns to distance visual acuity, being in line with previously reported results [20, 21]. On the basis of techniques' comparison, a small, clinically non-significant superiority of FS over CP has been reported in terms of efficacy, safety and

accuracy, as also stated in some studies [22], but further investigation and discussion are required as our study sample was relatively small.

Globally, our results tend to agree with most of the published studies pointing to the similarity of clinical outcomes between femtosecond laser-assisted cataract surgery treatment and CP [23 - 25]. Reported gains in visual acuity after femtosecond laser-assisted surgery, in most studies [26], tend to be early (1 week postoperatively) or late (at 6 months), but not between the 1- to 3-month timepoints [27]. The rationale for this might be that femtosecond laser-assisted cataract surgery, in the early postoperative phase, is associated with reduced ultrasound energy and reduced corneal edema resulting in faster visual rehabilitation, followed by equivalence in the interim, and possibly, with late differences after 6 months, as some studies also suggest [28 - 30]. In our study, refraction was stable in all FS eyes, whereas a change occurred in 2 of the 28 eyes (7.1%) operated with CP between 1st month and 6th month visits, but without statistical significance ($p > 0.05$).

It should be stressed, however, that the vast majority of the published evidence does not include nor differentiate the results obtained with each femtosecond delivery machine (namely both types of femtosecond pulse), neither at the visual outcomes nor at the adverse events level. In our study, no adverse events, including myosis after femtosecond delivery, were registered; regarding myosis, our results are in accordance with other studies involving the same type of femtosecond pulse [31]. We did not find the commonly reported reflective pupil constriction associated with other types (high-energy and low-frequency) of femtosecond pulse as it is delivered by most FS machines available in the market. A possible explanation for this difference may be that the “low-energy” concept (employing a high numerical aperture in the femtosecond laser optics) produces smaller laser spots, which is liable to reduce collateral damage to the neighbouring tissues. This, in turn, could result in lower amounts of prostaglandins with consequent negligible (if any) intraoperative pupil narrowing. Furthermore, the time expended in patient transfer, required for most “high-energy” pulse platforms, may account for the loss of previously pharmacological induced mydriasis. Similarly, in our study, no anterior or posterior capsular-related events were registered, such as incomplete capsulotomy, anterior capsular tags and anterior or posterior capsular tears, contrary to reports of several reviews [32, 33], which do not contemplate and/or differentiate between the two types of femtosecond pulse.

Regarding total procedure time (from first to final surgical step), we found no clinically significant difference between FLALS and CP ($p > 0.05$) in our study, with no expended extra time, mostly due to the fact that the employed femtosecond device is portable and it was used in the operating room, with the patient positioned in the surgical bed throughout the sequential femto-phaco procedure. These findings of none or little impact on total surgical time with portable femtosecond device are in agreement with few other studies [34]. Although some studies show a marginal gain in productivity with FLACS [35], the great majority of previous literature indicates

a negative impact on productivity by incorporating a femtosecond laser; this evidence can largely be attributed to transfer time between the laser and the surgical bed or between laser and operating room, since, for these studies, only non-portable femtosecond devices have been included [36 - 38].

CONCLUSION

The vast majority of the studies exclude femtosecond lasers of low-energy and high-frequency pulse in lens surgery. To our knowledge, until this date, this is the only intraindividual study evaluating low-energy and high-frequency femtosecond pulse in lens surgery for presbyopia correction, and also for a 1 to 4 years of follow-up period. Most of the several studies showed little overall differences in visual and refractive outcomes between femtosecond laser-assisted cataract surgery and CP, along with productivity concerns (time expenditure) generally associated with the use of femtosecond laser in lens surgery, which have been observed to be comparatively worse in conventional phacoemulsification. In the present study, total procedure time was similar between the techniques, and no adverse events were registered, including post-femtosecond delivery myosis. Altogether, there was no significant difference registered between the techniques regarding clinical outcomes. Stability, although not statistically significant, was slightly better with FLACS. The present study is limited with respect to the number of participants. As such, a larger sample size is recommended to confirm and investigate these findings further.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective cohort study was approved by the Ethics Committee at Hospital da Luz Arrabida (HLA), Porto, Portugal.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participants to ensure the confidentiality and anonymity of the study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Pedro Oliveira, PhD, University of Porto, provided assistance with statistics.

Ramiro Salgado, Antonio Marinho and Paulo Torres planned the study. Ramiro Salgado and Antonio Marinho conducted the study. Ramiro Salgado submitted the study and is responsible for the overall content as guarantor.

REFERENCES

- [1] Yamauchi T, Tabuchi H, Takase K, Ohsugi H, Ohara Z, Kiuchi Y. Comparison of visual performance of multifocal intraocular lenses with same material monofocal intraocular lenses. *PLoS One* 2013; 8(6):e68236 [http://dx.doi.org/10.1371/journal.pone.0068236] [PMID: 23840836]
- [2] Salerno LC, Tiveron MC Jr, Alió JL. Multifocal intraocular lenses: Types, outcomes, complications and how to solve them. *Taiwan J Ophthalmol* 2017; 7(4): 179-84. [http://dx.doi.org/10.4103/tjo.19_17] [PMID: 29296549]
- [3] Nagy Z, Takacs A, Filkom T, Sarayba M. Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery. *J Refract Surg* 2009; 25(12): 1053-60. [http://dx.doi.org/10.3928/1081597X-20091117-04] [PMID: 20000286]
- [4] Mastropasqua L, Toto L, Mattei PA, et al. Optical coherence tomography and 3-dimensional confocal structured imaging system-guided femtosecond laser capsulotomy versus manual continuous curvilinear capsulorhexis. *J Cataract Refract Surg* 2014; 40(12): 2035-43. [http://dx.doi.org/10.1016/j.jcrs.2014.05.032] [PMID: 25450242]
- [5] Mastropasqua L, Toto L, Mastropasqua A, et al. Femtosecond laser versus manual clear corneal incision in cataract surgery. *J Refract Surg* 2014; 30(1): 27-33. [http://dx.doi.org/10.3928/1081597X-20131217-03] [PMID: 24864325]
- [6] Reddy KP, Kandulla J, Auffarth GU. Effectiveness and safety of femtosecond laser-assisted lens fragmentation and anterior capsulotomy versus the manual technique in cataract surgery. *J Cataract Refract Surg* 2013; 39(9): 1297-306. [http://dx.doi.org/10.1016/j.jcrs.2013.05.035] [PMID: 23988242]
- [7] Toto L, Mastropasqua R, Mattei PA, et al. Postoperative IOL axial movements and refractive changes after femtosecond laser-assisted cataract surgery versus conventional phacoemulsification. *J Refract Surg* 2015; 31(8): 524-30. [http://dx.doi.org/10.3928/1081597X-20150727-02] [PMID: 26248345]
- [8] Kránitz K, Miháitz K, Sándor GL, Takacs A, Knorz MC, Nagy ZZ. Intraocular lens tilt and decentration measured by Scheimpflug camera following manual or femtosecond laser-created continuous circular capsulotomy. *J Refract Surg* 2012; 28(4): 259-63. [http://dx.doi.org/10.3928/1081597X-20120309-01] [PMID: 22496437]
- [9] Turuwhehena J. A theoretical study of intraocular lens tilt and decentration on perceptual image quality. *Ophthalmic Physiol Opt* 2005; 25(6): 556-67. [http://dx.doi.org/10.1111/j.1475-1313.2005.00314.x] [PMID: 16343131]
- [10] Oshika T, Kawana K, Hiraoka T, Kaji Y, Kiuchi T. Ocular higher-order wavefront aberration caused by major tilting of intraocular lens. *Am J Ophthalmol* 2005; 140(4): 744-6. [http://dx.doi.org/10.1016/j.ajo.2005.04.026] [PMID: 16226535]
- [11] Altmann GE, Nishimura LD, Lane SS, Pepose JS. Optical performance of 3 intraocular lens designs in the presence of decentration. *J Cataract Refract Surg* 2005; 31(3): 574-85. [http://dx.doi.org/10.1016/j.jcrs.2004.09.024] [PMID: 15811748]
- [12] Lee JA, Song WK, Kim JY, Kim MJ, Tehah H. Femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: Refractive and aberrometric outcomes with a diffractive multifocal intraocular lens. *J Cataract Refract Surg* 2019; 45(1): 21-7. [http://dx.doi.org/10.1016/j.jcrs.2018.08.032] [PMID: 30424904]
- [13] Wu BM, Williams GP, Tan A, Mehta JS. A comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol* 2015; 2015616478 [http://dx.doi.org/10.1155/2015/616478] [PMID: 26483973]
- [14] Yoo A, Kwag JY, Song IS, et al. Comparison of visual function after implantation of inferior sector-shaped intraocular lenses: low-add +1.5 D vs +3.0 D. *Eur J Ophthalmol* 2016; 26(6): 607-11. [http://dx.doi.org/10.5301/ejo.5000771] [PMID: 27646332]
- [15] Kohnen T, Herzog M, Hemkepler E, et al. Visual performance of a quadrifocal (trifocal) lens following removal of the crystalline lens. *Am J Ophthalmol* 2017; 184: 52-62. [http://dx.doi.org/10.1016/j.ajo.2017.09.016] [PMID: 28923587]
- [16] Lee S, Choi M, Xu Z, Zhao Z, Alexander E, Liu Y. Optical bench performance of a novel trifocal intraocular lens compared with a multifocal intraocular lens. *Clin Ophthalmol* 2016; 10: 1031-8. [http://dx.doi.org/10.2147/OPTH.S106646] [PMID: 27330273]
- [17] Carson D, Hill WE, Hong X, Karakelle M. Optical bench performance of AcrySof® IQ ReSTOR®, AT LISA® tri, and FineVision® intraocular lenses. *Clin Ophthalmol* 2014; 8: 2105-13. [PMID: 25342881]
- [18] Ye Z, Li Z, He S. A meta-analysis comparing postoperative complications and outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract. *J Ophthalmol* 2017; 20173849152 [http://dx.doi.org/10.1155/2017/3849152] [PMID: 28540082]
- [19] Chen X, Xiao W, Ye S, Chen W, Liu Y. Efficacy and safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: A meta-analysis of randomized controlled trials. *Sci Rep* 2015; 5: 13123. [http://dx.doi.org/10.1038/srep13123] [PMID: 26269445]
- [20] Rementería-Capelo LA, Contreras I, García-Pérez JL, Blázquez V, Ruiz-Alcocer J. Visual quality and patient satisfaction with a trifocal intraocular lens and its new toric version. *J Cataract Refract Surg* 2019; 45(1): 1584-90. [http://dx.doi.org/10.1016/j.jcrs.2019.06.014] [PMID: 31587937]
- [21] Böhm M, Petermann K, Hemkepler E, Kohnen T. Defocus curves of 4 presbyopia-correcting IOL designs: Diffractive panfocal, diffractive trifocal, segmental refractive, and extended-depth-of-focus. *J Cataract Refract Surg* 2019; 45(1): 1625-36. [http://dx.doi.org/10.1016/j.jcrs.2019.07.014] [PMID: 31706517]
- [22] Shaheen MS, AbouSamra A, Helaly HA, Said A, Elmassry A. Comparison between refractive outcomes of femtosecond laser-assisted cataract surgery and standard phacoemulsification. *BMC Ophthalmol* 2020; 20(1): 1. [http://dx.doi.org/10.1186/s12886-019-1277-9] [PMID: 31898534]
- [23] Day AC, Gore DM, Bunce C. Laser assisted versus manual phacoemulsification for lens extraction. *Cochrane Database Syst Rev* 2013; 9CD010735 [http://dx.doi.org/10.1002/14651858.CD010735]
- [24] Manning S, Barry P, Henry Y, et al. Femtosecond laser-assisted cataract surgery versus standard phacoemulsification cataract surgery: Study from the European registry of quality outcomes for cataract and refractive surgery. *J Cataract Refract Surg* 2016; 42(12): 1779-90. [http://dx.doi.org/10.1016/j.jcrs.2016.10.013] [PMID: 28007110]
- [25] Abell RG, Darian-Smith E, Kan JB, Allen PL, Ewe SYP, Vote BJ. Femtosecond laser-assisted cataract surgery versus standard phacoemulsification cataract surgery: Outcomes and safety in more than 4000 cases at a single center. *J Cataract Refract Surg* 2015; 41(1): 47-52. [http://dx.doi.org/10.1016/j.jcrs.2014.06.025] [PMID: 25466483]
- [26] Conrad-Hengerer I, Al Sheikh M, Hengerer FH, Schultz T, Dick HB. Comparison of visual recovery and refractive stability between femtosecond laser-assisted cataract surgery and standard phacoemulsification: six-month follow-up. *J Cataract Refract Surg* 2015; 41(7): 1356-64. [http://dx.doi.org/10.1016/j.jcrs.2014.10.044] [PMID: 26287876]
- [27] Roberts HW, Wagh VK, Sullivan DL, et al. A randomized controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery. *J Cataract Refract Surg* 2019; 45(1): 11-20. [http://dx.doi.org/10.1016/j.jcrs.2018.08.033] [PMID: 30413333]
- [28] Okada M, Hersh D, Paul E, van der Straeten D. Effect of centration and circularity of manual capsulorhexis on cataract surgery refractive outcomes. *Ophthalmology* 2014; 121(3): 763-70. [http://dx.doi.org/10.1016/j.ophtha.2013.09.049] [PMID: 24342022]
- [29] Kovács I, Kránitz K, Sándor GL, et al. The effect of femtosecond laser capsulotomy on the development of posterior capsule opacification. *J Refract Surg* 2014; 30(3): 154-8. [http://dx.doi.org/10.3928/1081597X-20140217-01] [PMID: 24763719]
- [30] Yu AY, Ni LY, Wang QM, et al. Preliminary clinical investigation of

- cataract surgery with a noncontact femtosecond laser system. *Lasers Surg Med* 2015; 47(9): 698-703.
[http://dx.doi.org/10.1002/lsm.22405] [PMID: 26311629]
- [31] Mirshahi A, A Ponto K. Changes in pupil area during low-energy femtosecond laser-assisted cataract surgery. *J Ophthalmic Vis Res* 2019; 14(3): 251-6.
[http://dx.doi.org/10.18502/jovr.v14i3.4780] [PMID: 31660103]
- [32] Wang J, Su F, Wang Y, Chen Y, Chen Q, Li F. Intra and post-operative complications observed with femtosecond laser-assisted cataract surgery *versus* conventional phacoemulsification surgery: a systematic review and meta-analysis. *BMC Ophthalmol* 2019; 19(1): 177.
[http://dx.doi.org/10.1186/s12886-019-1190-2] [PMID: 31399070]
- [33] Popovic M, Campos-Möller X, Schlenker MB, Ahmed II. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: A meta-analysis of 14 567 eyes. *Ophthalmology* 2016; 123(10): 2113-26.
[http://dx.doi.org/10.1016/j.ophtha.2016.07.005] [PMID: 27538796]
- [34] Vasquez-Perez A, Simpson A, Nanavaty MA. Femtosecond laser-assisted cataract surgery in a public teaching hospital setting. *BMC Ophthalmol* 2018; 18(1): 26.
[http://dx.doi.org/10.1186/s12886-018-0693-6] [PMID: 29394929]
- [35] Roberts HW, Wagh VK, Mullens IJM, Borsci S, Ni MZ, O'Brart DPS. Evaluation of a hub-and-spoke model for the delivery of femtosecond laser-assisted cataract surgery within the context of a large randomised controlled trial. *Br J Ophthalmol* 2018; 102(11): 1556-63.
[http://dx.doi.org/10.1136/bjophthalmol-2017-311319] [PMID: 29436401]
- [36] Bali SJ, Hodge C, Lawless M, Roberts TV, Sutton G. Early experience with the femtosecond laser for cataract surgery. *Ophthalmology* 2012; 119(5): 891-9.
[http://dx.doi.org/10.1016/j.ophtha.2011.12.025] [PMID: 22361311]
- [37] Abell RG, Vote BJ. Cost-effectiveness of femtosecond laser-assisted cataract surgery *versus* phacoemulsification cataract surgery. *Ophthalmology* 2014; 121(1): 10-6.
[http://dx.doi.org/10.1016/j.ophtha.2013.07.056] [PMID: 24120324]
- [38] Lubahn JG, Donaldson KE, Culbertson WW, Yoo SH. Operating times of experienced cataract surgeons beginning femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2014; 40(11): 1773-6.
[http://dx.doi.org/10.1016/j.jcrs.2014.03.024] [PMID: 25217069]

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4.2. Pupil versus 1st Purkinje capsulotomy centration with femtosecond laser: long term outcomes with a sinusoidal trifocal lens.

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RESEARCH ARTICLE

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Pupil versus 1st Purkinje capsulotomy centration with femtosecond laser: Long term outcomes with a sinusoidal trifocal lens

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Abstract

Purpose: To assess the role of femtosecond laser-assisted capsulotomy centration in the long-term intraocular positioning of a multifocal intraocular lens.

Design: Prospective comparative study.

Methods: A total of 60 eyes of 30 patients underwent femtosecond laser-assisted Refractive Lens Exchange (RLE). For every patient, capsulotomy centration was randomly performed according to pupil centre (PC) in one eye and first Purkinje reflex (FPR) in the other. The intraocular lens (IOL) positioning, visual acuities, spherical equivalent, internal aberrometry and quality of vision were assessed and compared at 3 years' follow-up between groups (PC and FPR).

Results: Intraocular lens positioning showed a statistically significant difference between groups, with a closer centration to the visual axis in the FPR patients ($p < 0.001$). Internal aberrometry showed higher values in the PC capsulotomy centration group ($p < 0.01$).

Conclusions: FPR centered capsulotomy is associated to a closer centration of the IOL to the visual axis.

KEYWORDS

capsulotomy, cataract, femtosecond, FLACS, IOL centration



1 | INTRODUCTION

The role of capsulotomy in the intraocular lens (IOL) final position has long been established [1–3], being consensually accepted that an optimal (curvilinear, continuous, 360° IOL edge overlapping) capsulotomy is required to obtain the best positioning of the IOL, by ensuring long-term stability and centration, taken the IOL–capsular bag interaction, namely, capsular adherence and time-related retraction. Femtosecond laser-assisted

capsulotomy has been regarded as an improvement in this matter, as it is associated to higher levels of effectiveness, predictability, and accuracy [4, 5]. IOL centration is of paramount importance in multifocal IOL implantation, since adequate IOL positioning is required for attaining the goals of best performance and patient satisfaction [6].

Ideally, the IOL should be centered on the visual axis, pursuing the biometry goal (usually emmetropia) in purely refractive terms. In practical terms, the vertex

normal is used instead of the theoretical visual axis, which correlates to the first Purkinje reflex (FPR) [7, 8]. Additionally, in the case of multifocal IOLs, pupil center must also be considered for adequate IOL positioning, since pupillary diameter directly impacts on the different foci (distance, intermediate and near, for trifocal lenses), influencing these IOL's performance [9]. However, the optics of the eye are not ideal, which renders it impossible to line up the optical centers of all ocular elements. This evidence is translated, amongst other concepts, into the angle alpha and angle kappa; whereas the former reports to the angle formed between the visual axis and the optical center, the latter, in particular, is of relevance when considering the implantation of a multifocal IOL, as it relates to the angle formed between the theoretical visual axis and the pupil center. For practical purposes, the kappa angular measure has been substituted for a more modern and functional equivalent, which is the chord mu, as described by Chang and Waring [10]; this is a two-dimensional vector measured across the corneal surface from the center of the pupil to the coaxially sighted subject-fixated corneal light reflex (CSFCLR). The CSFCLR can be described as a line-of-sight guided corneal reflex when the patient fixates on the coaxial lights of the surgical microscope, closest to the FPR.

In this line of thought, a large k angle may constitute a contraindication for multifocal IOL implantation, as this condition inhibits an efficient combination of the two reference centration points; although a well-defined limit is not established, it is commonly accepted for most authors that chord mu should be inferior to 500 micra [6]. Regarding IOL implantation, it is currently recommended that the lens should be manually centered half-way between the pupil center and the visual axis (or FPR) [8, 10], thus conjugating both requirements. However, this common gesture has two main pitfalls. Firstly, it assumes that the IOL will stay in that position, not contemplating the IOL-capsular bag interaction along time; this interaction depends on several factors such as lens- and capsular bag-related conditions. Secondly, pupil center changes with pharmacological pupillary dilatation prior to surgery traduced by a significant increase of chord mu length [11]; therefore, intraoperative pupil center is farther away from the ideal visual axis, which compromises the accuracy of such positioning endeavor.

This study's protocol proposed to manually center the IOL inner diffractive circle in the alignment of along the first (CSFCLR) and fourth Purkinje reflexes during surgery, as recommended by some authors [8, 12].

The methodology of IOL centration assessment varies in the literature. Methods based on measuring the distance between the IOL optic edge to the dilated pupil have the disadvantage of disregarding the fact that

dilation is often asymmetric and affects normal geometry, consequently it does not reproduce the physiological status. Some sophisticated methods of measuring IOL decentration using Scheimpflug imaging, and anterior segment ocular coherence tomography (OCT) have been described. These methods have their own limitations. Measurements from Scheimpflug imaging can be inaccurate because of magnification and distortion effects from the Scheimpflug camera and OCT imaging requires 3D algorithmic analyses [13, 14].

This study proposes to assess the influence of capsulotomy centration on the long term IOL positioning, by comparing femtosecond laser-assisted pupil-centered versus FPR-centered capsulotomy.

2 | METHODS

This prospective randomized comparative 2-armed study was approved by the Ethics Committee at Hospital da Luz Arrabida (HLA), Porto (ref: 04/2019/CES) and was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki", with signed informed consent given by each patient. All patients were proposed to undergo femtosecond laser-assisted RLE in both eyes for presbyopia correction. For each patient, capsulotomy centration was randomly assigned to pupil centre in one eye and FPR in the other. All patients had surgery between October 3, 2019, and March 2, 2020, at Hospital da Luz Arrabida (HLA). All surgeries were performed at HLA by a single comprehensive surgeon (R.S.) using the Centurion Vision (Alcon Laboratories, Inc.) phacoemulsification system and the LDV Z8 femtosecond laser platform (Ziemer, Inc.). The IOL power was calculated to achieve emmetropia in all cases.

2.1 | Inclusion and exclusion criteria

Patients were excluded from the study if they had previous ocular surgery, preoperative corneal astigmatism more than 0.75D, chord $\mu > 500 \mu\text{m}$, ocular pathology, corneal abnormalities, and an endothelial cell count less than 2000 cells/mm². Also, posterior capsule opacification above minimal was considered a bias for this study's conclusions and constituted an exclusion criterium.

2.2 | Measurement procedures and study devices

The Galilei G4 is a tomography system based on dual Scheimpflug imaging and Placido-disc technology.

Participants were asked to look at the fixation point, blink, and open their eyes widely before each image acquisition. Manual alignment of the red crosshair to the four Purkinje dots, corresponding to the FPR in the cornea, is performed and mesopic (mean of 5.5 lx) pupil diameter and center (PC) are acquired. The device calculates chord μ length, from FPR to PC; this chord μ is apparent, as it measures the distance between the FPR and the pupil center viewed through the cornea. Galilei G4 displays several maps, enabling visualization of IOL central diffractive rings, along with FPR (corneal vertex), pupil and optical centers, and limbus-to-limbus imaging (Figure 1).

Aberrometry assessment was performed with VX120 (Visionix, Inc.); this is a multimodal platform, combining Scheimpflug and Placido-disc technology, together with an Hartmann-Shack aberrometer which directly measures corneal and total ocular aberrations, inferring the internal aberrations from the aforementioned data. All measurements were performed under the same illumination conditions (mesopic pupil at 5.5 lx).

Regarding distance measurement between protocol landmarks and reference points, the authors have chosen a hybrid measuring method. For IOL positioning assessment, eye photographs were obtained with Galilei G4 at the protocol timepoint (36 months postoperatively) and subsequently processed with the Fiji's Image J program (software version 2.0.0-rc-49/1.51a), which allowed several measurements of the distance between FPR, PC, OC and IOL center. Regarding IOL centration, the postoperative FPR was defined as the reference point, as it closely relates to the visual axis. Henceforth, decentration was determined according to the measured distances between FPR and the IOL centre (inner diffractive circle).

Calibration was accomplished by using the constant limbus horizontal size as a reference, allowing pixel measurements conversion into millimetres for each eye.

Biometry was performed using optical interferometer Galilei G6 (Ziemer Ophthalmic systems AG) and every subsidiary examination (such as OCT, corneal topography and specular microscopy) was conducted by a technician, unaware of the type of capsulotomy centration. Participants' manifest refractions were collected (sphere, cylinder, and spherical equivalent), with objective refractive errors assessed by an autorefractor (Topcon Co. Ltd.).

Posterior capsule opacification was assessed at the 3 years postoperative visit, after pupil dilation, with a modified version of the Evaluation of Posterior Capsule Opacification (EPCO), as described by some authors. For that matter, retroillumination images were obtained with Visionix and subsequently processed with Image J, which allowed identification, marking and calculation of density areas by performing pixel counts. The density of the opacification behind the IOL was clinically graded as follows: 0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe. Then, individual PCO score for each eye was determined with Evaluation of Posterior Capsule Opacification (EPCO) by multiplying the density of the opacification (graded from 0 to 4) by the fractional PCO area involved behind the IOL optic.

Patient reported outcomes were assessed using a 5-point Likert scale questionnaire regarding the level of satisfaction (graded from 1—very dissatisfied; 2—dissatisfied; 3—neither satisfied nor dissatisfied; 4—satisfied; 5—very satisfied), whereas quality of vision was determined by a 4-point Likert scale questionnaire comprising the existence of visual disturbance or photic phenomena, graded from 0 (none) to 4 (very high).

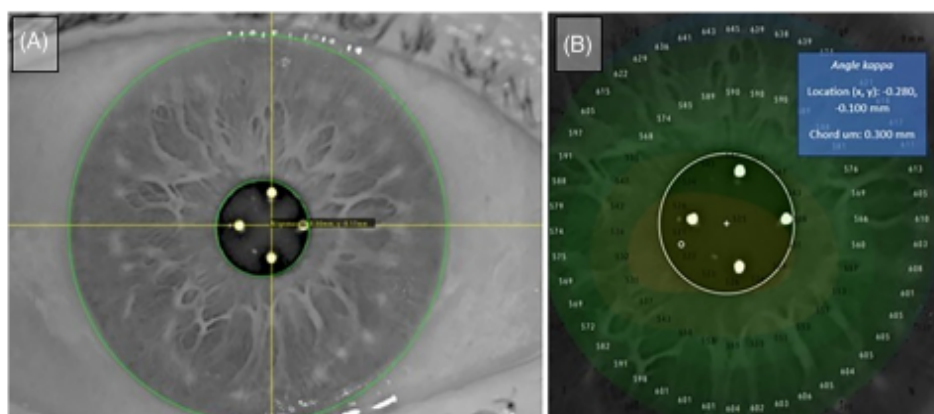


FIGURE 1 Top view imaging with Galilei G4. (A) Four dots hair cross (first Purkinje reflex). (B) Pupil center (small white cross), angle kappa and chord μ data (Galilei G4 software).

Lens transparency was assessed by slitlamp examination and assigned a grade according to the Lens Opacities Classification System (LOCS) III. Corneal topography and tomography were determined using a Placido—dual Scheimpflug device (Galilei G6). Macular spectral-domain optical coherence tomography was performed with a modular ophthalmic imaging platform (Carl Zeiss).

Postoperatively, all patients were evaluated at 1 day, 1 week, and at 1, 6, 12, 24 and every year thereafter and 36 months. Visual acuities were assessed with Snellen chart (for distance) and reading Jaeger chart (for near and for intermediate, with reading line conversion for the latest, keeping the same visual angle) and ultimately converted to LogMAR notation. Manifest refractions were collected (sphere, cylinder and spherical equivalent), with objective refractive errors assessed by an autorefractor (Topcon Co. Ltd.). At each visit, the uncorrected (UDVA) and corrected (CDVA) distance visual acuities at 6 m, uncorrected (UIVA) and corrected intermediate (CIVA) visual acuities at 60 cm, and uncorrected (UNVA) and corrected (CNVA) near visual acuities at 40 cm were measured. In the present study, and according to the proposed protocol, only the long-term (at the 3-years' visit) postoperative data are presented. All patients filled in the quality of vision and satisfaction level tests at 36 months.

2.3 | Intraocular lens

The Acriva^{UD} TrinovaTM (VSY Technology) is a plate-haptic, diffractive aspheric hydrophobic acrylic IOL with a blue light-filtering multifocal design. According to the

manufacturer, Sinusoidal Vision Technology (SVT[®]) has the aim of reducing photic phenomena.

2.4 | Surgical technique

One experienced surgeon (R.S.) performed all the surgeries. Capsulotomy, corneal incisions and lens fragmentation were accomplished by femtosecond laser (LDV Z8, Ziemer, Switzerland), followed by emulsification, irrigation and aspiration of lens material performed with the phacoemulsification machine (Centurion Vision, Alcon Laboratories, USA).

Capsulotomy was centered on the pupil center (PC) or the FPR, according to the protocol's randomized assignment. For this matter, in the FPR group of patients, the CSFCLR was marked on the cornea surface with an ink marker, immediately before femtosecond docking, and capsulotomy was centered on this point. In the PC group, pupil centration was achieved automatically with LDV OCT imaging upon docking and capsulotomy performed henceforth (Figure 2A,B).

After implantation, the IOL was positioned in the capsular bag with its innermost diffractive ring in alignment with the first (CSFCLR) and fourth Purkinje reflex, whilst the patient was asked to fixate on the coaxial light of the surgical microscope; after pressing the optic against the posterior capsule, the chamber was sealed with the IOL optic seated against the capsular bag.

2.5 | Statistical analysis

Comparisons were based on paired and unpaired Student's *t* test, or non-parametric analysis tests when the

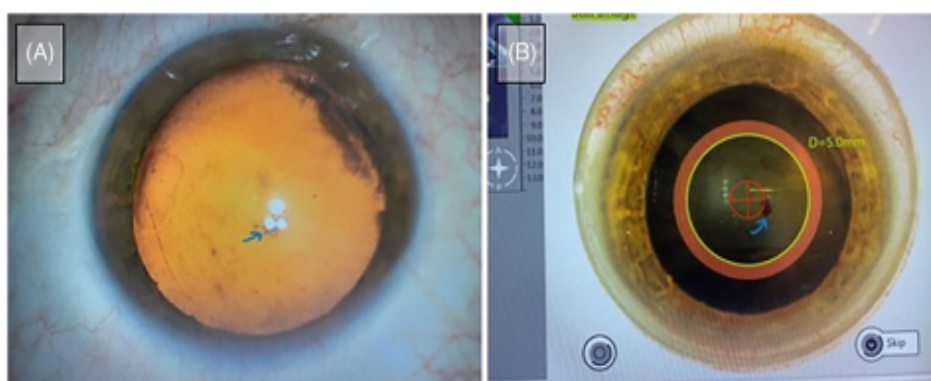


FIGURE 2 Centration points visualization with the surgical microscope (A) and with LDV Z8 femto machine after docking (B). (A) CSFCLR marked with ink (blue arrow) on the cornea surface (the left coaxial smaller light). (B) LDV Z8's display of a pupil centered capsulotomy preset (blue arrow signaling the CSFCLR, here presented with an enlarged ink mark). CSFCLR, coaxially sighted subject-fixed corneal light reflex.

TABLE 1 Patient demographic and clinical characteristics.

Parameter	Centration point		
	Mean $\pm$ SD		p value
	PC	FPR	
UDVA (logMAR)	0.32 $\pm$ 0.12	0.32 $\pm$ 0.11	0.917
CDVA (logMAR)	0.02 $\pm$ 0.06	0.02 $\pm$ 0.06	0.980
Spherical equivalent (D)	1.33 $\pm$ 2.01	1.37 $\pm$ 2.03	0.326
Total corneal astigmatism (D)	0.56 $\pm$ 0.29	0.62 $\pm$ 0.34	0.469
Nuclear sclerosis ^a	0.12 $\pm$ 0.63	0.12 $\pm$ 0.59	0.836
Axial length (mm)	21.98 $\pm$ 1.80	21.84 $\pm$ 1.90	0.876
Anterior chamber depth (mm)	3.18 $\pm$ 0.21	3.18 $\pm$ 0.22	0.862
White-to-white (mm)	11.83 $\pm$ 0.30	11.87 $\pm$ 0.27	0.989
Chord mu (mm)	0.250 $\pm$ 0.073	0.243 $\pm$ 0.070	0.339
Alpha distance (mm)	0.428 $\pm$ 0.08	0.426 $\pm$ 0.080	0.424

^aLens Opacities Classification System III grade.

Abbreviations: CDVA, corrected distance visual acuity (6 m); D, diopters; FPR, first Purkinje reflex centration; LogMAR, logarithm of the minimum angle of resolution; PC, pupil center centration; SD, standard deviation; UDVA, uncorrected distance visual acuity (6 m).

equality of variances was not observed. Correlations were assessed using Pearson's correlation test, and the results were confirmed with a non-parametric test (Spearman correlation test). All statistical tests were done using a significance level of $\alpha = 0.05$.

The distance between the postoperative FPR and the IOL center, was designated as the primary outcome, with internal aberrometry, UDVA, UIVA and UNVA and patient-reported quality of vision selected as secondary outcomes.

The sample size was determined a priori using G*Power, for a difference test between two dependent means, using a significance level of $\alpha = 0.05$, a power of 90%, and a medium to large, expected effect size. The minimum number of subjects needed was 27. The statistical analysis was performed using R (v. 4.3.0) in RStudio (v. 2023.03.1+446).

3 | RESULTS

3.1 | Preoperative patient data

Thirty-two patients had both eyes operated, achieving a total of 64 eyes operated. Two of them were withdrawn from the study, as they did not complete the 3 years follow up.

The study population included 19 (63.3%) female and 11 (36.7%) male patients, with a mean age of 71 $\pm$ 7 years old (range 59–87). The mean IOL power was +24.12 $\pm$ 4.05 D (range 13.0–29 D). Table 1 shows the patients' preoperative characteristics by capsulotomy centration:

pupil centration (PC) or FPR centration. There was no statistically significant difference between the two groups preoperatively.

3.2 | Postoperative data

As to the postoperative chord mu, there was no statistically significant difference between the two groups (95% CI: -0.004 to 0.017 ; $p = 0.182$); the same statistical findings regarding postoperative alpha distance were registered (95% CI: 0.000 – 0.00 ; $p = 0.067$). Nevertheless, a statistically significant difference was found between pre and postoperative chord mu in each group ($p < 0.001$), traducing a shorter distance between PC and FPR after surgery. Furthermore, when comparing the change in chord mu between groups, a statistically significant difference was found (95% CI: -0.026 to -0.002 ; $p = 0.022$), with a higher change in the PC group (Table 2).

The mean postoperative IOL center (IOLC)—FPR distance was 0.193 ± 0.088 mm in the PC group, whereas it was 0.159 ± 0.068 mm in the FPR group, representing a statistically significant difference between the two capsulotomy groups (mean difference: 0.034 ± 0.046 mm; 95% CI: 0.017 – 0.050 ; $p < 0.001$). Likewise, a statistically significant difference (mean difference: 0.015 ± 0.025 mm; 95% CI: 0.006 – 0.024 ; $p < 0.01$) was also found between groups regarding the IOLC-OC (optical center of the cornea). Considering IOLC-PC (pupil center) distance, no statistically significant difference was found between PC and FPR capsulotomy centration (mean difference: 0.020 ± 0.056 mm; 95% CI: 0.000 – 0.040 ; $p = 0.064$) (Table 3).

TABLE 2 Comparison between pre and postoperative chord mu and alpha distance.

Parameter (mm)		Centration point		
		Mean $\pm$ SD [95% CI]		p value [mean dif 95% CI]
		PC	FPR	
Alpha distance	Preop	0.428 $\pm$ 0.084 [0.396; 0.460]	0.426 $\pm$ 0.080 [0.395; 0.456]	0.424 [−0.007; 0.003]
	Postop	0.355 $\pm$ 0.057 [0.333; 0.377]	0.358 $\pm$ 0.053 [0.338; 0.378]	0.067 [0.000; 0.007]
	Mean dif. $\pm$ SD	0.073 $\pm$ 0.055 [0.052; 0.094]	0.067 $\pm$ 0.050 [0.049; 0.086]	0.111 [−0.012; 0.001]
	p value	<0.001*	<0.001*	
Chord mu	Preop	0.250 $\pm$ 0.073 [0.222; 0.277]	0.243 $\pm$ 0.070 [0.216; 0.269]	0.339 [−0.022; 0.007]
	Postop	0.158 $\pm$ 0.032 [0.146; 0.171]	0.165 $\pm$ 0.039 [0.150; 0.180]	0.182 [−0.004; 0.017]
	Mean dif. $\pm$ SD	0.091 $\pm$ 0.083 [0.060; 0.123]	0.077 $\pm$ 0.070 [0.051; 0.104]	0.022* [−0.026; −0.002]
	p value	<0.001*	<0.001*	

Abbreviations: CI, confidence interval; Dif, difference; FPR, first Purkinje reflex; mean dif., mean difference; PC, pupil center; SD, standard deviation.

*Statistically significant.

TABLE 3 Postoperative landmarks and IOL distances at 3 years.

Parameter (mm)		Centration point		
		Mean $\pm$ SD [95% CI]		p value [mean dif 95% CI]
		PC	FPR	
Chord mu		0.158 $\pm$ 0.032 [0.146; 0.171]	0.165 $\pm$ 0.039 [0.150; 0.180]	0.182 [−0.004; 0.017]
Alpha distance		0.355 $\pm$ 0.057 [0.333; 0.377]	0.358 $\pm$ 0.053 [0.338; 0.378]	0.067 [0.000; 0.007]
Distance IOL-FPR		0.193 $\pm$ 0.088 [0.159; 0.226]	0.159 $\pm$ 0.068 [0.133; 0.185]	<0.001* [0.017; 0.050]
Distance IOL-PC		0.221 $\pm$ 0.071 [0.194; 0.248]	0.201 $\pm$ 0.090 [0.167; 0.260]	0.064 [0.000; 0.040]
Distance IOL-OC		0.265 $\pm$ 0.115 [0.222; 0.308]	0.250 $\pm$ 0.111 [0.208; 0.291]	<0.01* [0.006; 0.024]

Abbreviations: CI, confidence interval; Dif, difference; FPR, first Purkinje reflex; IOL, intraocular lens; OC, optical center; PC, pupil center; SD, standard deviation.

*Statistically significant.

Figure 3 illustrates the difference in distance from IOL center to FPR between both eyes of the same patient, with a different capsulotomy centration per eye.

As shown in Table 4, at the 3 years postoperative evaluation, the mean UDVA was 0.01 ± 0.04 logMAR for the PC group and it was 0.01 ± 0.04 logMAR for the FPR group; the mean difference between groups was 0.00 ± 0.04 (95% CI: −0.02 to 0.01; $p = 0.662$). We registered a mean postop UIVA of 0.02 ± 0.04 logMAR for the PC group and a value of 0.02 ± 0.05 logMAR for the FPR group (mean dif.: 0.00 ± 0.03 , 95% CI: −0.01 to 0.01; $p = 0.573$), whereas mean postop UNVA was 0.14 ± 0.05 logMAR for the PC group and it was 0.14 ± 0.05 logMAR for the FPR group (mean dif.: 0.00 ± 0.02 , 95% CI: −0.01 to 0.00; $p = 0.645$).

The uncorrected distance visual acuity, the difference between UDVA and CDVA and the postoperative refractive cylinder for both groups are shown in Figure 4A,B,D. The accuracy was similar for both groups, regarding the

postoperative spherical equivalent (Figure 4C); in the FPR group, 100% of the eyes fell in ± 0.50 D range, compared to 96.7% of the eyes in the PC group. One eye (3.3%) in the PC group presented with negative postoperative spherical equivalent in the range of −0.51 to −1.25D.

For the Evaluation of Posterior Capsular Opacification (EPCO) analysis, based on picture quality, there were 60 eyes (of 30 patients) available at 3-years of follow up. The mean PCO score of the EPCO analysis was 0.338 ± 0.243 (range: 0.000–0.690) for the PC group and 0.347 ± 0.230 (range: 0.000–0.720) for the FPR group, reflecting no statistical difference between them (mean dif.: -0.009 ± 0.142 , 95% CI: −0.060 to −0.041; $p = 0.725$). Seven eyes (23.3%) of the PC group and six eyes (20%) of the FPR group did not display any signs of PCO, whereas 23 of the PC eyes (76.7%) and 24 of the FPR eyes (80%) displayed an EPCO score from >0 to 1 (none to minimal).

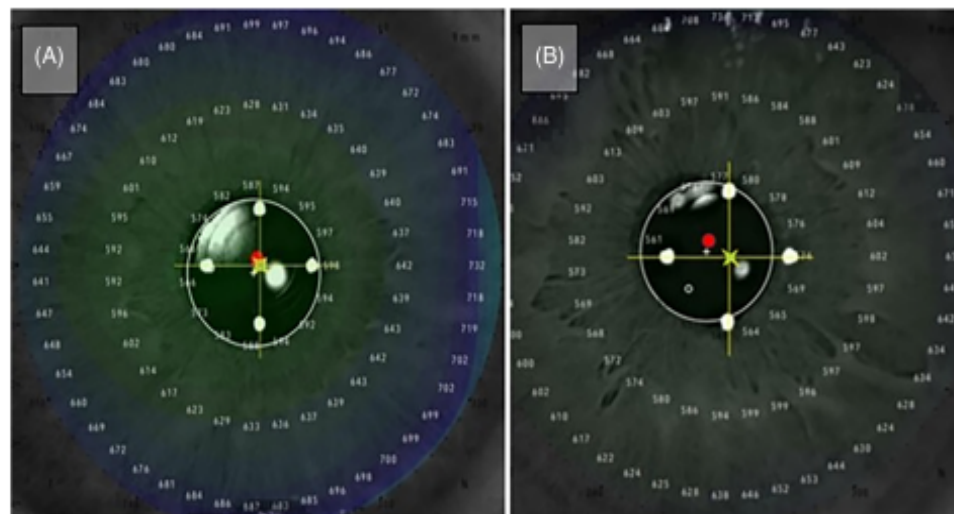


FIGURE 3 Postoperative landmarks with first Purkinje reflex (A) and pupil (B) centered capsulotomies. (A) Center of IOL (red dot) closer to first Purkinje reflex (green star) in a first Purkinje reflex capsulotomy centration. (B) Center of IOL farther from first Purkinje reflex (red dot) and closer to pupil center (small white cross) in a pupil center capsulotomy centration.

TABLE 4 Postoperative visual and refractive outcomes at 3 years (monocular).

Parameter	Centration point		p value [mean dif 95% CI]
	Mean $\pm$ SD [95% CI]		
	PC	FPR	
UDVA (LogMAR)	-0.01 ± 0.04 [-0.01 ; 0.02]	-0.01 ± 0.04 [-0.01 ; 0.03]	0.662 [-0.02 ; 0.01]
CDVA (LogMAR)	-0.01 ± 0.04 [-0.02 ; 0.01]	-0.01 ± 0.03 [-0.02 ; 0.00]	0.712 [-0.01 ; 0.02]
UIVA (LogMAR)	0.02 ± 0.04 [0.00 ; 0.4]	0.02 ± 0.05 [0.00 ; 0.03]	0.573 [-0.01 ; 0.01]
DCIVA (LogMAR)	0.05 ± 0.05 [0.03 ; 0.07]	0.06 ± 0.05 [0.04 ; 0.07]	0.423 [-0.02 ; 0.017]
UNVA (LogMAR)	0.14 ± 0.05 [0.12 ; 0.16]	0.14 ± 0.05 [0.12 ; 0.16]	0.645 [-0.01 ; 0.00]
DCNVA (LogMAR)	0.16 ± 0.05 [0.14 ; 0.18]	0.15 ± 0.05 [0.14 ; 0.17]	0.592 [-0.01 ; 0.02]
Spherical equivalent (D)	0.05 ± 0.21 [-0.03 ; 0.13]	0.04 ± 0.18 [-0.03 ; 0.11]	0.573 [-0.02 ; 0.04]

Abbreviations: CDVA, corrected distance visual acuity (6 m); CI, confidence interval; D, diopters; DCIVA, distance-corrected intermediate visual acuity (at 60 cm); DCNVA, distance-corrected near visual acuity (40 cm); Dif, difference; FPR, first Purkinje reflex; LogMAR, logarithm of the minimum angle of resolution; PC, pupil center; UDVA, uncorrected distance visual acuity (6 m); UIVA, uncorrected intermediate visual acuity (at 60 cm); UNVA, uncorrected near visual acuity (40 cm).

Regarding aberrometry data, the mean value of internal high-order aberrations (HOAs) was $0.170 \pm 0.046 \mu\text{m}$ in the PC group and $0.155 \pm 0.035 \mu\text{m}$ in the FPR group; for example, a statistically significant difference was found between groups (mean diff.: $0.016 \pm 0.023 \mu\text{m}$, 95% CI: 0.008 – 0.024 ; $p < 0.01$). Also, a statistically significant difference was registered between groups regarding total internal root-mean-square (RMS) aberrations (mean diff.: $0.007 \pm 0.008 \mu\text{m}$, 95% CI: 0.004 – 0.009 ; $p < 0.01$), with a mean value of $0.378 \pm 0.104 \mu\text{m}$ in the PC group and $0.372 \pm 0.103 \mu\text{m}$ in the FPR group.

Comparison of low-order aberrations (LOAs) between groups showed no statistically significant difference (mean diff.: $0.004 \pm 0.010 \mu\text{m}$, 95% CI: 0.000 – 0.007 ; $p = 0.073$), with a mean value of $0.265 \pm 0.077 \mu\text{m}$ in the PC group and $0.262 \pm 0.076 \mu\text{m}$ in the FPR group.

A positive significant but weak correlation (p value < 0.05 ; $R^2 < 0.05$) was found between distance from the IOL center to the visual axis (IOLC-FPR) and internal (HOAs and LOAs) RMS in the total eye population ($p < 0.001$; $R^2 = 0.38$) (Figure 5).

Quality of vision (QoV) and satisfaction were slightly better with FPR, but still not statistically significant, with

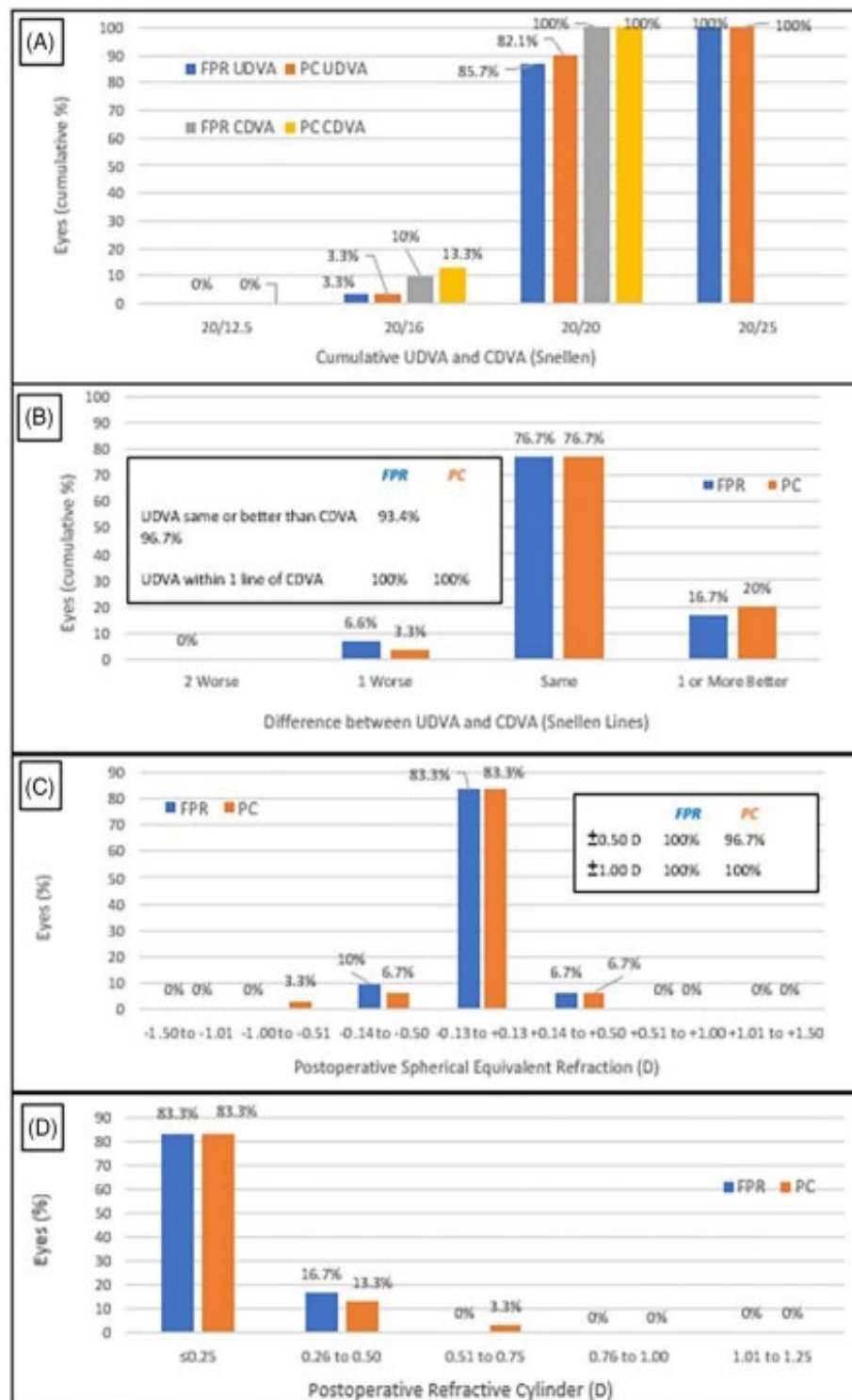


FIGURE 4 Postoperative refractive outcomes. (A) Uncorrected distance visual acuity. (B) Uncorrected distance visual acuity versus corrected distance visual acuity. (C) Spherical equivalent refraction accuracy. (D) Postoperative refractive cylinder ($n = 30$ eyes in each group). CDVA, corrected distance visual acuity; FPR, first Purkinje reflex; PC, pupil center; UDVA, uncorrected distance visual acuity.

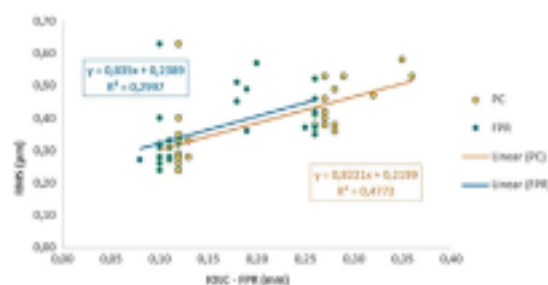


FIGURE 5 Correlation between internal aberrations (RMS) and distance IOLC-FPR. FPR, first Purkinje reflex; IOLC, intraocular lens center; PC, pupil center; RMS, root mean square.

a mean difference of 0.03 ± 0.56 (95% CI: -0.17 to 0.23 ; $p = 0.745$) for QoV and a mean difference of -0.07 ± 0.45 (95% CI: -0.23 to 0.09 ; $p = 0.423$) for the satisfaction questionnaire.

4 | DISCUSSION

Intraocular lens centration within the capsular bag is determined by various factors on the long-term [15]. Amongst them are IOL and capsular bags characteristics which interact with each other; IOL factors include the optic and haptic material, the overall IOL length in relation to the capsular bag diameter, and the inherent ability of the haptics to withstand compressive forces of a contracting capsular bag; capsular bag related factors include integrity, geometric features (such as size and morphology), and capsulotomy features. It is widely consensual the importance of a circular, continuous capsulotomy, as well as its centration, which impacts on the long-term positioning of the IOL [16]. Furthermore, the point of capsulotomy centration has been a topic of discussion, concerning the profile of multifocal diffractive IOLs. This profile demands an optimization of the IOL centration, eliciting the search for the best match of the eye's several reference points and lines, along with the pupil's paramount role; some recent studies have proposed different capsulotomy centration points other than the classical pupil center [17, 18].

Also, postoperative changes to the capsular bag such as anterior capsular contraction and posterior capsular opacification vary depending on the IOL material and amount of anterior capsule overlap of the IOL's edge [17]. In this study, posterior capsular opacification was none to minimal for both groups, thus not presenting itself as a major factor influencing IOL positioning. Capsular bag contraction exerts a force on the IOL and may lead to decentration. Improved centration is perceived as one of the features of femtosecond laser-assisted capsulotomy,

with increased efficacy and accuracy [6, 19]. Moreover, the low-energy femtosecond laser device used in this study is associated to an absence of intraoperative capsular-related complications (tags or ruptures), as several recent studies demonstrate [20, 21].

Regarding the magnitude of IOL center-visual axis decentration, a distance of less than 0.25 mm is seldom noticeable and a multifocal IOL would typically be described by most clinicians as "well-centered". A decentration in the range of 0.25–0.50 mm is noticeable in a slit-lamp examination, and it has been assumed that it is clinically insignificant; however, this assumption lacks some clinical strong evidence. Furthermore, not always is the visual axis (or its equivalent) chosen as the reference point for centration assessment, but rather the optical center or even the pupil center [22].

The present study shows modification of the IOL positioning along time, traduced by a lens displacement towards the optical center of the cornea; this fact is not influenced by the performed intraoperative manoeuvre of manually centration of the IOL aligned with the visual axis (as commonly recommended). This feature has been reported in the literature and it has been mostly described as an auto centration of the IOL in the capsular bag [23], with many factors being involved in this phenomena, mostly geometric at first hand. Furthermore, our results show evidence that the choice of the reference centration point regarding capsulotomy, influences the long-term positioning of the IOL. Therefore, beyond strengthening the fact that the IOL tends to adjust itself to the capsular bag (more than intraoperative IOL manual positioning), this study shows that capsulotomy centration on the FPR is associated to better IOL centration towards the visual axis, as compared to pupil centration. This fact is translated into a significant impact on aberrometric values. Total ocular aberrations consist of corneal and internal aberrations. The present study addressed the measurement of internal aberrations, related to the intervened surgical territory, as these aberrations are considered relevant to the final result of lens surgery, being ultimately associated to the IOL positioning [24–26]. Aberrations are classically divided into low and high order, according to Zernicke polynomials [27, 28]. On one hand, LOAs such as piston, tilt and mostly, defocus and regular astigmatism, account for approximately 90% of the overall ocular wave aberrations, and are generally perceived in the refractive error's domain [29]; hence, parameters such as spherical equivalent, cylinder and visual acuity are traditionally evaluated in a postoperative context, regarding the impact of LOAs [30, 31]. On the other hand, HOAs, such as coma, trefoil and spherical aberration (SA) are associated to halos, glare and other photic phenomena, especially with the more

demanding optical design of multifocal IOLs [32]. Also, in a prominent way, SA is described as impacting on the depth of focus, therefore potentially modifying visual acuity, particularly at near [33, 34].

Hence, in this context, the magnitude of internal HOAs reflects on a multifocal IOL's performance [35], as it correlates to the final quality of vision [36].

The magnitude of the observed difference between groups regarding HOAs was low and reflected little on the patient-reported outcomes, in this study; however, the mentioned difference was statistically significant and, taking into account that modes with the same radial order (e.g., SA, trefoil) tend to combine to decrease vision quality [37, 38], our results suggest that capsulotomy centration on FPR may be preferable to PC in the long-term.

In this study, only IOL centration was evaluated regarding IOL positioning, as a sole variable impacting on performance outcomes. Several publications point out to a reduced influence of tilt on multifocal IOLs performance [39, 40], as opposed to a significant impact of decentration in this type of intraocular lenses. Nevertheless, in this context, there was never intention to minorize the role of tilt on MIOL; rather than an oversimplification, the authors' choice of this single approach (isolating the centration factor in the context of IOL positioning) related to the feasibility of the IOL decentration assessment with respect to visual axis.

At last, the present study has some pitfalls: it contemplates only one type (plate-haptic) of IOL, restricting the evidence to this specific design; tilt is not measured in this paper, as mentioned above; aberrometry measurements were performed under a single (mesopic) illumination condition; and a larger series is recommendable to strengthen the evidence so far. However, this study does enhance the long-term relevance of capsulotomy centration of multifocal IOLs as close as possible to the visual axis, as a first-choice procedure when performing refractive lens surgery, and further introduces a novel marking procedure for achieving such purpose.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing/ conflicts of interest that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- [1] L. C. Rios, P. G. D. Silva, A. M. Canamary Junior, P. Rodrigues, C. V. S. Regatieri, M. Campos, B. K. Moscovici, *Arq Bras Oftalmol* **2020**, *83*, 76.
- [2] G. E. Altmann, L. D. Nichamin, S. S. Lane, J. S. Pepose, *J Cataract Refract Surg* **2005**, *31*, 574.
- [3] M. Okada, D. Hersh, E. Paul, D. van der Straaten, *Ophthalmology* **2014**, *121*, 763.
- [4] K. P. Reddy, J. Kandulla, G. U. Auffarth, *J Cataract Refract Surg* **2013**, *39*, 1297.
- [5] L. Mastropasqua, L. Toto, P. A. Mattei, L. Vecchiarelli, A. Mastropasqua, R. Navarra, M. Di Nicola, M. Nubile, *J Cataract Refract Surg* **2014**, *40*, 2035.
- [6] Z. Ashena, S. Maqsood, S. N. Ahmed, M. A. Nanavaty, *Vision (Basel)* **2020**, *4*, 41.
- [7] C. Y. Park, S. Y. Oh, R. S. Chuck, *Curr Opin Ophthalmol* **2012**, *23*, 269.
- [8] J. T. Holladay, *J Cataract Refract Surg* **2019**, *45*, 1198.
- [9] G. Cervantes-Coste, A. Tapia, C. Corredor-Ortega, M. Osorio, R. Valdez, M. Massaro, C. Velasco-Barona, R. Gonzalez-Salinas, *J Clin Med* **2022**, *11*, 896.
- [10] D. H. Chang, G. O. Waring IV, *Am J Ophthalmol* **2014**, *158*, 863.
- [11] R. Sella, K. Shouchane-Blum, O. Reitblat, I. Bahar, *Invest Ophthalmol Vis Sci* **2022**, *63*, 1698 F0016.
- [12] V. Thompson, J. Holladay, D. Sretavan, *J Cataract Refract Surg* **2021**, *47*, e60.
- [13] A. de Castro, P. Rosales, S. Marcos, *J Cataract Refract Surg* **2007**, *33*, 418.
- [14] U. Sridhar, K. Tripathy, *StatPearls*, StatPearls Publishing, Treasure Island (FL) **2023**.
- [15] R. Montés-Micó, A. Cerviño, T. Ferrer-Blasco, *Curr Opin Ophthalmol* **2009**, *20*, 33.
- [16] F. H. Oner, I. Durak, M. Soylev, M. Ergin, *Ophthalmic Surg Lasers* **2001**, *32*, 118.
- [17] T. Schultz, N. Tsiampalis, H. B. Dick, *J Refract Surg* **2017**, *33*, 74.
- [18] A. S. Mursch-Eidmayr, L. J. Pomberger, P. Hermann, H. Wagner, S. Beka, K. Waser, J. Wendelstein, D. Podkowinski, P. Laubichler, R. Siska, M. Bolz, *J Cataract Refract Surg* **2021**, *47*, 606.
- [19] L. Mastropasqua, L. Toto, A. Mastropasqua, L. Vecchiarelli, R. Mastropasqua, E. Pedrotti, M. Di Nicola, *J Refract Surg* **2014**, *30*, 27.
- [20] H. Y. Lin, Y. J. Chuang, P. J. Lin, *Sci. Rep.* **2021**, *11*, 9525.
- [21] C. Latz, T. Asshauer, C. Rathjen, A. Mirshahi, *Micromachines (Basel)* **2021**, *12*, 122.
- [22] S. Kimura, Y. Morizane, Y. Shiode, M. Hirano, S. Doi, S. Toshima, A. Fujiwara, F. Shiraga, *PLoS One* **2017**, *12*, e0184066.
- [23] E. I. Assia, J. X. H. Wong, Y. Shochot, *Clin Ophthalmol* **2020**, *14*, 3475.
- [24] C. Pérez-Vives, T. Ferrer-Blasco, D. Madrid-Costa, S. García-Lázaro, R. Montés-Micó, *Graefes Arch Clin Exp Ophthalmol* **2014**, *252*, 969.

- [25] C. Diao, Q. Lan, J. Liao, P. Lu, Z. Zhou, L. Li, S. Zeng, G. Yao, W. Huang, Q. Chen, J. Lv, F. Tang, M. Li, F. Xu, *BMC Ophthalmol* **2023**, 23, 332.
- [26] T. Fujikado, M. Saika, *Clin Ophthalmol* **2014**, 8, 2415.
- [27] L. N. Thibos, A. Bradley, X. Hong, *Ophthalmic Physiol Opt* **2002**, 22, 427.
- [28] T. O. Salmon, C. van de Pol, *J Cataract Refract Surg* **2006**, 32, 2064.
- [29] R. A. Applegate, C. Ballentine, H. Gross, E. J. Sarver, C. A. Sarver, *Optom Vis Sci* **2003**, 80, 97.
- [30] P. Mojzis, K. Majerova, A. B. Plaza-Puche, L. Hrcakova, J. L. Alio, *J Cataract Refract Surg* **2015**, 41, 2695.
- [31] S. A. J. Al-Amri, J. L. Alió, R. Milán-Castillo, F. D'Oria, A. Martinez-Abad, P. Yebana, N. Subirana, Z. Al-Harbi, A. B. Plaza-Puche, J. L. Alió Del Barrio, *J Refract Surg* **2023**, 39, 103.
- [32] M. R. Chalita, R. R. Krueger, *Ophthalmol Clin N Am* **2004**, 17, 135 v–vi.
- [33] T. Yamaguchi, Y. Satake, M. Dogru, K. Ohnuma, K. Negishi, J. Shimazaki, *Cornea* **2015**, 34, S128.
- [34] A. K. Schuster, J. Tesarz, U. Vossmerbaeumer, *Ophthalmology* **2013**, 120, 2166.
- [35] L. Wang, R. M. Santaella, M. Booth, D. D. Koch, *J Cataract Refract Surg* **2005**, 31, 1512.
- [36] D. Williams, G.-Y. Yoon, J. Porter, A. Guirao, H. Hofer, I. Cox, *J Refract Surg* **2000**, 16, S554.
- [37] C. E. Campbell, *J Refract Surg* **2004**, 20, S495.
- [38] R. A. Applegate, J. D. Marsack, R. Ramos, E. J. Sarver, *J Cataract Refract Surg* **2003**, 29, 1487.
- [39] T. Tandogan, H. S. Son, C. Y. Choi, M. C. Knorz, G. U. Auffarth, R. Khoramnia, *J Refract Surg* **2017**, 33, 808.
- [40] X. Y. Chen, Y. C. Wang, T. Y. Zhao, Z. Z. Wang, W. Wang, *World J Clin Cases* **2022**, 10, 3639.

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4.3. Pupil Status with Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification: An Intraindividual Comparative Study.

Pupil Status with Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification: An Intraindividual Comparative Study

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Purpose: To compare the pupil changes in low-energy femtosecond laser-assisted cataract surgery (FLACS) with conventional phacoemulsification (CP) intraindividually.

Patients and Methods: A retrospective review of registered surgical data from patients that undergone uncomplicated cataract surgery in a single centre, with randomly assigned femtosecond laser-assisted cataract surgery (FLACS) to one eye and conventional phacoemulsification (CP) to the other, was performed. The recorded pupil images were evaluated at pre and post laser treatment (after suction release) and at several surgical timepoints for both techniques (FLACS and CP). Pupil areas were calculated and compared in the same eye undergone FLACS (pre vs post laser treatment), between eyes (CP vs FLACS) in the same patient and between groups. Subgroups were built regarding age and ocular comorbidity.

Results: This study involved a total of 164 eyes of 82 patients (55 female, 27 male). No statistical differences regarding the total duration of surgery ($p=0.805$) between FLACS and CP. Pupil measurements between pre and post laser treatment in the FLACS group showed no statistically significant differences ($p=0.107$). The mean change in pupil area from the beginning until the end of surgery (total variation) was $6.59 \pm 2.08 \text{ mm}^2$ in the FLACS group and $6.67 \pm 2.13 \text{ mm}^2$ in the CP group, associated to less narrowing of pupil area with FLACS, although not statistically significant ($p=0.080$). Comorbidity group analysis revealed less, but not significant, pupil narrowing with the FLACS technique ($p=0.071$). No statistically significant differences between FLACS and CP concerning age subgroups were registered.

Conclusion: This study shows no significant pupil changes, namely myosis, after low-energy FLACS pre-treatment. Comparison between techniques showed less pupil variation in FLACS as compared to CP, more markedly in eyes with comorbidities (particularly with shallow anterior chamber), although non-statistically significant.

Keywords: low energy femtosecond laser, FLACS, myosis, pupil, phacoemulsification

Introduction

Femtosecond laser-assisted cataract surgery (FLACS) emerged as a novel technique in 2009.^{1,2} Since then, this technique has evolved considerably, covering several of the conventional surgical steps previously performed in a manual manner (incisions, lens fragmentation, and capsulotomy). The safety and effectiveness of FLACS is consensually established, with considerable evidence.³⁻⁵ However, intraoperative miosis has been associated with femtosecond laser-assisted cataract surgery,⁶⁻⁸ which renders inherent difficulties regarding nuclear fragmentation, cortex removal, intraocular implantation of the lens, and increases the risk of posterior capsule rupture.⁹ This undesired side effect is frequently reported in the vast majority of publications regarding FLACS, which, almost invariably, do not differentiate

femtosecond laser based on the pulse pattern, i.e., between low and energy pulse femtosecond lasers or do not contemplate low energy pulse at all.^{10,11}

As pointed out by Wu et al¹² there are different femtosecond laser devices, generating different pulse patterns, in terms of energy and frequency levels. Most commercially available devices produce high energy (μJ) and low frequency (KHz) pulses; this type of common, femtosecond emission, is driven by chirped pulse amplification (CPA). On the other hand, another type of device produces low energy (nJ) and high frequency (MHz) femtosecond pulses by means of increasing the laser focusing optics' aperture,¹³ therefore diminishing the laser spot diameter. The prevalence (in number and magnitude) of miosis with "high-energy" pulse femtosecond lasers has been shown to range between 9.5% and 32%.^{14,15} There is some evidence that the level of femtosecond laser cutting side effects are associated with prostaglandins release; these higher levels of prostaglandins (measured immediately after the laser pre-treatment), in turn, is accountable for the observed intraoperative myosis.^{16,17} Oppositely to the aforementioned "mainstream" reports, the few studies regarding pupillary changes with low energy pulse femtosecond lasers, show increasing evidence of minimal to absent narrowing of pupil size.^{18,19} This difference in behaviour may be related to the laser spots diameter and energy level, with smaller values achieved by "low-energy" devices, thus reducing an associate damage to the neighbour tissues. This fact is prone to reduce prostaglandins levels and, consequently, no significant intraoperative pupil narrowing.

Our present study aims to further investigate on the pupil area changes with low energy pulse FLACS and compare it against the standard phacoemulsification. For this matter, an intraindividual study was performed.

Materials and Methods

This retrospective cohort study was approved by the Ethics Committee at Hospital da Luz Arrabida (HLA), Porto, and adhered to the ethical principles stated in the "Declaration of Helsinki", with each patient having signed an informed consent. Data were extracted from the charts of all patients who had cataract surgery in both eyes, with randomly assigned conventional phacoemulsification surgery in one eye and femtosecond laser-assisted surgery in the other eye. All patients had surgery between February 2015, and September 2020, at Hospital da Luz Arrabida (HLA). Two cataract and refractive surgeons performed all surgeries at HLA.

Inclusion and Exclusion Criteria

Patients were excluded from the study if they had previous corneal scarring, ocular surgery other than cataract surgery, or relevant axial anisometropia (defined as a ≥ 1 mm-difference in axial length between eyes of the same patient).

Chart Review and Data Collection

Charts were reviewed from surgeries performed between February 2015 and September 2020, and extraction was performed of demographic, clinical, and video recording data such as age, sex, date, type of surgery (conventional phacoemulsification versus femtosecond laser-assisted), procedure's duration, axial length, anterior chamber depth, cataract degree, ocular comorbidity, surgical videos, and adverse events. Optical interferometer Galilei G6 (Ziemer Ophthalmic systems AG) was used for biometry. Assessment of lens transparency was achieved by examination at the slit lamp followed by a grading procedure according to the Lens Opacities Classification System (LOCS) III. A Placido - dual Scheimpflug device (Galilei G6) was used for corneal tomography and topography assessment. Macular evaluation, by means of spectral-domain optical coherence tomography, was accomplished by a modular ophthalmic imaging platform (Carl Zeiss).

For pupil measuring purposes, recorded images from surgical videos were withdrawn at several time points: (1) at the beginning of both CP and FLACS (immediately before laser docking), (2) immediately after the vacuum suction release (end of femtosecond laser pre-treatment) in the FLACS group, (3) at 5 minutes intraoperatively, (4) at 10 minutes intraoperatively, and (5) at the end of the surgical procedure.

Surgical Technique

Two experienced surgeons (R.S., A.M.). performed all surgeries. The femtosecond laser-assisted lens surgery was performed with a LDV Z8 (Ziemer, Inc., Port, Switzerland) device. Capsulotomy, corneal incisions and lens fragmentation were accomplished by femtosecond laser, with the phacoemulsification device being used for the

subsequent steps, such as emulsification, irrigation and aspiration of lens material. FLACS was sequentially performed (femtosecond laser followed by the phacoemulsification) keeping the patient on the same operating bed and in the same operating theatre, as the FS platform employed is a portable one. The phacoemulsification device employed was the Active Fluidics™ torsional phacoemulsification machine (Centurion Vision, Alcon Laboratories, Inc., Fort Worth, USA). All surgeries were unilateral, with one eye at a time. Surgical protocol was the same for both surgeons.

Preparation protocol of was the same for both groups of patients, ie, tropicamide 0.28 mg in association with phenylephrine hydrochloride 5.4 mg contained in the form of an ophthalmic insert, with placement in the lower conjunctival sac and oxybuprocaine hydrochloride 4 mg/l eyedrops 20 minutes before procedure. No specific medication for myosis prevention was administered in the femtosecond group, nor additional steroid or non-steroid anti-inflammatory drugs (NSAID) were administered in the preoperative period to any of the patients. This specific protocol, without preoperative use of NSAID drugs (as this use is currently regarded as a standard practice) was explained to all patients, with given consent by each one of them. Although available as a backup measure, no intraoperative agents, like intracameral mydriatic mixtures, needed to be administered. Intracameral cefuroxime was injected in every patient at the end of each surgery.

In the FLACS group, vacuum suction was set at approximately 420 mbar and the following laser procedures were performed: lens fragmentation (in six pieces with a 6-mm diameter) at 105% laser energy, corneal incisions (main of 2.8 mm and secondary paracentesis of 1.2 mm) and capsulotomy (5.2-mm diameter) at 90% laser energy. Further surgical steps followed immediately after suction release (phacoemulsification device employed for emulsification, irrigation, and aspiration of lens material) and were performed in the same way for both groups (FLACS and CP).

All patients were prescribed with prednisolone, ibuprofen and ofloxacin eyedrops postoperatively for 3 weeks.

Pupil Area Measurement

Pupil area was measured at the established time points, after analysing images from the recorded surgical videos. For that purpose, we have adopted the Fiji image processing program from ImageJ (software version 2.0.0-rc-49/1.51a) as suggested by Mirshahi et al,¹⁸ which enables direct area measurements by tracing pupil margin. Calibration was accomplished by using the constant limbus horizontal size as a reference, allowing pixel measurements conversion into millimetres for each eye.

Statistical Analysis

The analysis involved the examination of possible differences in pupil area from the baseline preoperative measurement and along the different timepoints, comparing both techniques intraindividually (within subjects) and interindividually (between subjects). Subgroup analysis was also performed to evaluate pupil area changes with respect to age and comorbidity.

Regarding pupil change pre-laser versus post-laser treatment in the FLACS group of eyes, a paired *t*-test was applied. Comparison of pupil size between the FLACS and CP in the same patient (within-subject) at each time point was accomplished by a paired *t*-test.

Differences in pupil size between groups at different times were compared using analysis of variance (ANOVA). A mixed-design ANOVA was applied, considering pathology (yes or no) and type of pathology (when associated) as a between-subjects factor. Regarding the within-subjects' factors, type of surgery (FLACS or CP) and time were used. Before the analysis, the sphericity assumption was tested using the Mauchly's Test, and when the assumption was not accomplished, the Greenhouse-Geisser correction results were reported.

A statistical significance level of $\alpha=0.05$ and a power of 95% were chosen, with P-values < 0.05 being considered statistically significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 28, Chicago, Illinois).

Results

Preoperative Patient Data

The study population consisted of 164 eyes of 82 patients, with 55 female (67%) and 27 male (33%), and a mean age of 73.4 ± 8.5 years (median: 74, range: 55–95). For each patient, one of the eyes underwent FLACS and the other was operated with CP; therefore, in the total population, 82 eyes (50%) had femtosecond laser-assisted surgery and 82 eyes (50%) underwent conventional phacoemulsification.

Table 1 shows the patients' preoperative characteristics by technique group. There was no statistically significant difference between the 2 groups preoperatively.

Preoperatively, the pupil area after dilation presented no statistically significant difference between the techniques, with $45.01 \pm 7.60 \text{ mm}^2$ in the FLACS group and $45.00 \pm 7.60 \text{ mm}^2$ in the CP group ($p=0.748$). Comorbidity, as shown in Table 2, was present in 47 eyes (28.7%) of 23 patients and distributed as follows: glaucoma and pseudo exfoliation in 22 eyes (13.4%); shallow (<2.5 mm depth) anterior chamber in 10 eyes (6%), mild non-proliferative diabetic retinopathy in 8 eyes (4.8%), Fuchs dystrophy in 4 eyes (2.4%), high myopia in 2 eyes (1.2%), and post-retinal central venous thrombosis in one eye (0.6%). No adverse events were registered.

Postoperative Data

In the FLACS group, pupil area comparison between pre and post laser treatment showed no statistically significant differences ($p=0.107$, 95% CI (Confidence Interval): -0.01 to 0.05), with a mean value of $45.01 \pm 7.60 \text{ mm}^2$ and 44.98

Table 1 Patient Demographic and Clinical Characteristics

Parameter	FLACS (n=82) CP (n=82)		p value
	Mean ± SD (mm ²)		
Nuclear sclerosis (LOCS III)	3.45 ± 0.71	3.41 ± 0.67	0.733
Time duration (s)	13.62 ± 1.03	13.66 ± 0.98	0.805
Axial length (mm)	21.87 ± 1.60	21.75 ± 1.64	0.776
Anterior chamber depth (mm)	3.17 ± 0.22	3.19 ± 0.26	0.831

Abbreviations: CP, conventional phacoemulsification; FLACS, femtosecond laser-assisted cataract surgery; LOCS III, Lens Opacities Classification System III; n, number of eyes; SD, standard deviation.

Table 2 Comorbidity

Comorbidity	Number of Eyes	%
Pseudoexfoliation glaucoma	22	13.4
Shallow anterior chamber	10	6
Mild non-proliferative diabetic retinopathy	8	4.8
Fuchs dystrophy	4	2.4
High myopia	2	1.2
Post-retinal central venous thrombosis ^a	1	0.6
TOTAL	47	28.7

Note: ^aCondition present in only one eye.

$\pm 7.61 \text{ mm}^2$, respectively (Figure 1). The mean change in pupil area between preoperative and post-laser treatment was $0.02 \pm 0.12 \text{ mm}^2$ (median: 0.01, minimum: -0.02 , maximum: 1).

Regarding the comparison between FLACS and CP, pupil area measurements were performed along surgical timepoints for both techniques (Figure 2). The intraindividual analysis (within-subjects) revealed a marked difference, close to the limit of significance, between FLACS and CP techniques at the end of surgery, with a mean pupular area of $38.41 \pm 7.01 \text{ mm}^2$ and $38.33 \pm 7.04 \text{ mm}^2$, respectively ($p=0.051$). More distinctly, a statistically significant difference between the techniques was shown at 10 minutes intraoperatively, with a slightly larger pupil in the FLACS group (mean difference of $0.09 \pm 0.38 \text{ mm}^2$) as opposed to CP ($p=0.032$, CI: 0.01 to 0.17).

The mean change in pupil area from the beginning until the end of surgery (total variation) was $6.59 \pm 2.08 \text{ mm}^2$ in the FLACS group and $6.67 \pm 2.13 \text{ mm}^2$ in the CP group; the mean difference between the two techniques was $0.07 \pm 0.38 \text{ mm}^2$, associated to less narrowing of pupil area with FLACS, although not statistically significant ($p=0.080$) (Table 3).

Pupil narrowing was correlated positively with the duration of surgery, being similar in both techniques ($R=-0.401$ and $R=-0.426$; $p<0.001$).

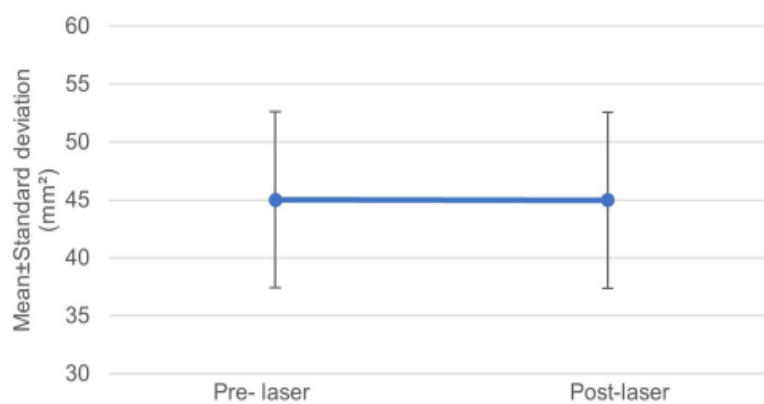


Figure 1 Means $\pm$ standard deviations of preoperative and post-laser pupil areas in 82 eyes undergoing low-energy femtosecond laser assisted cataract surgery (FLACS).

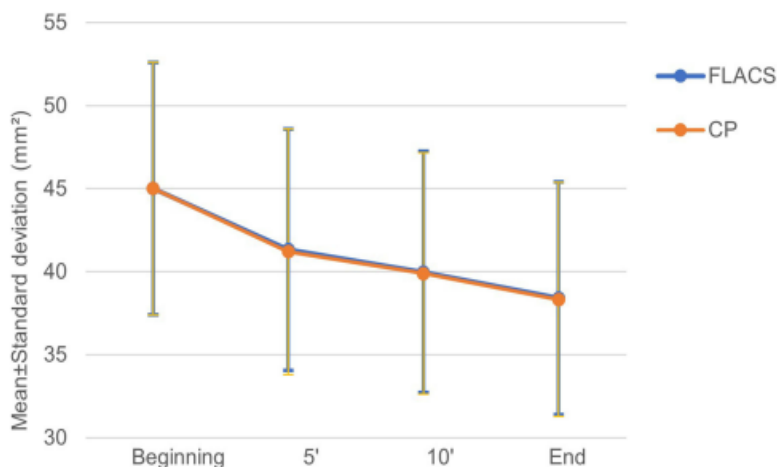


Figure 2 Mean $\pm$ standard deviation of pupil area in 164 eyes undergoing low-energy FLACS (82 eyes) and CP (82 eyes), along different timepoints.
Abbreviations: FLACS, femtosecond laser assisted cataract surgery; CP, conventional phacoemulsification.

Table 3 Comparison of Mean Pupil Area Along Surgical Timepoints Between FLACS and CP

Surgical Timepoints	FLACS	CP	p value
	Mean ± SD (mm ²)		
Beginning	45.01 ± 7.60	45.00 ± 7.60	0.748
5 minutes intra-op	41.33 ± 7.27	41.21 ± 7.40	0.076
10 minutes intra-op	39.98 ± 7.26	39.89 ± 7.27	0.032*
Final	38.41 ± 7.01	38.33 ± 7.04	0.051
Total variation	-6.59 ± 2.08	-6.67 ± 2.13	0.080

Note: *Statistically significant.

Abbreviation: SD, standard deviation.

Concerning the comparison of total pupil variation between techniques in eyes with ocular comorbidities versus eyes without ocular morbidities (as a between-subject factor), a non-statistically significant difference of 0.07 ± 0.04 mm², although close to the limit of significance, was shown ($p=0.071$; 95% CI: -0.01 to 0.16). When comorbidity was present, the mean difference between techniques in total pupil variation was 0.19 ± 0.59 mm², with less narrowing in the FLACS group, but not statistically significant ($p=0.131$, 95% CI: -0.06 to 0.44), whereas in eyes without comorbidity, the mean difference between techniques was 0.03 ± 0.22 mm² ($p=0.391$, 95% to CI: -0.03 to 0.08) (Figure 3).

Regarding the comorbidity subgroups analysis, the pseudo exfoliation syndrome subgroup showed the higher degree of myosis during surgery amongst all subgroups, which was similar for both techniques ($p=0.614$) (Table 4). However, comparison between the two techniques revealed a mean difference of 0.78 ± 0.95 mm² ($p=0.176$), close to the limit of significance, in eyes with shallow anterior chamber, associated with a lesser pupil narrowing in the FLACS group.

Two subgroups were created, considering the median age (74 years old). In eyes of patients aged ≤ 74 years, the mean difference in pupil variation between techniques was 0.06 ± 0.44 mm² ($p=0.379$), whereas the mean difference in pupil variation was 0.09 ± 0.28 mm² in eyes of patients above 74 years old, close to the limit of significance ($p=0.058$). An independent *t*-test (between-subjects) comparing the two age subgroups (above and below 74 years of age), showed no statistically difference significance between FLACS and CP ($p=0.716$).

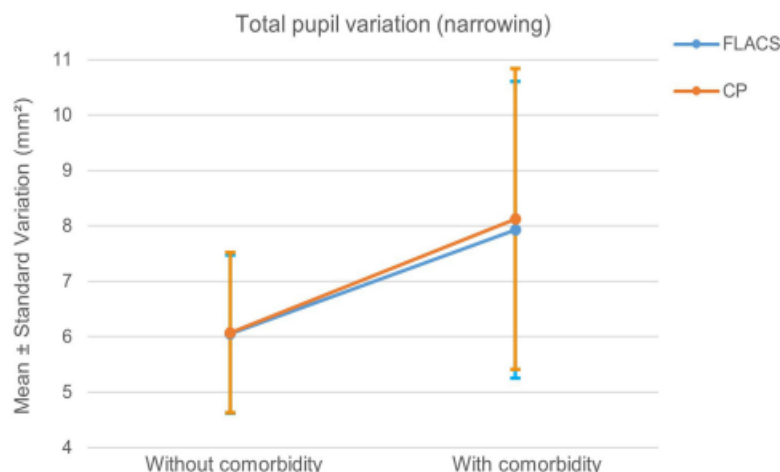


Figure 3 Mean $\pm$ standard deviation values of pupil area narrowing (total pupil variation) for both techniques and presence or absence of ocular comorbidity. Abbreviations: FLACS, femtosecond laser assisted cataract surgery; CP, conventional phacoemulsification.

Table 4 Comparison of Total Pupil Variation Between FLACS and CP According to Comorbidity

Ocular Comorbidity (n)	FLACS	CP	Mean Diff [95% CI]	p value
	Mean ± SD (mm ²)			
None (58)	6.05 ± 1.43	6.07 ± 1.44	0.03 [-0.03;0.08]	0.391
Pex (11)	8.69 ± 2.78	8.74 ± 2.85	0.06 [-0.19;0.31]	0.614
Shallow AC (5)	6.69 ± 0.78	7.47 ± 1.40	0.78 [-0.54;2.10]	0.176
Others (8)	7.67 ± 2.95	7.67 ± 2.94	0.003 [-0.08;0.09]	0.919

Abbreviations: CI, confidence interval; Diff, difference; n, number of eyes; SD, standard deviation.

Discussion

To this point, no other intraindividual study comparing low-energy femtosecond laser with conventional phacoemulsification was performed regarding pupil area variation.

The vast majority of publications approach mainly high-energy femtosecond laser devices, with strong evidence of laser-induced myosis by this type of laser.^{20,21} On the other hand, some recent evidence is being apparent that low-energy femtosecond laser does not induce such narrowing of the pupil.²²

Our study's results agree with the published literature regarding the same type of femtosecond pulse.^{18,19,22} No significant pupil changes were observed in the present study with low-energy FLACS, in contrast with the reported common association of laser-induced myosis with high-energy and low-frequency femtosecond pulse machines available in the market.^{23,24} Again, the rationale for this difference may be that smaller laser spots, as produced by a high numerical aperture in the laser optics of "low-energy" devices, would reduce associate damage to the neighbouring tissues. Consequently, this weaker impact would translate into a lower prostaglandins level, and thus producing lesser intraoperative myosis.

Aside from tissue interaction, another aspect may contribute to the loss of preoperative mydriasis, such as the patient transfer time. This transfer process is mandatory for most platforms using high-energy pulse,^{25,26} since the related FS machines are not portable; in contrast, portability is a feature of the low-energy pulse platform available in the market. Similarly, in our study, no complications regarding capsule-related events were observed; namely, no incomplete capsulotomies, anterior capsular tags, and anterior or posterior capsular tears were registered. This evidence is opposed to most reviews' conclusions about FLACS, but it should stressed that these reports neither contemplate "low-energy" devices or, if included, differentiate between the two types of femtosecond pulse.^{10,11,27}

This study found some differences in pupil area variation between FLACS and CP along surgical time (timepoints), although not statistically significant. Reports of a significant higher pupil area with FLACS immediately after suction,¹⁹ were not apparent in our study. In those studies, anti-inflammatory eye drops were placed preoperatively on the eye population. It should be stressed that opposed to such reports, no anti-inflammatory drug was administered in any of our study eyes. Therefore, no potential bias in laser interaction on ocular tissues due to the myosis inhibition's role of such drugs was registered in the present study.

The findings regarding a greater amount of pupil narrowing in eyes with comorbidities during conventional cataract surgery are consistent with the published literature. Nevertheless, the present study further reveals that there is a strong but non-statistically significant difference in eyes with a shallow anterior chamber (<2.5 mm), between FLACS and CP.

A possible explanation for this difference may rely on the fact that the time of anterior chamber exposure with CP is longer than with FLACS (as several surgical steps are performed with a “closed” eye globe, through laser). This, in turn, would facilitate reflective myosis upon “open-eye” manipulation with CP.

In this study, surgical procedure time (from beginning to the end), was similar in both techniques, with no statistically significant difference between FLACS and CP ($p > 0.05$); the portability of the employed femtosecond machine may contribute to this aspect, as the patient remains in the same surgical environment (same bed and a single operating room) during the whole femtosecond-phacoemulsification sequence. Our study results are in agreement with few other published reports,²⁸ regarding the negligible impact on surgical time associated to portable femtosecond devices.

Conclusion

In conclusion, this intraindividual study provides extended evidence of lack of laser-induced myosis with low-energy FLACS. Furthermore, regarding pupil status, low-energy femtosecond laser-assisted energy seems to compare favorably with conventional phacoemulsification in the presence of certain ocular comorbidities. Although not statistically significant, this difference arises an interesting discussion and, also in line with contemporary literature, it recommends revision of some established, global opinions on FLACS. Further studies on low-energy femtosecond laser-assisted cataract surgery, involving higher samples and rigorous variable control, are in demand for this matter.

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Disclosure

The authors have no financial conflicts of interest to disclose.

References

1. Nagy Z, Takacs A, Filkom T, Sarayba M. Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery. *J Refract Surg.* 2009;25:1053–1060. doi:10.3928/1081597X-20091117-04
2. Mastropasqua L, Toto L, Mastropasqua A, et al. Femtosecond laser versus manual clear corneal incision in cataract surgery. *J Refract Surg.* 2014;30:27–33. doi:10.3928/1081597X-20131217-03
3. Grewal DS, Schultz T, Basti S, Dick HB. Femtosecond laser-assisted cataract surgery—current status and future directions. *Surv Ophthalmol.* 2016;61:103–131. doi:10.1016/j.survophthal.2015.09.002
4. Dick HB, Schultz T. A review of laser-assisted versus traditional phacoemulsification cataract surgery. *Ophthalmol Ther.* 2017;6:7–18. doi:10.1007/s40123-017-0080-z
5. Mastropasqua L, Toto L, Mattei PA, et al. Optical coherence tomography and 3-dimensional confocal structured imaging system-guided femtosecond laser capsulotomy versus manual continuous curvilinear capsulorhexis. *J Cataract Refract Surg.* 2014;40:2035–2043. doi:10.1016/j.jcrs.2014.05.032
6. Nagy ZZ, Takacs AI, Filkom T, et al. Complications of femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg.* 2014;40:20–28. doi:10.1016/j.jcrs.2013.08.046
7. Roberts TV, Lawless M, Bali SJ, Hodge C, Sutton G. Surgical outcomes and safety of femtosecond laser cataract surgery: a prospective study of 1500 consecutive cases. *Ophthalmology.* 2013;120:227–233. doi:10.1016/j.ophtha.2012.10.026
8. Diakonis VF, Yesilimak N, Sayed-Ahmed IO, et al. Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms. *J Refract Surg.* 2016;32:84–88. doi:10.3928/1081597X-20151229-03
9. Hashemi H, Seyedian MA, Mohammadpour M. Small pupil and cataract surgery. *Curr Opin Ophthalmol.* 2015;26:3–9. doi:10.1097/ICU.0000000000000116
10. Ewe SY, Abell RG, Vote BJ. Femtosecond laser-assisted versus phacoemulsification for cataract extraction and intraocular lens implantation: clinical outcomes review. *Curr Opin Ophthalmol.* 2018;29:54–60. doi:10.1097/ICU.0000000000000433
11. Lundstrom M, Dickman M, Henry Y, et al. Femtosecond laser-assisted cataract surgeries reported to the European registry of quality outcomes for cataract and refractive surgery: baseline characteristics, surgical procedure, and outcomes. *J Cataract Refract Surg.* 2017;43:1549–1556. doi:10.1016/j.jcrs.2017.09.029
12. Wu BM, Williams GP, Mehta JS, Mehta JS. A comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol.* 2015;2015:616478. doi:10.1155/2015/616478
13. Chang JS, Chen IN, Chan WM, Ng JC, Chan VK, Law AK. Initial evaluation of a femtosecond laser system in cataract surgery. *J Cataract Refract Surg.* 2014;40:29–36. doi:10.1016/j.jcrs.2013.08.045
14. Diakonis VF, Kontadakis GA, Anagnostopoulos AG, et al. Effects of short-term preoperative topical ketorolac on pupil diameter in eyes undergoing femtosecond laser-assisted capsulotomy. *J Refract Surg.* 2017;33:230–234. doi:10.3928/1081597X-20170111-02

15. Jun JH, Hwang KY, Chang SD, Joo CK. Pupil-size alterations induced by photodisruption during femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2015;41:278–285. doi:10.1016/j.jcrs.2014.10.027
16. Jun JH, Yoo YS, Lim SA, Joo CK. Effects of topical ketorolac tromethamine 0.45% on intraoperative miosis and prostaglandin E2 release during femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2017;43:492–497. doi:10.1016/j.jcrs.2017.01.011
17. Schultz T, Joachim SC, Stellbogen M, Dick HB. Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. *J Refract Surg*. 2015;31:78–81. doi:10.3928/1081597X-20150122-01
18. Mirshahi A, Ponto K. Changes in pupil area during low-energy femtosecond laser-assisted cataract surgery. *J Ophthalmic Vis Res*. 2019;14(3):251–256. doi:10.18502/jovr.v14i3.4780
19. Germano C, Germano R, Cid F, Germano FA, Carricondo P, Germano J. Comparison of pupillary diameter variation between conventional phacoemulsification versus femtosecond laser-assisted cataract surgery. *Arq Bras Oftalmol*. 2022;85(1). doi:10.5935/0004-2749.20210091
20. Wang J, Su F, Wang Y, Chen Y, Chen Q, Li F. Intra and post-operative complications observed with femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):177. doi:10.1186/s12886-019-1190-2
21. Popovic M, Campos-Möller X, Schlenker MB, Ahmed II. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology*. 2016;123(10):2113–2126. doi:10.1016/j.ophtha.2016.07.005
22. Mirshahi A, Schneider A, Latz C, Ponto KA. Perioperative pupil size in low-energy femtosecond laser-assisted cataract surgery. *PLoS One*. 2021;16(5):e0251549. PMID: 33999970; PMCID: PMC8128224. doi:10.1371/journal.pone.0251549
23. Walter K, Delwadia N, Coben J. Continuous intracameral phenylephrine-ketorolac irrigation for miosis prevention in femtosecond laser-assisted cataract surgery: reduction in surgical time and iris manipulation. *J Cataract Refract Surg*. 2019;45:465–469. doi:10.1016/j.jcrs.2018.11.004
24. Schultz T, Joachim SC, Szuler M, Stellbogen M, Dick HB. NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2015;31:791–794. doi:10.3928/1081597X-20151111-01
25. Roberts H, Wagh VK, Mullens IJM, Borsci S, Ni MZ, O'Brart DPS. Evaluation of a hub-and-spoke model for the delivery of femtosecond laser assisted cataract surgery within the context of a large randomised controlled trial. *Br J Ophthalmol*. 2018;102(11):1556–1563. doi:10.1136/bjophthalmol-2017-311319
26. Lubahn JG, Donaldson KE, Culbertson WW, Yoo SH. Operating times of experienced cataract surgeons beginning femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2014;40:1773–1776. doi:10.1016/j.jcrs.2014.03.024
27. Roberts HW, Wagh VK, Sullivan DL, et al. A randomized controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery. *J Cataract Refract Surg*. 2019;45(1):11–20. doi:10.1016/j.jcrs.2018.08.033
28. Yu AY, Ni LY, Wang QM, et al. Preliminary clinical investigation of cataract surgery with a noncontact femtosecond laser system. *Lasers Surg Med*. 2015;47:698–703. doi:10.1002/lsm.22405

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4.4. Cataract Grade and Pupil: Comparison Between Conventional Phacoemulsification and Low-Energy Femtosecond Laser Assisted Cataract Surgery.

Cataract Grade and Pupil: Comparison Between Conventional Phacoemulsification and Low-Energy Femtosecond Laser Assisted Cataract Surgery

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Purpose: This study presents a comparison of pupil changes according to cataract grade between low-energy femtosecond laser-assisted cataract surgery (FLACS) and conventional phacoemulsification (CP) in the same patient.

Patients and Methods: Data from surgical records from patients submitted to cataract surgery with CP in one eye and FLACS in the other were retrospectively reviewed. The inclusion criterion was both eyes of the same patient having the same cataract grade in accordance with Lens Opacity Classification System (LOCS) III. Total pupil variation (TPV) was measured after recorded images, with intraindividual comparison between techniques, according to cataract grade (≤ 3 and > 3), age and cumulative dissipated energy (CDE).

Results: The study included a total of 124 eyes of 62 patients (mean age 72.65 ± 7.64 years). Analysis showed a statistically significant difference in TPV between techniques in the grade ≤ 3 cataract group ($0.08 \pm 0.22 \text{ mm}^2$; $p=0.034$), with less pupil narrowing with FLACS, but not in the grade > 3 group ($0.01 \pm 0.23 \text{ mm}^2$; $p=0.849$). Regarding CDE, a significant difference ($p<0.001$) was found between techniques in both softer and harder cataracts, with lower values for FLACS. Correlation between CDE and TPV was significant for CP ($p=0.021$) but not for FLACS ($p=0.922$). TPV was significantly lower in older patients (age > 74 years) for both techniques ($p<0.001$).

Conclusion: There was a statistically significant difference between techniques (although of mild clinical relevance), with less reduction of pupil area with FLACS in softer cataracts (grade ≤ 3), as compared to CP. Higher levels of CDE are associated with more pupil narrowing in CP.

Keywords: cataract grade, pupil, low energy FLACS, femtosecond laser, phacoemulsification

Introduction

Pupil size is of paramount importance in cataract surgery. Although considered a safe and efficient technique,^{1,2} femtosecond laser-assisted cataract surgery (FLACS) has been associated with intraoperative miosis as opposed to conventional phacoemulsification (CP).^{3,4} This counterback is prone to increase complication rates of the several surgical steps of cataract surgery, with posterior capsule rupture as a paramount risk. Intraoperative miosis is reported in most publications involving FLACS, regardless of the pattern of photo disruption pulse.⁵⁻⁷ Femtosecond lasers currently produce two different patterns: low-frequency (kHz) high-energy pulses (μJ) and high-frequency (MHz) low-energy pulses (nJ).⁸ Most of the published evidence concerns high-energy and low-frequency devices, not contemplating low-energy and high-frequency devices at all; or, very seldom, studies present global results without differentiating between the two types of pulse.^{9,10}

More recently, some published studies point to a nearly absent laser-induced miosis with low energy FLACS.¹¹⁻¹³ The explanation for this feature is liable to reside in the fact that a “low-energy” pulse is associated with smaller laser spots and lower energy delivered per pulse, thus reducing the impact on the neighbour tissues and resulting in lower

levels of prostaglandins; in the end, this would reflect on minor or absent intraoperative pupil narrowing. Moreover, cataract grade is known to have an impact on energy parameters during phacoemulsification,¹⁴ such as cumulative dispersed energy (CDE). Cumulative dissipated energy (CDE) is described as the amount of ultrasound energy employed to remove a cataractous lens¹⁵ and it is defined as the product of the total phacoemulsification time (in minutes) and the average phacoemulsification power (%) divided by 100.

Our present study aims to compare intraindividually (within-subject) pupil area variation between “low-energy” FLACS and CP according to cataract degree.

Materials and Methods

The charts of all patients submitted to cataract surgery with standard phacoemulsification in one eye and femtosecond laser-assisted surgery in the contralateral eye, between April 2015 and October 2020, at Hospital da Luz Arrabida (HLA) were reviewed. The choice of the technique (FLACS or CP) was based solely on the availability (as it rotates between hospitals) of the femtosecond platform: if available, FLACS was performed, otherwise CP was the employed technique. The surgical devices employed were the LDV Z8 femtosecond laser platform (Ziemer Ophthalmic Systems AG, Port, Switzerland) and the Centurion Vision (Alcon Laboratories, Inc., Fort Worth, TX, USA) phacoemulsification system.

The present retrospective study received the approval of the Ethics Committee at Hospital da Luz Arrabida (HLA), Porto, and complied with the tenets of the “Declaration of Helsinki”, all patients having signed a consent form regarding their medical records’ review.

Inclusion and Exclusion Criteria

The inclusion criterion was both eyes of the same patient having the same cataract degree in accordance with the Lens Opacity Classification System (LOCS) III. Exclusion criteria were ocular surgery besides cataract surgery, history of trauma, corneal scarring or pathology, abnormal iris, glaucoma, pseudoexfoliation syndrome or any other ocular comorbidity. Exclusion criteria also included significant axial anisometropia (a difference equal to or greater than 1 mm in axial length between eyes of same patient).

Chart Review and Data Collection

Clinical and video recording data were collected after chart review of surgeries performed between April 2015 and October 2020. The Lens Opacities Classification System (LOCS) III was chosen for cataract grading, upon lens evaluation at the slit lamp. Biometry, corneal topography and tomography were performed with a combined optical interferometer and Placido–dual Scheimpflug device (Galilei G6, Ziemer Ophthalmic Systems AG, Port, Switzerland). Macular spectral-domain optical coherence tomography was performed with an ophthalmic imaging platform (Carl Zeiss, Oberkochen, Germany).

Regarding pupil measurement, images were taken from recorded surgical videos at two time points: at the beginning of both CP and FLACS (just before docking) and at the end of the surgical procedure, for both techniques. In the FLACS group, additional pupil measurement from images taken after docking release (femtosecond laser administered) was performed.

Cataract subgroups were built following a cut-off value of 3, with a cataract grade ≤ 3 subgroup (soft/medium cataracts) and another subgroup with >3 (harder cataracts), according to LOCS III classification. Each scale on LOCS III is a decimalized scale ranging from 0.1 (a completely clear or colorless lens) to 5.9 (upper value on the cortical opacity (C) and posterior subcapsular opacity (P) scales, indicating complete opacification of the cortex or posterior capsule) and 6.9 on the nuclear opacity (NO) and nuclear color (NC) scales (indicating advanced opacification and brunescence of the nucleus). The final grade’s score is obtained by summing up the score in each parameter (scale).

Surgical Technique

Two comprehensive surgeons performed all surgeries (R.S., A.M.) and adopted the same surgical protocol. Phacoemulsification was accomplished by using the Active Fluidics™ torsional phacoemulsification device (Centurion Vision, Alcon Laboratories, Inc.), ensuring irrigation, emulsification, and aspiration of lens material. The femtosecond laser machine employed in all FLACS was the portable LDV Z8 (Ziemer, Inc.), and it was used to realize capsulotomy, lens fragmentation and corneal incisions. All operations were unilateral, for both CP and FLACS techniques. Phacoemulsification sequentially followed laser in the FLACS

patients, with no patient mobilization; these subsequent surgical steps, were accomplished equally in both groups (FLACS and CP).

The preoperative protocol was universal, consisting of placement of an ophthalmic insert containing tropicamide and phenylephrine hydrochloride, in the inferior conjunctival fornix, along with oxybuprocaine hydrochloride eye drops 20 minutes before the surgical intervention. No patient received any anti-inflammatory or miosis prevention drug preoperatively or intraoperatively (such as intracameral mydriatic agents); being widely integrated in surgical protocols in most centers elsewhere, this specific absence was explained to each patient, with respective given consent. Intracameral cefuroxime was universally administered for endophthalmitis prevention.

The laser parameters employed in the FLACS group were as follows: 100% laser energy for lens fragmentation (6-mm diameter radial pattern with six sectors) and 90% laser energy for capsulotomy (5.2-mm diameter) and corneal incisions (2.8 mm and 1.2 mm, respectively, main and secondary).

Pupil Area Measurement

In order to measure the pupil area, images were obtained from surgical videos at the protocol time points. The adopted imaging software was ImageJ (Fiji, version 2.0.0-rc-49/1.51a), as in previous studies,^{11,12} which converts pixels into millimeters and allows straightforward area measurements using the pupil margin as a boundary marker. For calibration purposes, the constant limbus horizontal diameter (as automatically provided by Galilei) was used.

Statistical Analysis

Analysis aimed at the assessment of pupil area changes between the beginning and the end of surgery, ie, the total pupil variation (TPV),^{12,13} comparing FLACS with CP. Intraindividual and interindividual subgroup analysis were performed to evaluate the variation in pupil area regarding cataract degree and age.

Regarding comparison of the total pupil variation (TPV) between FLACS and CP in the same patient (within-subject), a 2-tailed paired *t*-test was performed. Pupil size variation among subgroups subjected to the same surgery technique and cumulative dissipated energy (CDE) differences were tested using the same methodology (2-tailed *t*-test). Due to non-normality, all tests were validated with their non-parametric equivalent. A mixed-design analysis of variance (ANOVA) was employed in order to compare differences in pupil area between groups. For that matter, cataract grade (≤ 3 or > 3) and age ($\leq$ or $>$ the median age) were considered between-subjects factors. On the other hand, type of surgical technique (FLACS or CP) was considered a within-subjects factor.

Differences in CDE between groups were also compared using a mixed-design ANOVA with type of surgery as a within-subjects factor and cataract grade as a between-subjects factor. Mauchly's Test was used to assess sphericity assumption before the analysis; in the cases of no assumption compliance, the Greenhouse-Geisser correction was performed. A correlation between total pupil variation (TPV) and CDE was tested for both FLACS and CP. The Pearson correlation test was used, and the results were confirmed with a non-parametric test (Spearman correlation test). Correlations between TPV and surgery duration, and between CDE and surgery duration were also tested using the same methodology.

A significance level of $\alpha=0.05$ and a power of 95% was set for this study; a *p*-value of <0.05 was regarded as statistically significant. The statistical analysis software was R (v. 4.1.2) in RStudio (v. 2022.07.0+548), and JMP (v. 16.0).

Results

Preoperative Patient Data

A total of 124 eyes of 62 patients had cataract surgery, with the same cataract degree in both eyes for each patient. The population consisted of 45 female (73%) and 17 male (27%) patients, with a mean age of 72.65 ± 7.64 years (median: 74, range: 59–95). Femtosecond laser-assisted surgery was performed in 62 eyes and conventional phacoemulsification was performed in the other 62 eyes; every patient had FLACS in one eye and CP in the other. No unexpected intraoperative events (such as IFIS, capsule related or other) were registered.

The study population was divided according to cataract grade using the Lens Opacity Classification System III (LOCS III), with 34 patients (68 eyes) having grade ≤ 3 in both eyes and 28 patients (56 eyes) having grade > 3 . The

comparison of patients' preoperative anatomical features and surgical total time (including FLACS laser phase) duration between techniques, for each group of cataract grade, is shown in Table 1. No statistically significant difference was registered between CP and FLACS preoperatively in each group.

Postoperative Data

In the group of patients submitted to FLACS, pupil area was measured at pre (beginning of surgery) and post laser treatment time points, with a mean change in pupil area of $0.01 \pm 0.06 \text{ mm}^2$ for grade ≤ 3 cataract group and $0.01 \pm 0.04 \text{ mm}^2$ for grade >3 cataract group; no statistically significant difference between them was found ($p = 0.851$).

Preoperative mean pupil area was $45.77 \pm 7.69 \text{ mm}^2$ in the FLACS group and $45.78 \pm 7.69 \text{ mm}^2$ in the CP group ($p=0.414$, paired t -test). Pupil area was assessed at the main protocol time points (at the beginning and the end of surgery) for both groups and the respective change (total pupil variation) was registered. Considering cataract grade ≤ 3 , initial mean pupil area was $45.04 \pm 6.96 \text{ mm}^2$ in the FLACS group and $45.04 \pm 6.96 \text{ mm}^2$ in the CP group ($p=0.999$), whereas for cataract grade >3 , preoperative mean pupil area was $46.65 \pm 8.55 \text{ mm}^2$ in the FLACS group and $46.67 \pm 8.53 \text{ mm}^2$ in the CP group ($p=0.992$).

The mean difference between techniques in total pupil variation (TPV) was $0.08 \pm 0.22 \text{ mm}^2$ in the softer (grade ≤ 3) cataract group, and it was $0.01 \pm 0.23 \text{ mm}^2$ in the harder (>3) cataract subgroup. A paired t -test showed a statistically significant difference in total pupil variation (TPV) between techniques in the subgroup of eyes with cataract degree ≤ 3 group (95% CI: 0.01 to 0.16; $p=0.034$), with less pupil narrowing with FLACS, but not in the harder (>3) cataract group (95% CI: -0.08 to 0.10 ; $p=0.849$). In the group of eyes with cataract degree >3 , no statistically significant difference was registered (95% CI: -0.08 to 0.10 ; $p=0.849$), between techniques (Table 2).

Regarding within-technique analysis, a statistically significant difference in total pupil variation (TPV) was found between the cataract grade subgroups in FLACS, but not in CP. The mean difference between softer (grade ≤ 3) and

Table 1 Patient Preoperative Anatomical Data and Surgical Time Duration

Cataract Grade (LOCS III)	Parameters	Mean $\pm$ SD		p-value
		FLACS	CP	
≤ 3 (n=34)	AL (mm)	24.08 ± 1.69	24.02 ± 1.64	0.793
	ACD (mm)	3.12 ± 0.42	3.14 ± 0.46	0.782
	Time duration (min)	13.14 ± 0.90	13.14 ± 0.84	0.990
>3 (n=28)	AL (mm)	23.96 ± 1.89	23.99 ± 1.84	0.806
	ACD (mm)	2.98 ± 0.48	2.99 ± 0.46	0.899
	Time duration (min)	14.27 ± 0.91	14.24 ± 0.93	0.635

Abbreviations: ACD, anterior chamber depth; AL, axial length; LOCS III, Lens Opacity Classification System III; SD, standard deviation.

Table 2 Total Pupil Variation (mm^2) versus Cataract Grade

Cataract Grade LOCS III	TPV FLACS Mean $\pm$ SD	TPV CP Mean $\pm$ SD	Mean Diff. $\pm$ SD [95% CI]	Paired t-test (p-value)	Mixed Design ANOVA
≤ 3 (n=34)	-5.77 ± 1.40	-5.85 ± 1.40	0.08 ± 0.22 [0.01;0.16]	0.034*	$F_{1,60} = 2.60$
>3 (n=28)	-6.53 ± 1.57	-6.53 ± 1.65	0.01 ± 0.23 [-0.08;0.10]	0.849	0.112
Mean Diff. $\pm$ SD [95% CI] t-test (p-value)	0.77 ± 3.01 [0.00;1.53] 0.049*	0.68 ± 3.08 [-0.11;1.46] 0.089			

Note: *Statistically significant.

Abbreviations: LOCS III, Lens Opacity Classification System III; Mean Diff., mean difference; n, number of patients; SD, standard deviation.

harder (>3) cataract groups was $0.77 \pm 3.0 \text{ mm}^2$ (95% CI: 0.00 to 1.53; $p=0.049$) in the FLACS group and it was $0.68 \pm 3.08 \text{ mm}^2$ (95% CI: -0.11 to 1.46; $p=0.089$) in the CP group.

When comparing the cumulative dissipated energy (CDE) in each cataract grade subgroup, a statistically significant difference ($p<0.001$) was found between techniques in both softer and harder cataracts; namely with CDE mean values of 2.33 ± 0.58 with FLACS and 3.69 ± 0.89 with CP in the softer cataract subgroup, and 2.28 ± 0.62 and 11.41 ± 1.34 , respectively with FLACS and CP in the harder cataract subgroup. The analysis within each technique revealed a statistically significant CDE mean difference of 7.72 ± 2.37 between cataract grade subgroups with CP (95% CI: 7.11 to 8.33; $p<0.001$), associated to higher CDE values in the harder cataract's subgroup. On the contrary, no statistically significant difference in CDE was registered with FLACS and cataract grade subgroups, with a CDE mean difference of 0.04 ± 1.23 (95% CI: -0.26 to 0.36; $p=0.754$) (Figure 1).

Correlation between total pupil variation (TPV) and cumulative dissipated energy (CDE) was tested for both techniques. In the FLACS group, no correlation was found between the TPV and CDE (Pearson's $r=0.01$; $p=0.922$; $R^2=0.00$), whereas in the CP group, a weak negative but statistically significant correlation was found (Pearson's $r=-0.29$; $p=0.021$; $R^2=0.09$), meaning that the higher the CDE values, the more negative the TPV (more pupil narrowing) (Figure 2).

Considering total pupil variation and duration of surgery, correlation (Pearson's test) was expectedly significant for both techniques, with $r=-0.50$ and $R^2=0.25$ ($p<0.001$) in the FLACS group and $r=-0.46$ and $R^2=0.21$ ($p<0.001$) in the CP group.

Regarding age, two subgroups were built, below and above the median age (73 years). Preoperative mean pupil area was $40.53 \pm 4.31 \text{ mm}^2$ in the FLACS group and $40.55 \pm 4.31 \text{ mm}^2$ in the CP group ($p=0.985$) in the older (age >73 years) subgroup, while initial mean pupil area was $51.01 \pm 6.71 \text{ mm}^2$ in the FLACS group and $51.01 \pm 6.71 \text{ mm}^2$ in the CP group ($p=0.999$) in the younger (age ≤ 73 years) subgroup.

Regarding TPV, there was no statistically significant difference between techniques in either age subgroup. However, a statistically significant and similar difference occurred between age subgroups within each technique, with less pupil narrowing in the older (age >73 years) patients' subgroup as compared to the younger (age ≤ 73 years); for both techniques the p -value was <0.001 (Table 3).

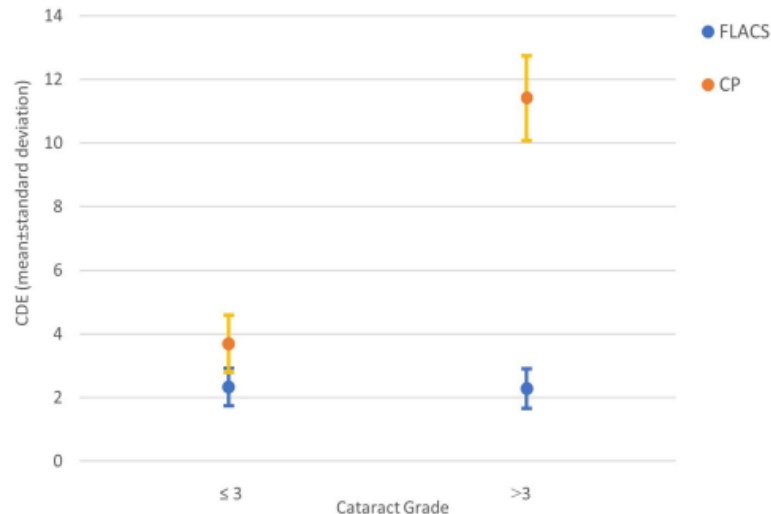


Figure 1 Mean $\pm$ standard deviation of CDE by cataract grade, for CP and FLACS.

Abbreviations: CDE, Cumulative Dissipated Energy; FLACS, femtosecond laser assisted cataract surgery; CP, conventional phacoemulsification.

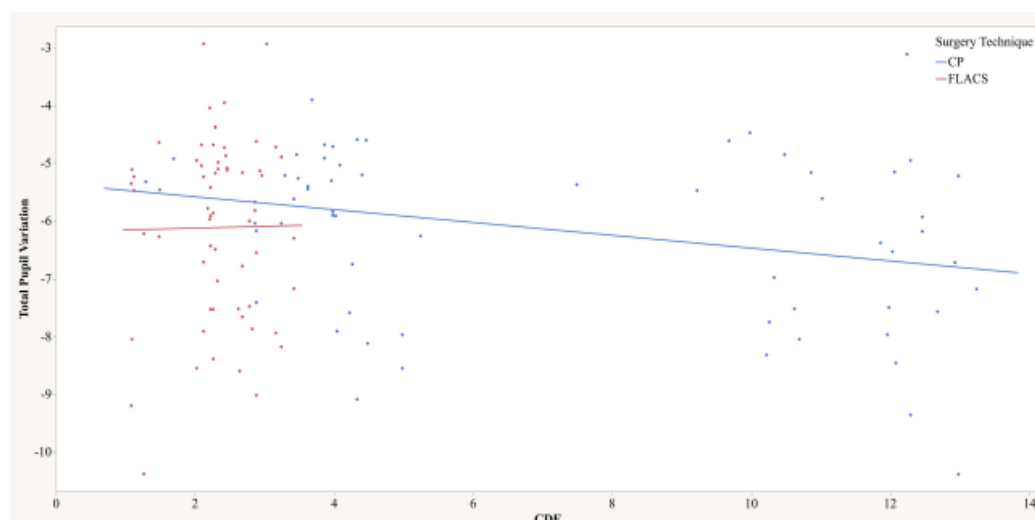


Figure 2 Relationship between Total Pupil Variation and Cumulative Dissipated Energy (CDE). Results separated by surgical technique: CP (blue) and FLACS (red). **Abbreviations:** CDE, Cumulative Dissipated Energy; FLACS, femtosecond laser assisted cataract surgery; CP, conventional phacoemulsification.

Discussion

This study introduces a novel comparison between low-energy femtosecond laser with conventional phacoemulsification addressing pupil area changes and cataract grade. Furthermore, the study is based on an intraindividual comparative assessment.

Laser-induced miosis has been associated with FLACS, with most of the literature mainly involving high-energy femtosecond laser devices.^{16,17}

Our results add some more evidence to recently published literature^{18–20} pointing to an absence of laser-induced pupil constriction (pupil size immediately after laser application did not change) with the low-energy and high-frequency type of femtosecond pulse, as opposed to the high-energy and low-frequency kind, which often demands the perioperative use of supplementary anti-inflammatory drugs.^{21,22} The rationale for this contrast is liable to reside on the “low-energy” concept: the use of a high numerical aperture in the femtosecond laser optics, enabling the production of smaller laser spots, which, in turn, allows a reduction of the collateral damage to the neighbour tissues. Furthermore, the absence of preoperative anti-inflammatory drugs, as established in the authors’ protocol in other studies,¹² did not reflect on pupil constriction, also corroborated by recent published articles.²³

Cataract grade influences the energy level of ultrasound energy employed, according to the literature.^{15,24} The impact of higher levels of energy (for harder cataracts) may be accountable for pupillary constriction, by means of the stimulated release of inflammatory mediators. Cumulative dissipated energy (CDE) has been commonly used as a measure of such ultrasound expenditure.^{14,15,24}

Table 3 Total Pupil Variation (mm²) versus Age

Age	TPV FLACS Mean ± SD	TPV CP Mean ± SD	Mean Diff. ±SD [95% CI]	Paired t-test (p-value)	Mixed Design ANOVA (p-value)
≤73 (n=31)	−6.81 ± 1.52	−6.84 ± 1.51	0.03 ± 0.14 [−0.02;0.08]	0.246	F _{1,60} = 0.17
>73 (n=31)	−5.41 ± 1.52	−5.47 ± 1.51	0.05 ± 0.29 [−0.05;0.16]	0.306	0.682
Mean Diff. ± SD [95% CI] t-test (p-value)	1.40 ± 2.71 [0.71;2.09] <0.001*	1.38 ± 2.75 [0.68;2.07] <0.001*			

Note: *Statistically significant.

Abbreviations: Mean Diff., mean difference; n, number of patients; SD, standard deviation.

In this study, it is given further evidence that cataract grade influences ultrasound energy expenditure, as it is measurable by the CDE. It is shown that there is a negative correlation between total pupil variation and CDE with conventional phacoemulsification, associating a more negative TPV with higher CDE values. It is also consensual that the use of femtosecond laser in cataract surgery reduces the amount of ultrasound (US) employed, ergo, the CDE.^{25,26} In agreement with this knowledge, the present study reinforces the evidence that energy expenditure relates to cataract hardness: for softer cataracts, CDE levels are expectedly low in CP and even more with the assistance of femtosecond laser in FLACS; for harder cataracts, the ultrasound energy requisites (CDE) are significantly high in CP. The rationale will be that lower CDE levels, by means of using femtosecond laser in cataract surgery, contribute to less pupil narrowing as compared to conventional phacoemulsification. It should be stressed that the magnitude of the detected difference, although of statistical significance, is, quantitatively, of little clinical impact on surgical practice. However, these results help to demonstrate that low-energy FLACS performs similarly to conventional phacoemulsification regarding pupil status (namely pupil constriction) and may support an evidence-based decision upon choosing this technique in cataract surgery.

Regarding total pupil variation and age, no statistically significant difference was found between CP and FLACS, in the present study. However, concerning age subgroups and TPV, a statistically significant difference was shown between younger and older patients, similar for each technique. Our findings may be explained by the well-known physiological profile of the ageing pupil,^{27–29} characterized by a lesser pupil responsiveness and slower recovery from dilation, traduced by lower TPV values in the older subgroup of patients.

The limitations inherent to this study are the following: a suboptimal (as very large series are in demand to reinforce these findings) sample size of eyes and the assessment of prostaglandins levels. Nevertheless, the clinical evidence here collected should stimulate further studies regarding the thorough evaluation of the specific profile and role of low-energy femtosecond laser in cataract surgery.

Conclusion

The present study brings new evidence regarding the association of cataract grade with pupil status during cataract surgery. In particular, it shows a statistically significant difference in pupil behavior according to cataract grade, between CP and FLACS, favorable to the latter. Although of mild clinical relevance, this evidence does deliver a new perspective upon the real effects of the different types of femtosecond laser, thus optimizing the indications and choice of the cataract surgical technique.

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Disclosure

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References

1. Dick HB, Schultz T. A review of laser-assisted versus traditional phacoemulsification cataract surgery. *Ophthalmol Ther*. 2017;6:7–18. doi:10.1007/s40123-017-0080-z
2. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT non-inferiority RCT. *Health Technol Assess*. 2021;25(6):1–68. doi:10.3310/hta25060
3. Grewal DS, Schultz T, Basti S, Dick HB. Femtosecond laser-assisted cataract surgery—current status and future directions. *Surv Ophthalmol*. 2016;61:103–131. doi:10.1016/j.survophthal.2015.09.002
4. Agarwal K, Hatch K. Femtosecond laser assisted cataract surgery: a review. *Semin Ophthalmol*. 2021;36(8):618–627. doi:10.1080/08820538.2021.1890792
5. Diakonis VF, Yesilirmak N, Sayed-Ahmed IO, et al. Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms. *J Refract Surg*. 2016;32:84–88. doi:10.3928/1081597X-20151229-03
6. Kancelerz P, Alio JL. The benefits and drawbacks of femtosecond laser-assisted cataract surgery. *Eur J Ophthalmol*. 2021;31(3):1021–1030. doi:10.1177/1120672120922448
7. Popiela MZ, Young-Zvandasara T, Nidamanuri P, Moore T, Leccisotti A, Kumar V. Factors influencing pupil behavior during femtosecond laser assisted cataract surgery. *Cont Lens Anterior Eye*. 2019;42(3):295–298. doi:10.1016/j.clae.2018.10.010
8. Wu BM, Williams GP, Tan A3, Mehta JS. A comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol*. 2015;2015:616478. doi:10.1155/2015/616478

9. Ewe SY, Abell RG, Vote BJ. Femtosecond laser-assisted versus phacoemulsification for cataract extraction and intraocular lens implantation: clinical outcomes review. *Curr Opin Ophthalmol*. 2018;29:54–60. doi:10.1097/ICU.0000000000000433
10. Lundstrom M, Dickman M, Henry Y, et al. Femtosecond laser-assisted cataract surgeries reported to the European registry of quality outcomes for cataract and refractive surgery: baseline characteristics, surgical procedure, and outcomes. *J Cataract Refract Surg*. 2017;43:1549–1556. doi:10.1016/j.jcrs.2017.09.029
11. Mirshahi A, Ponto K. Changes in pupil area during low-energy femtosecond laser-assisted cataract surgery. *J Ophthalmic Vis Res*. 2019;14(3):251–256. doi:10.18502/jovr.v14i3.4780
12. Salgado R, Torres PF, Marinho A. Pupil status with low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: an intraindividual comparative study. *Clin Ophthalmol*. 2023;17:331–339. doi:10.2147/OPTH.S399788
13. Germano C, Germano R, Cid F, Germano FA, Carricondo P, Germano J. Comparison of pupillary diameter variation between conventional phacoemulsification versus femtosecond laser-assisted cataract surgery. *Arq Bras Oftalmol*. 2022;85(1). doi:10.5935/0004-2749.20210091
14. Feng L, Zhao F, Ke X, Zhao J, Shi M. Correlation between degree of lens opacity and the phacoemulsification energy parameters using different imaging methods in age-related cataract. *Transl Vis Sci Technol*. 2022;11(3):24. doi:10.1167/tvst.11.3.24
15. Bui AD, Sun Z, Wang Y, et al. Factors impacting cumulative dissipated energy levels and postoperative visual acuity outcome in cataract surgery. *BMC Ophthalmol*. 2021;21(1):439. doi:10.1186/s12886-021-02205-w
16. Wang J, Su F, Wang Y, Chen Y, Chen Q, Li F. Intra and post-operative complications observed with femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):177. doi:10.1186/s12886-019-1190-2
17. Popovic M, Campos-Möller X, Schlenker MB, Ahmed II. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology*. 2016;123(10):2113–2126. doi:10.1016/j.ophtha.2016.07.005
18. Lin H-Y, Chuang Y-J, Lin P-J. Surgical outcomes with high and low pulse energy femtosecond laser systems for cataract surgery. *Sci Rep*. 2021;11(1):9525. doi:10.1038/s41598-021-89046-1
19. Mirshahi A, Schneider A, Latz C, Ponto KA, Liu Y-C. Perioperative pupil size in low-energy femtosecond laser-assisted cataract surgery. *PLoS One*. 2021;16(5):e0251549. doi:10.1371/journal.pone.0251549
20. Salgado R, Torres P, Marinho A. Femtosecond laser-assisted lens surgery with low-energy pulse versus conventional phacoemulsification for presbyopia correction: an Intraindividual Study. *Open Ophthalmol J*. 2021;15(1):43–53. doi:10.2174/1874364102115010043
21. Jun JH, Bang SP, Yoo YS, Joo CK. Efficacy of 0.015% intracameral epinephrine for significant miosis induced by photodisruption during femtosecond laser-assisted cataract surgery. *Medicine*. 2018;97(31):e11693. doi:10.1097/MD.00000000000011693
22. Schultz T, Joachim SC, Szuler M, Stellbogen M, Dick HB. NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2015;31:791–794. doi:10.3928/1081597X-20151111-01
23. Schwarzenbacher L, Schartmüller D, Leydolt C, Menapace R. Prostaglandin release after low-energy femtosecond laser-assisted cataract surgery without anti-inflammatory drug premedication. *Am J Ophthalmol*. 2022;238:103–109. doi:10.1016/j.ajo.2022.01.002
24. Shajari M, Rusev V, Mayer W, Diakonis V, Petermann K, Kohnen T. Impact of lens density and lens thickness on cumulative dissipated energy in femtosecond laser-assisted cataract surgery. *Lasers Med Sci*. 2019;34(6):1229–1234. doi:10.1007/s10103-019-02715-6
25. Yesilirmak N, Diakonis VF, Batlle JF, et al. Comparison of phacoemulsification parameters between manual and femtosecond laser-assisted cataract surgery. *Can J Ophthalmol*. 2018;53(5):542–547. doi:10.1016/j.jco.2018.01.009
26. Saeedi OJ, Chang LY, Ong SR, et al. Comparison of cumulative dispersed energy (CDE) in femtosecond laser-assisted cataract surgery (FLACS) and conventional phacoemulsification. *Int Ophthalmol*. 2019;39(8):1761–1766. doi:10.1007/s10792-018-0996-x
27. Baldascino A, Carlà MM, Giannuzzi F, et al. Femtosecond laser-assisted cataract surgery: analysis of surgical phases and comparison with standard phacoemulsification in uncomplicated cataracts. *Vision*. 2022;6(4):72. doi:10.3390/vision6040072
28. Fotiou DF, Brozou CG, Tsitsios DJ, et al. Effect of age on pupillary light reflex: evaluation of pupil mobility for clinical practice and research. *Electroencephalogr Clin Neurophysiol*. 2007;47(1):11–22.
29. Lee YS, Kim HJ, Lim DK, Kim MH, Lee KJ. Age-specific influences of refractive error and illuminance on pupil diameter. *Medicine*. 2022;101(27):e29859. doi:10.1097/MD.00000000000029859

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4.5. Update on Femtosecond Laser Assisted Cataract Surgery: A Review.

Update on Femtosecond Laser-Assisted Cataract Surgery: A Review

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Abstract: The advent of femtosecond lasers has resulted in a new standard in cataract surgery, intended to overmatch the paradigm of conventional phacoemulsification. Femtosecond laser-assisted cataract surgery (FLACS) enables a higher level of reproducibility, precision, accuracy, and customization when performing several steps of cataract (or lens) surgery. Capsulotomy, corneal incisions, lens fragmentation, and arcuate incisions are the main procedures performed using FLACS. As the demand for better refractive outcomes and spectacle independence increases, the features of FLACS are highly relevant, especially when considering the implantation of premium intraocular lenses, such as toric, enhanced depth-of-focus, or multifocal lenses. The present article reviews the state of the art of femtosecond laser-assisted cataract (lens) surgery, contemplating the advantages and limitations of the two types of femtosecond laser pulses available (high and low energy) by evaluating their reported outcomes and complications.

Keywords: femtosecond laser, FLACS, laser-assisted surgery, cataract surgery

Introduction

Current cataract surgery is not merely the removal of an opacified lens. It assumes intraocular lens (IOL) implantation, which characteristics (including power and design) are purposely chosen through a careful preoperative assessment.^{1,2} This quest for better postoperative refractive results, supported by a continuous commitment to the development of biometry formulas, is unequivocal evidence of the refractive nature of cataract surgery. This refractive-driven concern clearly dilutes the old dichotomy between cataract removal and the so-called refractive lens surgery and has thrust the investment in technology regarding new techniques and IOLs, creating an unsurprisingly high status of expectation and demand from patients. Instead of a clear separation between pure cataract removal and refractive lens (or premium) surgery, and because the essence of the surgical steps is the same, the indications are better set in a continuous spectrum of patient-based needs. For example, a patient presenting with a cataract, however mature it may be, is ultimately intervened depending on the patient's informed decision, which is directly based on how autonomous he or she feels, despite the condition. The elective character of refractive lens surgery will stand on the farthest point of this spectrum, in which the autonomy of spectacles is the patient's highest desire. Expectation and deliverance, like most human activities, are turning wheels in the evolution of cataract surgery. With this regard, femtosecond laser-assisted cataract surgery (FLACS) emerged as a technique liable to offer higher standards in terms of efficacy and safety.

The proven high reproducibility and precision of femtosecond laser-assisted capsulotomy stimulated the development of femtosecond laser technology, expanding its role in substituting for the classical surgical steps of cataract surgery (as established by conventional phacoemulsification). Hence, laser-assisted lens fragmentation and corneal incisions became integrated in the FLACS scope of action, increasing the expectations of an optimization of the surgical outcomes.

Implantation of premium intraocular lenses requires no less than an optimal technique and, in this context, predictability and accuracy are of paramount relevance. This review aimed to provide an update on the role of femtosecond laser-assisted cataract (lens) surgery by visiting the technique's outcomes and related current evidence on its effectiveness and safety.

Technology

Femtosecond Lasers

Femtosecond laser technology derives its name from the generated pulse duration of the order of 10^{-15} s.^{3,4} Produced in the near-infrared range (1053 nm), the extremely short pulse time of this solid-state laser is liable to achieve photodisruption in target tissues, avoiding the undesired effects of previous lasers, such as thermal impact.^{5–7} When in association with other adjustable laser parameters such as power, repetition rate, and spot size, the laser-tissue interaction can be further customized and optimized. Photodisruption is a sequential three-step process involving plasma formation, shock wave generation, and cavitation. Henceforth, femtosecond (FS) laser separates tissue by ablation and cleaving; the relative weight of each is determined mainly by the pulse energy level.⁷ To achieve photodisruption, an energy threshold must be surpassed, depending on the nature of treated tissue and different laser features: numerical aperture (NA) and wavelength. The higher the energy pulse, the greater the ablated tissue through expanding gas bubbles; the lower the energy pulse, the lesser the ablated tissue, and separation is dependent on the cleaving occurrence (implying higher pulse frequencies and tighter spots).⁸

Types of Femtosecond Laser Pulse

Presently, there are two different FS laser pulse patterns regarding energy level and frequency. On one hand, there are devices (the majority of laser systems available) that produce high-energy and low-frequency pulses on the order of μJ and KHz, respectively. On the other hand, there is a laser platform producing low-energy high-frequency pulses in the range of nJ and MHz, respectively. The latter pulse pattern (low energy with high repetition rates) offers some advantages: high laser focusing accuracy and cutting precision, accompanied by less gas generation, which reflects on a reduced collateral damage to the surrounding tissue.^{8,9} The mechanical thrust on adjacent tissues is, by this physical evidence, substantially bigger with high-energy pulse FS.

The energy level of an FS laser pulse at a certain wavelength depends on the focal spot size, which is inversely proportional to the numerical aperture (NA) of the focusing optics. The larger the NA, the smaller the focal spot and, ultimately, the lower the energy. There are two ways of producing an augmented NA: by increasing the lens diameter of the focusing optics or by positioning the focusing optics closer to the eye. Most of the available laser platforms, such as LenSx (Alcon Laboratories, Fort Worth, Inc.), VICTUS (Bausch & Lomb, Inc.), Catalys (Johnson & Johnson Vision Care, Inc.), and LensAR (LensAR, Inc.), have opted for the first approach, whereas Femto LDV Z8 (Ziemer Ophthalmic Systems AG) has chosen the second approach.^{9–11} The former devices have large optics requiring relatively immobile platforms. With the latter device, the laser beam is guided through an articulated mirror arm into a handpiece that contains the focusing optics; this feature allows a reduction in pulse energy by a factor of 10 or more. Furthermore, this design enables the handpiece use under a surgical microscope, thereby rendering the whole platform more compact and portable.

Delivery Procedure

In order to correctly apply an FS laser to the eye, an adequate, stable, and well-tolerated patient interface is of paramount importance. This device-patient engagement, described as docking, is currently achieved by means of two different methods: eye appplanation (with a curved lens) or liquid interface.^{12,13} While the current literature shows no difference between the two methods regarding capsulotomy regularity,¹⁴ there is some evidence of increased incidence of anterior capsular tears or tags with appplanating interfaces due to the occurrence of corneal folds.¹³ Among the features of non-appplanating interfaces (which use a scleral suction ring and a fluid immersion chamber) are a lower induced intraocular pressure, larger treatment area, and a more proficient compensation regarding lens tilt.¹³

Docking adds an additional, time-consuming step when compared to conventional phacoemulsification (CP),¹⁵ and it inherently has a rate of possible complications, from mildly frequent transient conjunctival redness or hemorrhage to a very rare incomplete laser treatment due to suction loss.^{16–19}

Supporting Imaging Technology

Accurate and reliable imaging is necessary to perform the proposed laser-assisted surgical steps (capsulotomy, corneal incisions, and lens fragmentation). A thorough three-dimensional reconstruction of the anterior eye structures is currently provided by either optical coherence tomography (most FS platforms) or 3D confocal structured illumination combined with Scheimpflug imaging (LensAR).^{11,19–21} In addition, most FS devices present an integrated camera system that allows a frontal view of the eye.

Clinical Outcomes

Surgical Steps

Capsulotomy

The dimensions (shape and size) of capsulotomy are determinant variables affecting the effective lens position, which in turn affects the postoperative refractive results. Inadequate sizing of the capsulotomy may result in IOL tilt, decentration, and increased posterior lens capsule opacification.^{22–25} Furthermore, for premium IOLs (toric, enhanced-depth-of-focus, or multifocal), which have more demanding optical designs, capsulotomy centration is most relevant for achieving optimal results.^{26–28}

Precision, predictability, and reproducibility of FS capsulotomy are the features that have been demonstrated to be superior to CP.^{24,28,29}

The surgical step sequence differs according to the available platform. Thus, most FS devices perform capsulotomy before lens fragmentation, whereas one of them (Ziemer's) executes capsulotomy afterwards. This feature does have a clinical impact, since for white cataracts (generally, a contraindication for FS laser with most platforms), it is liable for performance with the latter device, as nucleus fragmentation equalizes the gradient pressure inside the capsular bag before capsular opening, preventing the Argentinian Flag Syndrome.³⁰

FS platforms enable customization of the diameter and centration of the capsulotomy, adequately set via OCT (or equivalent) imaging upon docking; safety margins (from the iris) are usually adjustable, as well.

A six-fold better IOL centration with FSL capsulotomy compared to manual capsulorrhexis was found in some studies.²⁶ Capsulotomy can be centered on several landmarks or reference points: pupil, optical (corneal) or capsule center or custom placement (such as the lens apex or the first Purkinje reflex);³¹ the available FS platforms share at least two of the aforementioned referential possibilities. Some authors have reported that more favorable results regarding capsule-IOL overlap with capsular bag-centered capsulotomy as opposed to pupil-centered capsulotomy;³² an anterior capsule overlap of 360 degrees on the IOL anterior surface is consensually associated with a reduced incidence of posterior capsule opacification.

Regarding preoperative pupil size, normally, a diameter not inferior to 4 mm, is compatible for the FS devices available.³³ As to pupil size after the laser pretreatment, constriction (miosis) has been commonly reported for femtosecond laser-assisted surgery, casting this shadow on femtosecond laser-assisted cataract surgery (FLACS), in general, and presenting it as a feature of this technique in the published literature. However, the vast majority of the publications available refer to high-energy FLACS or seldom include low-energy pulse devices but without data results differentiation. In fact, recent literature on low-energy FLACS does not show evidence of miosis with this technique, demonstrating comparable results with CP, regarding pupil behavior. This may be related to the lower level of pulse energy, causing less impact on the surrounding tissue and prostaglandins release. It has also been described that applanation can decrease pupil size, by means of transient ischemia of the iris sphincter induced by applanation docking.³⁴

Strategies have been adopted to resolve this laser-induced miosis with high-energy pulse devices. Intraoperative measures, such as intracameral viscoelastic, epinephrine (injection or perfusion), or mechanical dilation, have been used, generating a profuse literature on this particular counterback.^{35–37}

Anterior capsule strength is related to the amount of energy applied during capsulotomy. Some studies with electron microscopy scanning have shown manual capsulorrhexis to be stronger than FSL capsulotomy, the magnitude of this difference being related to the capsulotomy edge properties; these, in turn, depend on the laser energy pulse. The higher the energy pulse, the more irregular the edges; the lower the energy pulse, the smoother the capsulotomy edges.^{29,38,39}

Accordingly, recently published studies show a lower incidence of capsular complications (tears, tags) with low-energy pulse as compared to high-energy pulse FLACS.^{10,40,41}

Although capsulotomy sizing can be adjusted with FS platforms, an average diameter of 5–5.25 mm is generally chosen for most cases;^{42,43} however, this reference value may be limited by pupillary dilation and laser-specific pupil safety margins.

To summarize, in favor of FLACS, capsulotomies are more precise (in size and shape), reproducible, and better centered than manual capsulorhexis.^{25,44–46}

However, this technique has two limitations: maintenance of pupil dilation and a considerable rate of capsule-related complications, both after laser treatment with high-energy pulse devices.

Lens Fragmentation

Femtosecond laser allows lens nucleus fragmentation, substituting this surgical step conventionally performed by ultrasound with the CP technique. The different platforms allow fragmentation customization according to the available patterns on the laser system,⁴⁷ beyond ensuring anterior and posterior safety margins, as displayed upon imaging of the capsular bag;³⁶ these margins are adjustable within the program range of each FS device. Laser pre-cutting of the nucleus precludes the oxidative stress, heat, inflammation, and tissue damage associated with ultrasound as it shortens the phacoemulsification time and cumulative dissipated energy (CDE).⁴⁸

Capsular block syndrome with subsequent posterior capsule rupture is an extremely rare complication that occurs when excessive pressure is generated inside the capsular bag during lens fragmentation. This phenomenon is caused by the expanding gas bubbles, a feature of the tissue ablation produced with high-energy pulse systems;⁴⁹ this rare occurrence is not reported with low-energy FLACS, as its lower pulse energy produces cleaving rather than ablation.

In synthesis: FLACS has proven to be advantageous over CP, as it reduces the amount of phacoemulsification energy delivered by 33–70% by softening the lens.^{44,45} On the other hand, FS requires adequate pupillary dilation to ensure safe completion. In addition, high-energy FLACS is contraindicated in patients with white cataract.

Corneal Incisions

Femtosecond laser technology enables customized, precise and predictable sizing (width, length, and depth), shaping and location of full-thickness corneal incisions.⁵⁰ Corneal incisions constructed with FS have been proven stable, repeatable and safe as compared with CP in numerous studies.^{51–53} Namely, it has been found that there is less wound gape and decreased wound edema with laser-created incisions than with manual incisions.⁵⁴

The main corneal incision and paracentesis are accomplished using FS platform customizable settings, generally upon imaging of the eye. Laser allows the construction of a more complex wound shape (such as biplanar or triplanar), with higher consistency regarding reproducibility when compared to CP. Likewise, the incidence of Descemet's membrane detachment, endothelial misalignment, and posterior wound contraction is low in FLACS.^{53,54}

However, as a counter back of FS, peripheral vascularization of the cornea prevents completion of the laser cut (forcing manual aid) because of the suction-driven blanching of the limbic vasculature; therefore, less vascularized areas should be looked for (if possible) when adjusting the laser cut parameters upon imaging.⁵⁵

Therefore, in favor of FLACS, incisions are less prone to wound gape and leakage;⁴⁵ also, surgically induced astigmatism is more predictable. The limitations include the location and completion of the FSL wounds in some cases.

Arcuate Keratotomy

Corneal partial-thickness incisions are included in the armamentarium of corneal astigmatism surgical correction. Classically performed in a manual (blade) manner, keratotomy with FS technology shows higher predictability and repeatability, adding the possibility of completely intrastromal incisions beyond the standard anterior penetration.⁵⁶ These designated arcuate incisions (AIs) can be performed by the FS laser at the surgeon's predetermined depth, length, location and treatment axis; additionally, anterior penetrating AIs can be opened up manually intraoperatively or post-operatively to enhance the effect.^{57,58} Femtosecond laser-assisted arcuate keratotomy (FSAK) is associated to less irritation, epithelial ingrowth or loss of corneal sensation, beyond diminishing the risk of infection for patients;⁵⁹ thus, it can be safely used in patients with ocular surface disease or after keratoplasty. Nevertheless, it is believed that

intrastromal AIs may have a reduced astigmatic effect when compared to anterior-penetrating AIs because the former does not involve Bowman's membrane.

Intrastromal incisions are also used for non-refractive marking of the implantation axis of toric IOLs.⁶⁰

Several studies point out to comparable results between FS laser-assisted corneal incision and toric IOLs implantation for correcting mild (<1.25 D), central, and with-the-rule astigmatism in terms of safety, efficacy and stability.^{61–64}

However, most available studies show some superiority of toric IOLs implantation over FSAK in moderate-to-high (>1.25 D), against-the-rule, or limbus-to-limbus astigmatism correction.^{64–66}

Literature on nomograms for femtosecond laser-created AIs is scarce. Wortz & Gupta developed a nomogram for correction of low levels of astigmatism.^{67,68} Baharozian et al's FSL anterior penetrating AI nomogram was designed for patients with <1.25 D of astigmatism, which is a modification of Donnenfeld's manual LRI nomogram; it accounts for the influence of posterior corneal astigmatism relative to the type of astigmatism being treated and uses a 9.0 mm optical zone.⁶⁹

Hence, FLACS has notable advantages over CP. First, the treatment of astigmatism is much more accurate with FSAK than with manual keratotomy, given the ability to control depth and location.⁴⁵ Secondly, the ability to perform intrastromal incisions is unique to FSL. Finally, postoperative tuning of the astigmatic correction is feasible with the opening of laser-assisted incisions (at the slit lamp).

Nevertheless, FLACS' range of correction is limited to low levels of corneal astigmatism, and improved FSAK-specific nomograms are yet to be developed.

Refractive and Visual Outcomes

It has been reported in several studies that no statistically significant differences between FLACS and CP were found regarding corrected, uncorrected distance vision acuities, and refractive outcomes in the long term.^{70–74} Meanwhile, some systematic reviews and meta-analyses⁴⁰ have shown better medium-term uncorrected and corrected visual acuities with FLACS than with CP; however, this finding, although statistically significant, does not translate into a clinically significant difference (inferior to 0.05 logMAR).

Visual acuity can be affected in the long term by capsular bag-IOL interactions, such as tilt, decentration, or posterior capsule opacification. These events have been reported to occur less frequently after FLACS.^{75,76} Long-term IOL positioning relates to several factors, with capsular bag shrinkage standing out as a major factor for tilt and decentration; this phenomenon is more prominent in CP.⁷⁷

IOL positioning affects the effective lens position (which is essential for IOL power calculations), ergo, the refractive results. Furthermore, such positioning impacts decisively on the performance of premium IOLs such as toric, EDOF, and multifocal lenses. Kranitz et al identified significantly higher levels of IOL decentration and worse CDVA in the CP group.²⁶ In addition, Reddy et al registered a higher IOL decentration with CP when compared to FLACS.⁷⁸

Regarding posterior capsule opacification, most studies show a higher incidence with FLACS,^{19,79} probably related to adjacent laser treatment, which may induce mesenchymal transformation of lens epithelial cells (LEC). This impact is assumed to override the expected benefits of a laser driven LEC apoptosis close to the capsulotomy edge; again, laser pulse energy and duration are relevant features regarding this impact.^{80–82} Subgroup analysis of PCO with different pulse energy (high vs low) FLACS is almost inexistent.

However, Nd: YAG capsulotomy rates in FLACS are reportedly lower than those in CP. This may be accounted for by a lower PCO grade and, consequently, a minor impact on visual acuity; such grading is lacking in most published literature.

Another measure of refractive predictability is mean absolute error (MAE). Depending on the number and study design of the included trials, review and meta-analysis reports are not clear regarding the superiority of FLACS over CP in terms of postoperative SE. Hence, large reviews based on randomized control trials (RCTs) point to a higher predictability of FLACS in the short term but not in the long term,⁸³ whereas reviews based on a small number of RCTs⁷⁸ report an advantage in favor of FLACS MAE at 12 months follow-up. Other systematic reviews, including both prospective and retrospective trials, found a clinically important difference in MAE only in the mid-term (1 month to 3 months follow-up).⁴⁰

Surgical induced astigmatism (SIA) is caused by the wound healing process after corneal incision.⁸⁴ This form of astigmatism is caused by the processes at the place where the corneal incision took place, and it is most relevant to toric

IOLs implantation. Differences between FLACS and CP regarding SIA only seem to be clinically significant at the predictability level (achieved vs attempted), without statistically significant differences with respect to the overall magnitude of the SIA.^{40,55}

Other Surgical Outcomes

Commonly assessed surgical endpoints are effective phacoemulsification time (EPT), cumulative dissipated energy (CDE), and circularity of capsulotomy. EPT represents the value of the phacoemulsification time length at 100% power in continuous mode,⁴⁰ whereas CDE is the EPT in seconds divided by 6000 or the EPT in minutes divided by 100. There is sufficient evidence that FLACS is superior to CP in every and each of the aforementioned parameters.^{24,43,54,83,85–90} A more precise and reproducible capsulotomy circularity is registered with FLACS, which allows for better lens centration and a lower risk of lens mispositioning;^{91,92} this, in turn, is liable to translate into better optical performance.⁹³

Patient Reported Outcomes

Literature on patient-reported outcomes (PROs) is very scarce. The heterogeneity of the methodology is employed to assess patient satisfaction and other subjective parameters, the difficult global assessment of differences between FLACS and CP.⁹⁴ Patient-reported outcome measures (PROMs) vary greatly among several studies. Given the increasing number of refractive cataract or lens surgeries and their inherent elective nature, patient-reported outcomes are paramount when choosing an adequate premium IOL. Thus, more comprehensive and standardized PROMs are required for a rigorous analysis.

Complications

Complications associated with FLACS can be either intraoperative or postoperative. Intraoperative complications usually include suction loss, subconjunctival hemorrhage, and capsule- or pupil-related complications.^{18,46}

Suction loss is a consequence of deficient docking driven by interface defects, patient movement, anatomical particularities, or conjunctival chemosis. Among the anatomic conditions, conjunctivochalasis, pinguecula, pterygia, or bleb filtration surgery are the most frequent. Some FS platforms have suction rings with different diameters to improve the fitting of the docking piece. In the event of suction loss, laser treatment is to be immediately suspended to avoid mistreatment.

Subconjunctival hemorrhage is caused by the vacuum applied, total treatment time, and specific docking interface; this complication is more frequent with applanation docking than with liquid-interface.¹⁰

Posterior capsule rupture (PCR) has been reported to be less frequent with FLACS than with CP.^{40,75} Regarding anterior capsule complications (tears or tags), the reported evidence of a higher incidence with FLACS is two-fold: first, it is described to be variable, ranging from 0.1% to as high as 4%,^{17,95} and second, this complication is mostly related to high-energy pulse FS platforms.^{18,28,40,95} These findings can be explained by the microscopically different capsulotomy edges, as produced by the different laser settings. Commonly, high-energy FLACS produces less smooth and notched capsulotomy edges than low-energy pulse FS;^{9,96} this microscopic difference may account for the very low incidence of anterior capsule complications in low-energy FLACS, comparable to CP.^{10,41,97}

Either way, the overall implications of all capsule-related complications (such as the need for vitreoretinal or affecting visual outcomes) seem to be not statistically significant in a global comparison between FLACS and CP.^{40,79,98} Nevertheless, the impact of such events should not be underestimated in the context of premium IOL implantation, as it irrevocably compromises surgical success, as capsular integrity and further optimal centration are paramount in the final result. Unfortunately, literature comparing low-energy FLACS and CP that contemplates this niche or subgroup of refractive cataract surgery is scarce, although not absent.^{41,99}

Pupil constriction is a commonly reported feature of FLACS,^{18,34,96} and is associated with prostaglandin release during laser treatment of the anterior capsule.^{47,71,100,101} Pupil miosis is a severe and undesirable event as it affects the feasibility of cataract surgery. The consensual use of pre-operative non-steroid anti-inflammatory drugs (NSAIDs) in cataract surgery is among the strategies for preventing the loss of dilation with FLACS. However, pre-operative NSAIDs administration is normally insufficient to avoid the laser-induced miosis associated with FLACS. Therefore, a multitude

of actions, either single or in combination, have arisen to address this issue.^{42,102} It is also recommended to observe specific laser-related conditions, such as the distance from the intended capsulotomy edge and pupillary margin (>1 mm recommended) and duration of laser treatment.^{103,104}

However, most published literature reports this complication without differentiating between types of FS pulses, ie, high or low energy (or even excluding the latter type). Recent publications show evidence of the absence of laser-induced miosis with low-energy FLACS.^{10,99,105} Moreover, in the few systematic reviews and meta-analyses that include low-energy FLACS and subgroup analysis, the reported incidence of laser-induced pupil miosis is virtually null and comparable to CP;^{9,106} on the contrary, high-pulse energy FLACS is associated with pupil constriction almost universally.^{40,74,94,96} The impact of such evidence should not be ignored and is still to be integrated in the common knowledge of femtosecond laser-assisted cataract surgery.

With regard to postoperative complications, endothelial and retinal status have been the subject of several studies. Although recently published literature based on well-powered randomized controlled trials (RCTs) do not present evidence of a statistically significant difference between the techniques in normal eyes,^{107–111} endothelial cell loss (ECL) has been reported to be lower in FLACS than in CP in several reviews and meta-analyses.^{40,78,83,85,112} Laser-assisted lens fragmentation reduces phacoemulsification time with less volume irrigation and EPT, especially in harder cataracts;^{85,109} this, in turn, translates into less ECL. Moreover, some studies have enhanced the evidence of this protective effect in corneal dystrophies (such as Fuchs') through the above cited mechanisms.^{113–115}

Regarding the incidence of cystoid macular edema (CME), most systematic reviews and meta-analyses showed no significant differences between FLACS and CP.^{83,85,112} Similarly, measurement of most retinal parameters (total macular volume, foveal thickness, and outer macular ring) showed comparable results in both techniques,^{116–118} although a short term, postoperative lower central macular volume with FLACS was reported in some studies involving patients with age-related macular degeneration (AMD).¹¹⁹ Hence, FLACS may be advantageous in patients with macular vulnerability;⁴⁰ this indication being further supported by evidence of the higher impact of ultrasound energy on the inflammatory response of the posterior segment compared with FLACS.^{52,117,120}

A considerable learning curve is in demand for FLACS, with an estimate minimum of 100–200 cases, depending on the surgeons' experience; above these numbers, a significant decrease in intraoperative complications is registered in most studies.^{16,17,36,121,122}

Indications and Contraindications

Indications

FLACS has been advocated for refractive cataract or lens surgery with premium IOL implantation because of its ability to produce a highly precise, reproducible, and customizable capsulotomy (regarding width and centration), surpassing CP standards. This is paramount for achieving an optimized IOL centration, essential to a premium IOL's performance. Furthermore, low-to-moderate amounts of astigmatism can be addressed by FS arcuate keratotomy (FSAK).

Hard or dense cataracts can be an indication for FLACS, as laser fragmentation of the lens nucleus reduces the total phacoemulsification time, EPT, and CDE, lowering the risk of corneal endothelial loss.¹²³

FLACS may be indicated in complex cases with challenging capsulotomies, such as traumatic subluxated cataracts or zonular instability, intumescent cataracts, and pseudoexfoliation syndrome, by reducing the stress on the zonular fibers and posterior capsule, consequently lowering the rate of postoperative complications. Cataract grade can help determining the choice of FLACS over CP, as the lower EPT or CDE associated with FLACS can be beneficial in hard cataracts, translated into a faster visual recovery;^{124,125} in the same manner, eyes with particular conditions, such as shallow anterior chambers, can benefit from such approach.¹²⁶

The reported lower impact of FLACS on endothelial cell count compared to CP may indicate that the former technique in cases of Fuchs' dystrophy and other types of endothelial degeneration.¹²⁷

FSL can also be used to enlarge the anterior capsulotomy to the desired size in cases of capsular contraction syndrome.¹²⁸

Likewise, regarding pupil status, recent literature shows strong evidence that pupil constriction after FS laser delivery, classically attributed to FLACS in general, is not a feature of low-energy pulse FLACS. This difference should not be taken lightly, as it has a relevant impact on the performance of the several surgical step onwards.

Contraindications

Patients with several conditions may not be ideal candidates for FLACS treatment. Anatomical characteristics affecting docking feasibility, such as deep-set eye globe, narrow palpebral fissure, prominent nose, or brow or inability to lay supine, present as contraindications for FLACS.^{35,129} In addition, any condition affecting OCT (or equivalent) imaging of the anterior segment, namely, previous corneal additive (eg, ring or inlay implants) surgery, severe corneal opacity, or edema, are the main contraindications for FLACS.^{45,129}

Other conditions can pose an increased challenge to FS laser-assisted cataract surgery and can be considered relative contraindications. Among them are poor pupillary dilation (<6 mm diameter), corneal surgeries (such as keratoplasty), glaucoma surgery, white cataracts, mild corneal scarring, and edema.

Poor preoperative pupillary dilation has been addressed using multiple approaches, including several preoperative administration schemes, contemplating topical medications such as phenylephrine, cyclopentolate, atropine, and/or nonsteroidal anti-inflammatory drugs (NSAIDs),^{130,131} intracameral epinephrine or phenylephrine, viscomydriasis with viscoelastic, or placement of iris expansion devices. It should be stressed that deficient pupil dilation poses a different challenge, depending on the pulse energy level of the FLACS platform. As has been extensively described, laser-induced miosis with high-energy FLACS adds extra difficulty to a narrow preoperative pupil. This fact gave birth to a vast body of literature covering multiple strategies to address pupil constriction with high-energy FS platforms.^{70,73,132,133} In contrast, low-energy pulse FLACS is reportedly not associated with pupil narrowing and therefore poses no additional dilation strategies compared with conventional phacoemulsification.¹³⁴

Lens fragmentation is not advised in white cataracts due to the low feasibility of adequate imaging of opaque tissue.^{45,135} Laser energy absorption is also affected by variations in water content, as is the case of white or brunescant cataracts. For FS platforms performing lens fragmentation after the capsulotomy step, intumescent cataracts pose an additional risk of posterior capsule rupture, caused by a posterior capsule depth change after capsulotomy decompression.¹³⁶ This feature is not shared by other FS platforms that perform a different step sequence, accomplishing capsulotomy after lens fragmentation.^{9,99}

Although the completeness of capsulotomy and fragmentation may be jeopardized in the presence of corneal opacities (scar or edema), there are isolated case reports of successful FLACS,¹³⁷ undoubtedly, the magnitude of such opacities is a relevant parameter in this context. Distortions in normal anatomy, either natural (pterygium or pinguecula) or iatrogenic (filtering blebs or tubes, as in glaucoma surgery), present themselves as challenging cases but should not constitute absolute contraindications, rather demanding additional care; with this regard, success has been reported in such cases.¹³⁸

Another concern is the impact of docking on intraocular pressure, due to suction and type of docking; applanating systems are associated with higher pressure upon docking than liquid interfaces.^{13,33} So far, however, there is no evidence of disease progression with well-controlled glaucoma or other optic neuropathies, for such matter.^{83,112}

Cost-Effectiveness

Although performing major steps in cataract or lens surgery has high standards of efficacy and safety, FLACS currently presents itself as a more expensive technology than CP. The weight of the platform acquisition costs plus the consumables attached to it render FLACS a less cost-effective procedure than CP.^{77,139–141} Another point is the fact that an FS laser platform cannot substitute for CP altogether. To accomplish the full steps of cataract or lens removal, a phacoemulsification/aspiration device is required; that is, aspiration of the lens material and further polishing of the capsular bag. Some attempts have been made to reduce the need for phacoemulsification machines in the context of low-grade cataract or refractive lens surgery,¹²² such endeavor is understandable, taken that FLACS may be beneficial in such cases by enabling higher precision and customization for capsulotomy and its impact on premium IOL positioning.

Conclusions

Current evidence of the low rate of anterior capsule complications and near absence of laser-induced miosis with low-energy FLACS (comparable to CP) is relevant to the field of knowledge regarding this technology. This evidence obviates the historically associated counter backs of FLACS, with reports traditionally disregarding the clinical impact of different pulse energy levels of femtosecond lasers.

With this updated view, FLACS has proven to be non-inferior to CP in terms of the rates of complications and adverse events. Furthermore, there is evidence that FLACS can be safer than CP in more demanding cases such as corneal dystrophies, lens subluxation, zonular instability (eg, pseudoexfoliation or Marfan syndrome), harder cataracts, or macular vulnerability. Regarding visual outcomes, some evidence has been collected on the mid-term advantages of FLACS over CP. This evidence may expand further in the universe of toric or presbyopia lens surgery, since higher levels of precision and customization are paramount for the efficacy of such procedures. However, there are limitations regarding the evaluation of FLACS in the context of premium IOLs implantation, with the vast majority of published studies not presenting subgroup analyses of the type of IOL implanted.

Time duration related to FLACS is another concern when compared to CP. Most FS platforms require patient mobilization from the laser device to the surgical bed or the operating room. This translation is time-consuming and lengthens the overall duration of surgery. However, one platform is portable, thus obviating this counterback and enabling comparable surgical time durations between FLACS and CP.

Regarding cost-effectiveness, it is evident that FLACS cannot currently compete with CP, the main difference being the high cost of the laser equipment and consumables. Therefore, CP keeps the crown of the standard technique of cataract surgery, limiting the use of FLACS as an option, mainly for the above indications; this choice has inherent additional expenses, usually charged to the patient. However, taking the attractive grounds of attractive laser-based techniques, this high-cost scenery is liable to change, subject to the old laws of offer and demand; for this matter, further developments on delivery outcomes are on the wait.

The behavioral differences between different low- and high-energy FS pulses are currently being unveiled, although they are seldom published. Increased knowledge of the spectrum of differences in FS technologies allows for better judgment and appraisal of surgical planning.

In summary, FLACS has evolved technically since its dawn, namely with the development of different types of pulse energy levels and broader surgical step coverage and refinement. Among the benefits of FLACS, there is gathered evidence of some advantage over CP regarding visual outcomes on the mid-term. Customization of capsulotomy can be an advantageous feature of FLACS over CP, notably in the universe of premium IOLs. The rate of complications and adverse events is similar to CP when taken into consideration the behavioral difference between the FS pulse patterns. FLACS can also be a first option in eyes with comorbidities. To these improvements, portability (for at least one FS platform) should be added as a favorable feature.

Like other surgical techniques in its youth, the indications have been simultaneously widened and fine-tuned; this enlargement of the spectrum of indications may impact on the use of FLACS and, by the law of offer and demand, reflect favorably on its costs. Further improvements in this technique should be expected, along with larger studies approaching the different laser systems.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lundström M, Dickman M, Henry Y, et al. Risk factors for refractive error after cataract surgery: analysis of 282,811 cataract extractions reported to the European registry of quality outcomes for cataract and refractive surgery. *J Cataract Refract Surg*. 2018;44(447):52. doi:10.1016/j.jcrs.2018.01.031
2. National Guideline Alliance. *Cataracts in Adults: Management*. London, UK: National Institute for Health and Care Excellence (UK); 2017.
3. Strickland D, Mourou G. Compression of amplified chirped optical pulses. *Opt Commun*. 1985. doi:10.1016/0030-4018(85)90120-8
4. Ali MH, Javadi M, Jamal S, Butt NH. Femtosecond laser assisted cataract surgery, beginning of a new era in cataract surgery. *Oman J Ophthalmol*. 2015;8(3):141–146. doi:10.4103/0974-620X.169892

5. Vogel A, Busch S, Jungnickel K, Birngruber R. Mechanisms of intraocular photodisruption with picosecond and nanosecond laser pulses. *Lasers Surg Med*. 1994;15:32–43. doi:10.1002/lsm.1900150106
6. Heisterkamp A, Ripken T, Mamom T, et al. Nonlinear side effects of fs pulses inside corneal tissue during photodisruption. *Appl Phys B*. 2002;74:419–425. doi:10.1007/s003400200825
7. Loesel FH, Tien A-C, Backus SJ, et al. Effect of reduction of laser pulse width from 100 ps to 20 fs on the plasma-mediated ablation of hard and soft tissue. In: *Thermal Therapy, Laser Welding, and Tissue Interaction*. roc SPIE; 1999:3565.
8. Latz C, Asshauer T, Rathjen C, Mirshahi A. Femtosecond-Laser Assisted Surgery of the Eye: overview and Impact of the Low-Energy Concept. *Micromachines*. 2021;12(2):122. PMID: 33498878; PMCID: PMC7912418. doi:10.3390/mi12020122
9. Asshauer T, Latz C, Mirshahi A, et al. Femtosecond lasers for eye surgery applications: historical overview and modern low pulse energy concepts. *Adv Opt Technol*. 2021;10(6):393–408. doi:10.1515/aot-2021-0044
10. Lin HY, Chuang YJ, Lin PJ. Surgical outcomes with high and low pulse energy femtosecond laser systems for cataract surgery. *Sci Rep*. 2021;11:9525. doi:10.1038/s41598-021-89046-1
11. Chang JS, Chen IN, Chan WM, et al. Initial evaluation of a femtosecond laser system in cataract surgery. *J Cataract Refract Surg*. 2014;40(1):29–36. doi:10.1016/j.jcrs.2013.08.045
12. Doors M, Berendschot TT, de Brabander J, et al. Value of optical coherence tomography for anterior segment surgery. *J Cataract Refract Surg*. 2010;36(7):1213–1229. doi:10.1016/j.jcrs.2010.05.002
13. Talamo JH, Gooding P, Angeley D, et al. Optical patient interface in femtosecond laser-assisted cataract surgery: contact corneal apposition versus liquid immersion. *J Cataract Refract Surg*. 2013;39(4):501–510. doi:10.1016/j.jcrs.2013.01.021
14. Al Harthi K, Al Shahwan S, Al Towerki A, et al. Comparison of the anterior capsulotomy edge created by manual capsulorhexis and 2 femtosecond laser platforms: scanning electron microscopy study. *J Cataract Refract Surg*. 2014;40:2106–2112. doi:10.1016/j.jcrs.2014.10.001
15. Feldman BH. Femtosecond laser will not be a standard method for cataract extraction 10 years from now. *Surv Ophthalmol*. 2015;60:360–365. doi:10.1016/j.survophthal.2015.02.002
16. Bali SJ, Hodge C, Lawless M, et al. Early experience with the femtosecond laser for cataract surgery. *Ophthalmology*. 2012;119:891–899. doi:10.1016/j.ophtha.2011.12.025
17. Nagy ZZ, Takacs AI, Filkorn T, et al. Complications of femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2014;40:20–28. doi:10.1016/j.jcrs.2013.08.046
18. Manning S, Barry P, Henry Y, et al. Femtosecond laser-assisted cataract surgery vs. standard phacoemulsification cataract surgery: study from the European registry of quality outcomes for cataract and refractive surgery. *J Cataract Refract Surg*. 2016;42:1779–1790. doi:10.1016/j.jcrs.2016.10.013
19. Zhang X, Yu Y, Zhang G, et al. Performance of femtosecond laser-assisted cataract surgery in Chinese patients with cataract: a prospective, multicenter, registry study. *BMC Ophthalmol*. 2019;19:77. doi:10.1186/s12886-019-1079-0
20. Ambrosio R, Valbon BF, Faria-Correia F, et al. Scheimpflug imaging for laser refractive surgery. *Curr Opin Ophthalmol*. 2013;24(4):310–320. doi:10.1097/ICU.0b013e3283622a94
21. Grewal DS, Schultz T, Basti S, Dick HB. Femtosecond laser-assisted cataract surgery—current status and future directions. *Surv Ophthalmol*. 2016;61(2):103–131. doi:10.1016/j.survophthal.2015.09.002
22. Sanders DR, Higinbotham RW, Opatowsky IE, et al. Hyperopic shift in refraction associated with implantation of the single-piece Collamer intraocular lens. *J Cataract Refract Surg*. 2006;32(12):2110–2112. doi:10.1016/j.jcrs.2006.07.030
23. Baumeister M, Bühren J, Kohnen T. Tilt and decentration of spherical and aspheric intraocular lenses: effect on higher-order aberrations. *J Cataract Refract Surg*. 2009;35(6):1006–1012. doi:10.1016/j.jcrs.2009.01.023
24. Friedman NJ, Palanker DV, Schuele G, et al. Femtosecond laser capsulotomy. *J Cataract Refract Surg*. 2011;37:1189–1198. doi:10.1016/j.jcrs.2011.04.022
25. Kránitz K, Miháitz K, Sándor GL, et al. Intraocular lens tilt and decentration measured by Scheimpflug camera following manual or femtosecond laser-created continuous circular capsulotomy. *J Refract Surg*. 2012;28(4):259–263. doi:10.3928/1081597X-20120309-01
26. Kránitz K, Takacs A, Miháitz K, et al. Femtosecond laser capsulotomy and manual continuous curvilinear capsulorhexis parameters and their effects on intraocular lens centration. *J Refract Surg*. 2011;27(8):558–563. doi:10.3928/1081597X-20110623-03
27. Holland D, Rüfer F. Neue Intraokularlinsendesigns für die Femtosekundenlaser-assistierte Kataraktoperation: Chancen und Nutzen [New intraocular lens designs for femtosecond laser-assisted cataract operations: chances and benefits]. *Ophthalmologe*. 2020;117(5):424–430. German. doi:10.1007/s00347-020-01092-8
28. Abouzeid H, Ferrini W. Femtosecond-laser assisted cataract surgery: a review. *Acta Ophthalmol*. 2014;92(7):597–603. doi:10.1111/aos.12416
29. Mastropasqua L, Toto L, Caliendo R, et al. Scanning electron microscopy evaluation of capsulorhexis in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2013;39:1581–1586. doi:10.1016/j.jcrs.2013.06.016
30. Adams M, Diakonis V, Weinstock R. Argentinian flag sign and its management during femtosecond laser-assisted cataract surgery in a case with intumescent cataracts. *Case Rep Ophthalmol*. 2021;12(1):129–133. doi:10.1159/000513483
31. Mursch-Eidlmayr AS, Pomberger LJ, Hermann P, et al. Prospective comparison of apex-centered vs standard pupil-centered femtosecond laser-assisted capsulotomy in cataract surgery. *J Cataract Refract Surg*. 2021;47(5):606–611. doi:10.1097/jcrs.0000000000000496
32. Schultz T, Tsiampanis N, Dick HB. Laser-assisted capsulotomy centration: a prospective trial comparing pupil versus OCT-based scanned capsule centration. *J Refract Surg*. 2017;33(2):74–78. doi:10.3928/1081597X-20161219-01
33. Agarwal K, Hatch K. Femtosecond laser assisted cataract surgery: a review. *Semin Ophthalmol*. 2021;36(8):618–627. doi:10.1080/08820538.2021.1890792
34. Diakonis VF, Yesilirmak N, Sayed-Ahmed IO, et al. Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms. *J Refract Surg*. 2016;32(2):84–88. doi:10.3928/1081597X-20151229-03
35. Wu BM, Williams GP, Tan A, et al. Comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol*. 2015;2015:616478. doi:10.1155/2015/616478
36. Roberts TV, Lawless M, Bali SJ, et al. Surgical Outcomes and safety of femtosecond laser cataract surgery. *Ophthalmol*. 2013;120(2):227–233. doi:10.1016/j.ophtha.2012.10.026

37. Malyugin BE. Recent advances in small pupil cataract surgery. *Curr Opin Ophthalmol*. 2018;29(1):40–47. doi:10.1097/ICU.0000000000000443
38. Reyes Lua M, Oertle P, Camenzind L, et al. Superior rim stability of the lens capsule following manual over femtosecond laser capsulotomy. *Invest Ophthalmol Vis Sci*. 2016;57:2839–2849. doi:10.1167/iov.15-18355
39. Williams G, George B, Wong YR, et al. The effects of a low-energy, high frequency liquid optic interface femtosecond laser system on lens capsulotomy. *Sci Rep*. 2016;6:24352. doi:10.1038/srep24352
40. Kolb CM, Shajari M, Mathys L, et al. Comparison of femtosecond laser-assisted cataract surgery and conventional cataract surgery: a meta-analysis and systematic review. *J Cataract Refract Surg*. 2020;46(8):1075–1085. doi:10.1097/j.jcrs.0000000000000228
41. Salgado R, Torres P, Marinho A. Femtosecond laser-assisted lens surgery with low-energy pulse versus conventional phacoemulsification for presbyopia correction: an intraindividual study. *Open Ophthalmol J*. 2021;15(1):43–53. doi:10.2174/1874364102115010043
42. Bethke W. Femtosecond cataract: dodge the pitfalls. *Rev Ophthalmol*. 2016;2016:1.
43. Packer M, Teuma EV, Glasser A, Bott S. Defining the ideal femtosecond laser capsulotomy. *Br J Ophthalmol*. 2015;99(8):1137–1142. doi:10.1136/bjophthalmol-2014-306065
44. Nagy ZZ, McAlinden C. Femtosecond laser cataract surgery. *Eye Vis Lond Engl*. 2015;2:11. doi:10.1186/s40662-015-0021-7
45. Sun H, Fritz A, Dröge G, et al. Femtosecond-laser assisted cataract surgery (FLACS). In: Bille JF, editor. *High Resolution Imaging in Microscopy and Ophthalmology*. Springer International Publishing; 2019:301–317.
46. Aristidou A, Taniguchi EV, Tsatsos M, et al. The evolution of corneal and refractive surgery with the femtosecond laser. *Eye Vis Lond Engl*. 2015;2:12. doi:10.1186/s40662-015-0022-6
47. Kaur M, Titiyal JS, Surve A, et al. Effect of lens fragmentation patterns on phacoemulsification parameters and postoperative inflammation in femtosecond laser-assisted cataract surgery. *Curr Eye Res*. 2018;43:1228–1232. doi:10.1080/02713683.2018.1485951
48. Chung SH, Mazur E. Surgical applications of femtosecond lasers. *J Biophotonics*. 2009;2:557–572. doi:10.1002/jbio.200910053
49. Roberts TV, Sutton G, Lawless MA, et al. Capsular block syndrome associated with femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2011;37(11):2068–2070. doi:10.1016/j.jcrs.2011.09.003
50. Palanker DV, Blumenkranz MS, Andersen D, et al. Femtosecond laser-assisted cataract surgery with integrated optical coherence tomography. *Sci Transl Med*. 2010;2(58):58–85. doi:10.1126/scitranslmed.3001305
51. Masket S, Sarayba M, Ignacio T, Fram N. Femtosecond laser-assisted cataract incisions: architectural stability and reproducibility. *J Cataract Refract Surg*. 2010;36(6):1048–1049. doi:10.1016/j.jcrs.2010.03.027
52. Alio JL, Abdou AA, Soria F, et al. Femtosecond laser cataract incision morphology and corneal higher-order aberration analysis. *J Refract Surg*. 2013;29:590–595. doi:10.3928/1081597X-20130819-01
53. Uy HS, Shah S, Packer M. Comparison of wound sealability between femtosecond laser-constructed and manual clear corneal incisions in patients undergoing cataract surgery: a pilot study. *J Refract Surg*. 2017;33(11):744–748. doi:10.3928/1081597X-20170921-01
54. Mastropasqua L, Toto L, Mastropasqua A, et al. Femtosecond laser versus manual clear corneal incision in cataract surgery. *J Refract Surg*. 2014;30(1):27–33. doi:10.3928/1081597X-20131217-03
55. Ranjini H, Murthy PR, Murthy GJ, et al. Femtosecond laser-assisted cataract surgery versus 2.2 mm clear corneal phacoemulsification. *Indian J Ophthalmol*. 2017;65(10):942–948. doi:10.4103/ijo.IJO_152_17
56. Mirshahi A, Latz C. Astigmatische Keratotomien mit dem Femtosekundenlaser [Femtosecond laser-assisted astigmatic keratotomy]. *Ophthalmologie*. 2020;117(5):415–423. doi:10.1007/s00347-020-01058-w
57. Roberts HW, Day AC, O'Brart DP. Femtosecond laser-assisted cataract surgery: a review. *Eur J Ophthalmol*. 2020;30(3):417–429. doi:10.1177/1120672119893291
58. Awdeh R, Hanafey H, Canto A-P. Using a laser for arcuate incisions. *Cataract Refract Surg Today*. 2011;2011:1.
59. Desai N, McCabe C, Tauber S, Visco D, Whitman J. Laser arcs for astigmatic correction. *Cataract Refract Surg Today*. 2015;2015:1.
60. Cao D, Xu Y, Wang Y. Comparison of toric intraocular lens alignment between femtosecond laser-assisted capsular marking and manual corneal marking. *J Refract Surg*. 2020;36:536–542. doi:10.3928/1081597X-20200602-01
61. Roberts HW, Wagh VK, Sullivan DL, et al. Refractive outcomes after limbal relaxing incisions or femtosecond laser arcuate keratotomy to manage corneal astigmatism at the time of cataract surgery. *J Cataract Refract Surg*. 2018;44:955–963. doi:10.1016/j.jcrs.2018.05.027
62. Vickers LA, Gupta PK. Femtosecond laser-assisted keratotomy. *Curr Opin Ophthalmol*. 2016;27:277–284. doi:10.1097/ICU.0000000000000267
63. Visco DM, Bedi R, Packer M. Femtosecond laser-assisted arcuate keratotomy at the time of cataract surgery for the management of preexisting astigmatism. *J Cataract Refract Surg*. 2019;45:1762–1769. doi:10.1016/j.jcrs.2019.08.002
64. Yoo A, Yun S, Kim JY, et al. Femtosecond laser-assisted arcuate keratotomy versus toric IOL implantation for correcting astigmatism. *J Refract Surg*. 2015;31(9):574–578. doi:10.3928/1081597X-20150820-01
65. Noh H, Yoo YS, Shin KY, et al. Comparison of penetrating femtosecond laser-assisted astigmatic keratotomy and toric intraocular lens implantation for correction of astigmatism in cataract surgery. *Sci Rep*. 2021;11:7340. doi:10.1038/s41598-021-86763-5
66. Hernandez R, Almenara C, Soriano D, et al. Toric intraocular lens implantation vs. femtosecond laser-assisted arcuate keratotomy for correction of moderate astigmatism in cataract surgery. *J Cataract Refract Surg*. 2022;48:887–893. doi:10.1097/j.jcrs.0000000000000879
67. Wortz G, Gupta PK, Goernert P, et al. Outcomes of femtosecond laser arcuate incisions in the treatment of low corneal astigmatism. *Clin Ophthalmol*. 2020;14:2229–2236. doi:10.2147/OPTH.S264370
68. Popiela MZ, Young-Zvandasara T, Nidamanuri P, et al. Factors influencing pupil behaviour during femtosecond laser assisted cataract surgery. *Contact Lens Anterior Eye*. 2019;42(3):295–298. doi:10.1016/j.clae.2018.10.010
69. Baharozian CJ, Song C, Hatch K, et al. A novel nomogram for the treatment of astigmatism with femtosecond-laser arcuate incisions at the time of cataract surgery. *Clin Ophthalmol*. 2017;11:1841–1848. doi:10.2147/OPTH.S141255
70. Fernandez J, Rodríguez-Vallejo M, Martínez J, et al. Prediction of surgically induced astigmatism in manual and femtosecond laser-assisted clear corneal incisions. *Eur J Ophthalmol*. 2018;28:398–405. doi:10.1177/1120672117747017
71. Ferreira TB, Ribeiro FJ, Pinheiro J, et al. Comparison of surgically induced astigmatism and morphologic features resulting from femtosecond laser and manual clear corneal incisions for cataract surgery. *J Refract Surg*. 2018;34:322–329. doi:10.3928/1081597X-20180301-01

72. Roberts HW, Wagh VK, Sullivan DL, et al. A randomized controlled trial comparing femtosecond laser-assisted cataract surgery vs. conventional phacoemulsification surgery. *J Cataract Refract Surg*. 2019;45:11–20. doi:10.1016/j.jcrs.2018.08.033
73. Stanojic N, Roberts HW, Wagh VK, et al. A randomised controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: 12-month results. *Br J Ophthalmol*. 2021;105:631–638. doi:10.1136/bjophthalmol-2020-316311
74. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery vs. phacoemulsification cataract surgery (FACT): a randomized noninferiority trial. *Ophthalmology*. 2020;127:1012. doi:10.1016/j.ophtha.2020.02.028
75. Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery vs. standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev*. 2016;7:CD010735. doi:10.1002/14651858.CD010735.pub2
76. Kovacs I, Kranitz K, Sandor GL, et al. The effect of femtosecond laser capsulotomy on the development of posterior capsule opacification. *J Refract Surg*. 2014;30:154–158. doi:10.3928/1081597X-20140217-01
77. Dick HB, Conrad-Hengerer I, Schultz T. Intraindividual capsular bag shrinkage comparing standard and laser-assisted cataract surgery. *J Refract Surg*. 2014;30:228–233. doi:10.3928/1081597X-20140320-01
78. Reddy KP, Kandulla J, Auffarth GU. Effectiveness and safety of femtosecond laser-assisted lens fragmentation and anterior capsulotomy versus the manual technique in cataract surgery. *J Cataract Refract Surg*. 2013;39:1297–1306. doi:10.1016/j.jcrs.2013.05.035
79. Lundstrom M, Dickman M, Henry Y, et al. Femtosecond laser-assisted cataract surgeries reported to the European Registry of quality outcomes for cataract and refractive surgery: baseline characteristics, surgical procedure, and outcomes. *J Cataract Refract Surg*. 2017;43:1549–1556. doi:10.1016/j.jcrs.2017.09.029
80. Toto L, Caliendo R, Curcio C, et al. Induced inflammation and apoptosis in femtosecond laser-assisted capsulotomies and manual capsulorhexis: an immunohistochemical study. *J Refract Surg*. 2015;31:290–294. doi:10.3928/1081597X-20150423-01
81. Pisciotto A, De Maria M, Verdina T, et al. Anterior capsule of the lens: comparison of morphological properties and apoptosis induction following FLACS and standard phacoemulsification surgery. *Biomed Res Int*. 2018;2018:7242837. doi:10.1155/2018/7242837
82. Sun W, Liu J, Li J, et al. Human lens epithelial cell apoptosis and epithelial to mesenchymal transition in femtosecond laser-assisted cataract surgery. *Int J Ophthalmol*. 2018;11:401–407. doi:10.18240/ijo.2018.03.09
83. Popovic M, Campos-Moller X, Schlenker MB, et al. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology*. 2016;123:2113–2126. doi:10.1016/j.ophtha.2016.07.005
84. Nagy ZZ, Dunai A, Kranitz K, et al. Evaluation of femtosecond laser-assisted and manual clear corneal incisions and their effect on surgically induced astigmatism and higher-order aberrations. *J Refract Surg*. 2014;30:522–525. doi:10.3928/1081597X-20140711-04
85. Chen X, Chen K, He J, et al. Comparing the curative effects between femtosecond laser-assisted cataract surgery and conventional phacoemulsification surgery: a meta-analysis. *PLoS One*. 2016;11:e0152088.
86. Chen X, Xiao W, Ye S, et al. Efficacy and safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: a meta-analysis of randomized controlled trials. *Sci Rep*. 2015;5:13123. doi:10.1038/srep13123
87. Hatch KM, Schultz T, Talamo JH, et al. Femtosecond laser-assisted compared with standard cataract surgery for removal of advanced cataracts. *J Cataract Refract Surg*. 2015;41:1833–1838. doi:10.1016/j.jcrs.2015.10.040
88. Hida WT, Tzelikis PF, Vilar C, et al. Outcomes study between femtosecond laser-assisted cataract surgery and conventional phacoemulsification surgery using an active fluidics system. *Clin Ophthalmol*. 2017;11:1735–1739. doi:10.2147/OPTH.S136136
89. Panthier C, Costantini F, Rigal-Sastourne JC, et al. Change of capsulotomy over 1 year in femtosecond laser assisted cataract surgery and its impact on visual quality. *J Refract Surg*. 2017;33:44–4997. doi:10.3928/1081597X-20161028-01
90. Schultz T, Joachim SC, Tschopp I, et al. Histologic evaluation of in vivo femtosecond laser-generated capsulotomies reveals a potential cause for radial capsular tears. *Eur J Ophthalmol*. 2015;25:112–118. doi:10.5301/ejo.5000484
91. Norrby S. Sources of error in intraocular lens power calculation. *J Cataract Refract Surg*. 2008;34:368–376. doi:10.1016/j.jcrs.2007.10.031
92. Lawu T, Mukai K, Matsushima H, et al. Effects of decentration and tilt on the optical performance of 6 aspheric intraocular lens designs in a model eye. *J Cataract Refract Surg*. 2019;45:662–668. doi:10.1016/j.jcrs.2018.10.049
93. Lee JA, Song WK, Kim JY, et al. Femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: refractive and aberrometric outcomes with a diffractive multifocal intraocular lens. *J Cataract Refract Surg*. 2019;45:21–27. doi:10.1016/j.jcrs.2018.08.032
94. Narayan A, Evans JR, O'Brart D, et al. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev*. 2023;6. doi:10.1002/14651858.CD010735.pub3
95. Day AC, Gartry DS, Maurino V, et al. Efficacy of anterior capsulotomy creation in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2014;40:2031–2034. doi:10.1016/j.jcrs.2014.07.027
96. Kekic M, Schweitzer C. Femtosecond laser-assisted cataract surgery: update and perspectives. *Front Med*. 2023;2023:10.
97. Pajic B, Pajic-Eggspuehler B, Rathjen C, et al. Why use ultrashort pulses in ophthalmology and which factors affect cut quality. *Medicina*. 2021;57(7):700. doi:10.3390/medicina57070700
98. Song C, Baharozian CJ, Hatch KM, et al. Rate of unplanned vitrectomies in femtosecond laser-assisted cataract surgery compared to conventional phacoemulsification. *J Refract Surg*. 2018;34:610–614. doi:10.3928/1081597X-20180726-01
99. Riemey J, Latz C, Mirshahi A. Intraoperative complications of cataract surgery using a low-energy femtosecond laser: results from a real-world high-volume setting. *PLoS One*. 2022;17(12):e0279023. doi:10.1371/journal.pone.0279023
100. Schultz T, Joachim SC, Kuehn M, et al. Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2013;29:742–747. doi:10.3928/1081597X-20131021-03
101. Schultz T, Joachim SC, Stellbogen M, et al. Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. *J Refract Surg*. 2015;31:78–81. doi:10.3928/1081597X-20150122-01
102. Schultz T, Joachim SC, Szuler M, et al. NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2015;31:791–794. doi:10.3928/1081597X-20151111-01
103. Kent C. Femto laser cataract: avoiding complications. *Rev Ophthalmol*. 2014;2014:1.
104. Jun JH, Hwang KY, Chang SD, et al. Pupil-size alterations induced by photodisruption during femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2015;41:278–285. doi:10.1016/j.jcrs.2014.10.027
105. Salgado R, Torres PF, Marinho A. Pupil status with low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: an intraindividual comparative study. *Clin Ophthalmol*. 2023;17:331–339. doi:10.2147/OPTH.S399788

106. Liu YC, Setiawan M, Chin JY, et al. Randomized controlled trial comparing 1-year outcomes of low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification. *Front Med Lasers*. 2021;8:11093. doi:10.3389/fmed.2021.811093
107. Schweitzer C, Brezin A, Cochener B, et al. Femtosecond laser-assisted vs. phacoemulsification cataract surgery (FEMCAT): a multicentre participant-masked randomised superiority and cost-effectiveness trial. *Lancet*. 2020;395:212–224. doi:10.1016/S0140-6736(19)32481-X
108. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery compared with phacoemulsification cataract surgery: randomized noninferiority trial with 1-year outcomes. *J Cataract Refract Surg*. 2020;46:1360–1367. doi:10.1097/jcrs.0000000000000257
109. Bascaran L, Albendi T, Martinez-Soria I, et al. Differences in energy and corneal endothelium between femtosecond laser-assisted and conventional cataract surgeries: prospective, intraindividual, randomized controlled trial. *Int J Ophthalmol*. 2018;11:1308–1316. doi:10.18240/ijo.2018.08.10
110. Dzhuber D, Mustafa O, Alsaleh F, et al. Comparison of changes in corneal endothelial cell density and central corneal thickness between conventional and femtosecond laser-assisted cataract surgery: a randomised, controlled clinical trial. *Br J Ophthalmol*. 2020;104:225–229. doi:10.1136/bjophthalmol-2018-313723
111. Lin CC, Rose-Nussbaumer JR, Al-Mohtaseb ZN, et al. Femtosecond laser-assisted cataract surgery: a report by the American Academy of ophthalmology. *Ophthalmology*. 2022;129(946):54. doi:10.1016/j.ophtha.2022.04.003
112. Ye Z, Li Z, He S. A meta-analysis comparing postoperative complications and outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract. *J Ophthalmol*. 2017;2017:3849152. doi:10.1155/2017/3849152
113. Fan W, Yan H, Zhang G. Femtosecond laser-assisted cataract surgery in Fuchs endothelial corneal dystrophy: long-term outcomes. *J Cataract Refract Surg*. 2018;44:864–870. doi:10.1016/j.jcrs.2018.05.007
114. Wei Dayna YW, Hui-Chen Charmaine C, Liang S, et al. Comparing outcomes of phacoemulsification with femtosecond laser assisted cataract surgery in patients with Fuchs endothelial dystrophy. *Am J Ophthalmol*. 2018;196:173–180. doi:10.1016/j.ajo.2018.08.006
115. Zhu DC, Shah P, Feuer WJ, et al. Outcomes of conventional phacoemulsification versus femtosecond laser-assisted cataract surgery in eyes with Fuchs endothelial corneal dystrophy. *J Cataract Refract Surg*. 2018;44:534–540. doi:10.1016/j.jcrs.2018.03.023
116. Asena BS, Karahan E, Kaskaloglu M. Retinal and choroidal thickness after femtosecond laser-assisted and standard phacoemulsification. *Clin Ophthalmol*. 2017;11:1541–1547. doi:10.2147/OPTH.S127792
117. Conrad-Hengeler I, Hengeler FH, Al Jaburi M, et al. Femtosecond laser-induced macular changes and anterior segment inflammation in cataract surgery. *J Refract Surg*. 2014;30:222–226. doi:10.3928/1081597X-20140321-01
118. Nagy ZZ, Ecsedy M, Kovacs I, et al. Macular morphology assessed by optical coherence tomography image segmentation after femtosecond laser-assisted and standard cataract surgery. *J Cataract Refract Surg*. 2012;38:941–946. doi:10.1016/j.jcrs.2012.02.031
119. Enz TJ, Faes L, Bachmann LM, et al. Comparison of macular parameters after femtosecond laser assisted and conventional cataract surgery in age-related macular degeneration. *J Cataract Refract Surg*. 2018;44:23–27. doi:10.1016/j.jcrs.2017.09.030
120. Abell RG, Allen PL, Vite BJ. Anterior chamber flare after femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2013;39:1321–1326. doi:10.1016/j.jcrs.2013.06.009
121. Roberts TV, Lawless M, Sutton G, et al. Anterior capsule integrity after femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2015;41:1109–1110. doi:10.1016/j.jcrs.2014.11.044
122. Dick HB, Schultz T. On the way to zero phaco. *J Cataract Refract Surg*. 2013;39:1442–1444.
123. Ou Y, Wang Y, Wu T. Comparison of ultrasound energy consumption between low-energy femtosecond laser-assisted cataract surgery and conventional phacoemulsification cataract surgery in patients with different cataract densities. *Eur J Ophthalmol*. 2023;33(3):1373–1379. doi:10.1177/11206721221147952
124. Chen X, Yu Y, Song X, Zhu Y, Wang W, Yao K. Clinical outcomes of femtosecond laser-assisted cataract surgery vs. conventional phacoemulsification surgery for hard nuclear cataracts. *J Cataract Refract Surg*. 2017;43(486):91. doi:10.1016/j.jcrs.2017.01.010
125. Salgado R, Torres P, Marinho A, Ribeiro FJ. Cataract grade and pupil: comparison between conventional phacoemulsification and low-energy femtosecond laser assisted cataract surgery. *Clin Ophthalmol*. 2023;17:2193–2200. doi:10.2147/OPTH.S420931
126. Vasavada VA, Vasavada S, Vasavada AR, et al. Comparative evaluation of femtosecond laser-assisted cataract surgery and conventional phacoemulsification in eyes with a shallow anterior chamber. *J Cataract Refract Surg*. 2019;45:547–552. doi:10.1016/j.jcrs.2018.11.037
127. Yong WWD, Chai HC, Shen L, et al. Comparing outcomes of phacoemulsification with femtosecond laser-assisted cataract surgery in patients with fuchs endothelial dystrophy. *Am J Ophthalmol*. 2018;196:173.
128. Gerten G, Schultz M, Oberheide U. Treating capsule contraction syndrome with a femtosecond laser. *J Cataract Refract Surg*. 2016;42(9):1255–1261. doi:10.1016/j.jcrs.2016.07.020
129. Dick HB, Schultz TA. Review of laser-assisted versus traditional phacoemulsification cataract surgery. *Ophthalmol Ther*. 2017;6(1):7–18. doi:10.1007/s40123-017-0080-z
130. Maskat S, Belani S. Combined preoperative topical atropine sulfate 1% and intracameral nonpreserved epinephrine hydrochloride 1:2500 for management of intraoperative floppy-iris syndrome. *J Cataract Refract Surg*. 2007;33(4):580–582. doi:10.1016/j.jcrs.2006.10.059
131. Antsivova NS, Arbinov LB, Petrovski G, et al. Effect of NSAIDs on pupil diameter and expression of aqueous humor cytokines in FLACS versus conventional phacoemulsification. *J Refract Surg*. 2018;34(10):646–652. doi:10.3928/1081597X-20180814-02
132. Kiss HJ, Takacs AI, Krantz K, et al. One-day use of preoperative topical nonsteroidal anti-inflammatory drug prevents intraoperative prostaglandin level elevation during femtosecond laser-assisted cataract surgery. *Curr Eye Res*. 2015;41:1–4. doi:10.3109/02713683.2014.999947
133. Jirasková N, Rozsival P, Lešák L. Use of Malyugin pupil expansion ring in femtosecond laser-assisted cataract surgery. *J Clin Exp Ophthalmol*. 2013;4:6. doi:10.4172/2155-9570.1000312
134. Meshabi A, Schneider A, Latz C, et al. Perioperative pupil size in low-energy femtosecond laser-assisted cataract surgery. *PLoS One*. 2021;16(5):e0251549. doi:10.1371/journal.pone.0251549
135. Conrad-Hengeler I, Hengeler FH, Joachim SC, et al. Femtosecond laser-assisted cataract surgery in intumescent white cataracts. *J Cataract Refract Surg*. 2014;40(1):44–50. doi:10.1016/j.jcrs.2013.08.044
136. Chee S-P, Chan NS-W, Yang Y, et al. Femtosecond laser-assisted cataract surgery for the white cataract. *Br J Ophthalmol*. 2019;103:544–550. doi:10.1136/bjophthalmol-2018-312289
137. Huang P-W, Huang W-H, Tai Y-C, et al. Femtosecond laser-assisted cataract surgery in a patient with traumatic cataract and corneal opacity after LASIK: a case report. *BMC Ophthalmol*. 2020;20(1):218. doi:10.1186/s12886-020-01491-0

138. Noecker R. Laser cataract surgery in the glaucoma patient. *Ophthalmol Manag.* 2017;21:8–10.
139. Vasquez-Perez A, Simpson A, Nanavaty MA. Femtosecond laser-assisted cataract surgery in a public teaching hospital setting. *BMC Ophthalmol.* 2018;18:26. doi:10.1186/s12886-018-0693-6
140. Bartlett JD, Miller KM. The economics of femtosecond laser-assisted cataract surgery. *Curr Opin Ophthalmol.* 2016;27:76–81. doi:10.1097/ICU.0000000000000219
141. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT noninferiority RCT. *Health Technol Assess.* 2021;25:1–68. doi:10.3310/hta25060

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5. General discussion

The visual and refractive outcomes of presbyopia correction with femtosecond laser assisted lens surgery have been approached in studies 4.1 and 4.2. Study 4.1⁴⁶ pointed to a statistical similarity of visual and refractive outcomes between femtosecond laser-assisted lens surgery treatment and CP^{19,78,195,196}. However, some points are to be highlighted in this study. Firstly, a long-term comparison showed a higher percentage of eyes reaching uncorrected and corrected visual acuity of 20/20 and above for far with FS. Similarly, a higher accuracy regarding postoperative SE was registered with FS: in the FS group, 96.4% of the eyes fell in ± 0.50 diopters (D) range, compared to 84% of the eyes in the CP group. Although based in a relatively small sample and not statistically significant, the clinical magnitude of the difference is relevant, considering the electiveness of refractive lens exchange. These clinical differences between techniques regarding efficacy, safety, and accuracy, point out to the related literature^{45,80,102,196,197}. The assessment of the procedure's safety at the refractive level was achieved by means of the calculation of the safety Index^{197,198}. The safety Index is classically defined as the best spectacle-corrected visual acuity (BSCVA) after treatment divided by the BSCVA before treatment (post BSCVA/pre BSCVA). For the matter, the corrected distance visual acuity (CDVA) stands as the equivalent of BSCVA for far, as it is reported in most published studies¹⁹⁹⁻²⁰¹. Regarding efficacy, evaluation of the procedure was achieved by calculating the efficacy Index^{197,198}. This index is defined as the uncorrected visual acuity (UCVA) after treatment divided by BSCVA before treatment (post UCVA/pre BSCVA) and is commonly assessed in the context of refractive (corneal or lens-based) surgery¹⁹⁹⁻²⁰⁵. Again, the uncorrected distance visual acuity (UDVA) stands for UCVA for far, while maintaining CDVA as a substitute for BSCVA for far. This comparison is most relevant when evaluating the efficacy of lens-based refractive surgery in a non-cataractous population, being further recommended to graphically present the post UDVA and pre CDVA cumulative visual acuities and respective differences, according to Reinstein et al.²⁰⁶.

The refractive accuracy or predictability of the procedure is determined by the values of postoperative spherical equivalent refraction relative to the intended target and it is further recommended to be illustrated in a dedicated histogram.

The quality of vision (as a patient reported outcome) was determined by a 4-point Likert scale questionnaire comprising the existence of visual disturbance or photic phenomena, graded from 0 to 4: 0 (none), 1 (mild), 2 (moderate), 3 (high) and 4 (very high).

The reported gains in visual acuity after femtosecond laser–assisted surgery, in most studies, tend to be early (1 week postoperatively) or late (at 6 months^{79,80,100,113,207}, notwithstanding the fact that some reviews show a mid-term advantage of FS over CP (Kolb *et al*, 2020)⁴⁵. This apparently contradictory evidence may relate to an absence of subgroup analysis of the implanted IOLs in the cited literature, rather than the design of the studies; also, the forementioned studies have shorter follow-ups and are based in a cataract removal context, not contemplating multifocal IOLs implantation specifically. Related to this matter, the reported uncorrected visual acuities, which are most pertinent in assessing the premium procedure’s efficacy, lack in most of the published literature (including systematic reviews and metanalysis). This study focused on presbyopia lens surgery, showing a higher stability, close to statistical significance. In fact, the requirement of stability is paramount in the context of multifocal IOLs implantation (and premium lenses, in general) in particular, as long-term success depends on maintaining the IOL centration. Since the positioning of the IOL relies on time-dependent variables such as capsular factors (shrinkage, for example), the results shown in study 4.1 strengthen the evidence of an earlier refractive stabilization of refraction with FS and further demonstrates its long-term stability feature. Hence the relevance of study 4.1 findings. The rationale for an early stabilization with FS, might be that femtosecond laser–assisted cataract surgery, in the early postoperative phase is associated with reduced ultrasound energy and reduced corneal edema resulting in faster visual rehabilitation^{80,100,143}. Regarding long-term stability, FS is liable to produce more stable IOL-capsular bag interactions^{80,108}.

Study 4.2 further elaborates on the importance of multifocal IOL centration and related factors such as capsulotomy centration. This prospective randomized intraindividual study compares the long-term clinical (visual and refractive) outcomes between 1st Purkinje reflex versus pupil centre capsulotomy centration, in the context of presbyopia lens surgery. Additionally, the study proposes a novel marking procedure for achieving such purpose.

IOL centration is required for optimal performance^{208,209}, particularly when it comes to multifocal IOL implantation²¹⁰. Relevant for this matter are IOL and capsular bag characteristics which interact with each other. IOL factors include the optic and haptic material, the overall IOL length in relation to the capsular bag diameter, and the inherent ability of the haptics to withstand compressive forces of a contracting capsular bag. Capsular bag related factors include integrity, geometric features (such as size and morphology) and capsulotomy features. It is widely consensual the importance of a circular, continuous capsulotomy, as well as its centration, which impacts on the long-

term positioning of the IOL^{211,212}. Capsulotomy centration has been a topic of discussion, concerning the profile of multifocal diffractive IOLs²¹³. This profile demands an optimization of the IOL centration, eliciting the search for the best match of the eye's several reference points and lines, along with the pupil's significant role; some recent studies have proposed different capsulotomy centration points other than the classical pupil center, such as OCT-based scanned capsule or apex centration^{34,36}.

Postoperative changes to the capsular bag such as anterior capsular contraction and posterior capsular opacification vary depending on the IOL design, material and amount of anterior capsule overlap of the IOL's edge^{82,83}. In this study, with a longer follow-up than related published literature, posterior capsular opacification was none to minimal for both groups, thus not presenting itself as a major factor influencing IOL positioning.

Regarding the magnitude of IOL center – visual axis decentration, a distance in the range of 0.25–0.50 mm is noticeable in a slit-lamp examination, and it has been assumed that it is clinically insignificant²¹⁴. However, this assumption lacks clinical strong evidence, particularly in the context of multifocal IOLs. Furthermore, and most importantly, not always is the visual axis (or its equivalent) chosen as the reference point for centration assessment, but rather the optical center or even the pupil center²².

With respect to multifocal IOLs performance, several publications point out a reduced influence of tilt, as opposed to a significant impact of decentration in this type of intraocular lenses^{24,209,215}. However, it was not the author's intention to minorize the role of tilt on MIOL in study 4.2. Rather than an oversimplification, the author's choice of this single approach (isolating the centration factor in the context of IOL positioning) related to the feasibility of the IOL decentration assessment with respect to visual axis, as a sole factor.

The present study shows modification of the IOL positioning along time, traduced by a lens displacement towards the optical center of the cornea; this fact is not influenced by the performed intraoperative maneuver of manually centration of the IOL aligned with the visual axis (as commonly recommended). This phenomenon has been reported in the literature²¹⁶ and it was described as an auto centration of the IOL in the capsular bag²¹⁷, with many factors being involved in these phenomena, mostly geometric at first hand. Furthermore, and in a novel manner, the results of study 4.2 show evidence that the choice of the reference centration point regarding capsulotomy, influences the long-term positioning of the IOL. Therefore, beyond strengthening the fact that the IOL tends to adjust itself to the capsular bag (more than intraoperative IOL manual positioning), this study shows that capsulotomy centration on the first Purkinje reflex is associated to

better IOL centration towards the visual axis, as compared to pupil centration. This fact has a significant impact on aberrometric values, with a statistically significant superiority of FS over CP. However, such evidence did not influence, with statistical significance, the quality of vision or patient satisfaction scores, in this study. Likewise, the refractive outcomes did not seem to be influenced by capsulotomy centration. A possible explanation for this apparent asynchrony can be assigned to a specific optical design of the implanted MIOL, which may increase the tolerance to deviations from the ideal aberrometry profile. This tolerance may not be reproducible with every type of multifocal IOLs. In this way, some limitations are identified in this study: only one type (plate-haptic) of IOL was implanted, restricting the evidence to this specific design; tilt is not measured in this paper, as mentioned above; aberrometry measurements were performed under a single (mesopic) illumination condition; and a larger series is recommendable to strengthen the evidence so far.

Regarding non-refractive safety outcomes, both studies (4.1 and 4.2) showed an absence of capsule-related complications, historically associated to FLACS. In fact, several studies (reviews included) report anterior capsule complications (as tears or tags) as more frequent in FLACS than in CP^{45,111,115}; when subgroup analysis is performed (seldomly) in the above-mentioned reviews, capsule complications are significantly higher with high-energy pulse FS platforms. Other published reviews (again, without discrimination of type of pulse), point to a similarity of capsular complications' global incidence between FS and CP^{80,113,114}.

With low-energy pulse FS devices, as employed in this research, the reported incidence of capsule-related complications is almost null, which is in accordance with current studies involving low-energy femtosecond pulse¹²⁵ in crystalline lens removal. The research's studies 4.1 and 4.2 provide an extended and more specifically oriented evidence of those findings in the context of presbyopia lens surgery; this contribution is invaluable since the impact of an intraoperative capsule complication is decisive upon a multifocal IOL implantation, almost invariably condemning the procedure to failure.

An intimate adverse event, with an even larger impact on the feasibility of crystalline lens (either clear or cataractous) surgery is pupil constriction. This long-time established association with FLACS is, again, a feature of high-energy FS^{111,114}, not being verified with low-energy pulse devices. Recent published literature shows evidence that low-energy femtosecond laser does not induce narrowing of the pupil^{9,125,134,218}.

Study 4.3¹³⁵ and 4.4¹⁷³ strengthen and extend this evidence, by comparing pupil status between FS and CP in a novel and more comprehensive way. In study 4.3, this was

achieved by assessing pupil area variation between FLACS and CP along the surgical timeline, including pre- and post-laser treatment. Even though clinical comparison favoured FSL surgery results (with less pupil variation as compared to CP), pupil behaviour was considered similar between techniques, as statistical analysis showed no significant differences between techniques. Reports of a significant higher pupil area with FLACS immediately after suction²¹⁹, found no evidence in this study. In those reports, anti-inflammatory eye drops were placed preoperatively on the eye population; on the contrary, no anti-inflammatory drug was administered in any of our study eyes, eliminating a potential bias in laser interaction with ocular tissues due to the myosis inhibition's role of such drugs.

Another objective of study 4.3 was to perform a comparative analysis of pupil status and ocular comorbidity between FLALS and CP; moreover, both eyes in the same individual were considered (similar comorbidity expression). Consistent with the published literature, a greater amount of intraoperative pupil narrowing in eyes with comorbidities is commonly reported during conventional cataract surgery: this occurrence was also identified with FSL in study 4.3. Nevertheless, the study further revealed that there is a nearly statistically significant difference in eyes with a shallow anterior chamber (<2.5 mm), between FLALS and CP. A possible explanation for this difference may rely on the fact that the time of anterior chamber exposure with CP is longer than with FLALS (as several surgical steps are performed with a “closed” eye globe, through laser). This, in turn, would facilitate reflective myosis upon “open” eye manipulation with CP.

Regarding total pupil variation (TPV) and age, no statistically significant difference was found between CP and FLALS, in the present study. Furthermore, strengthened evidence was provided by our study, concerning age subgroups and TPV, as a statistically significant difference was shown between younger and older patients, being similar for each technique. This evidence may be explained by the well-known physiological profile of the ageing pupil²²⁰⁻²²², characterized by a lesser pupil responsiveness and slower recovery from dilation, traduced by lower TPV values in the older subgroup of patients.

The limitations inherent to this study are the following: a suboptimal sample size of eyes (as very large series are in demand to reinforce these findings), and the assessment of prostaglandins levels. Nevertheless, the clinical evidence here collected should stimulate further studies regarding the thorough evaluation of the specific profile and role of low-energy femtosecond laser in lens surgery.

Study 4.4 aimed at assessing the impact of cataract grade on pupil behaviour. In this study, population included cataractous patients with different grades of lens opacification. Cataract grade influences the energy level of ultrasound energy employed, according to literature^{223,224}. The impact of higher levels of energy (for harder cataracts) may be accountable for pupillary constriction, by means of the stimulated release of pro-inflammatory mediators. Cumulative dissipated energy (CDE) has been commonly used as a measure of such ultrasound expenditure⁴⁵.

In our study, it is given further evidence that cataract grade influences ultrasound energy expenditure, as it is measurable by the CDE. It is shown that there is a negative correlation between total pupil variation and CDE with conventional phacoemulsification, associating a more negative TPV to higher CDE values. It is also consensual that the use of femtosecond laser in cataract surgery reduces the amount of ultrasound (US) employed, ergo, the CDE^{107,225}. In agreement with this knowledge, the present study reinforces the evidence that energy expenditure relates to cataract hardness. For softer cataracts, CDE levels are expectedly low in CP and even more with the assistance of femtosecond laser in FLALS. For harder cataracts, the ultrasound energy requisites (CDE) are significantly high in CP. The rationale will be that lower CDE levels, by means of using femtosecond laser in lens surgery, contribute to less pupil narrowing as compared to conventional phacoemulsification. In this study, there was a statistically significant difference between techniques (although of mild clinical relevance), with less reduction of pupil area with FLALS in softer cataracts (grade ≤ 3), as compared to CP. As an offspring of this evidence, it is reasonable to assume that “zero” ultrasound energy will have the least impact on pupil status. Higher levels of CDE are associated with more pupil narrowing in CP. It should be stressed that, although the magnitude of the detected difference may have a little clinical impact on surgical practice, it is statistically significant. Therefore, these results help to demonstrate that low-energy FLALS may perform similarly or superiorly to conventional phacoemulsification regarding pupil status (namely pupil constriction) and, thus, support an evidence-based decision upon choosing this technique in lens surgery.

Study 4.5 reports the gathered evidence regarding the current state of the art of femtosecond laser assisted lens surgery. Namely, the known outcomes and complications reported with this technique are comprehensively approached, and further extended, in the light of the new insight given by our research. In this way, visual outcomes of FLALS are proven to be non-inferior to CP in the long-term, with reported evidence of superiority to CP in the short and mid-term.

On the grounds of non-refractive outcomes, surgical endpoints such as total and effective phacoemulsification time, cumulative dissipated energy, and circularity of the capsulotomy were shown to compare better with FLALS than CP^{19,45,80,93,100,108,207,226}.

Capsule events occur rarely with both procedures. Posterior capsule ruptures are reportedly less with FLALS than CP in most reviews^{63,108,114}. On the other hand, conflicting evidence has been reported, regarding the incidence of anterior capsule complications (tears or tags) with FLALS in general, when compared to CP. In fact, whereas some studies^{45,111,117,119,120,122} report a higher incidence of anterior capsule complications with FLALS, others point to no differences between the two techniques^{80,113,114}. Most commonly to these studies, the incidence is reported as global data, regardless of the laser platform(s) or type of energy pulse employed and with scarce subgroup analyses. It is a fact that most of the forementioned studies predominantly involve high-energy pulse laser devices (some exclusively); nevertheless, in the few cases of subgroup analyses, the incidence of anterior capsule complications is higher with high energy pulse laser platforms, with nearly null incidence with low energy laser devices (when included in the studies). The occurrence of such an event is prone to have a clear impact on postoperative lens stability, the effective lens position, and, thus, the final visual outcome. This intraoperative capsule-related (anterior or posterior) complication did not occur in our research population. This may be due to the use of a low-energy pattern in our study, as the reported evidence of a higher rate of anterior capsule complications than with CP is essentially related to high-energy pulse FS, being seldomly described in low-energy FLALS^{125,227}. For this purpose, a lower pulse energy may allow a higher cut quality with smoother edges⁴⁰, liable to produce a stronger capsulotomy; hence, this pulse pattern factor may be paramount for the difference registered. Other explanations for these higher rates reside in additional aberrant pulses, postage-stamp radial patterns and/or eventual fixational eye movements¹¹⁵.

In our study, no intra or postoperative complications were registered during the clinical follow-up.

Postoperative complications, such as elevated intraocular pressure (IOP), cystoid macular edema (CME), central corneal edema, endothelial cell loss (ECL) are reportedly low with FLALS in general.

The published literature reports no statistically significant differences between FLALS and CP, regarding CME^{113,148,156,228} or IOP^{194,229,230}.

Endothelial cell loss and corneal edema have shown consistently better results with FLACS than with CP^{45,93,108,143,144,231}. This may be relevant in the long term and especially beneficial in cases of associated endothelial pathology.

It should be added that surgical procedure time (from beginning to the end), showed no statistically significant difference between FLALS and CP in our research. Portability of the employed femtosecond machine may contribute to this aspect, as the patient remains in the same surgical environment (a single operating room and the same bed) during the whole femtosecond-phacoemulsification sequence. These results are in line with a few other published reports^{232,233}, suggesting a negligible impact of portable femtosecond platforms on surgery duration.

The literature is very scarce regarding patient reported outcomes. The heterogeneity of the methodology employed to assess patient satisfaction and other subjective parameters, difficult global assessment of differences between FLALS and CP⁹⁵. Patient reported outcomes measures (PROMs) vary greatly among the several studies. Given the increasing number of refractive crystalline lens (with or without opacification) surgery and its inherent elective nature, patient reported outcomes are paramount in choosing the adequate premium IOL. Thus, more comprehensive, and standardized PROMs are in need, for rigorous analysis purposes.

Although performing major steps in lens surgery, with high standards of efficacy and safety, FLALS currently presents itself as a more expensive technology than CP. The weight of the platform acquisition costs plus the consumables attached to it, renders FLALS as a less cost-effective procedure than CP^{87,196,234-236}. Another point is the fact that an FS laser platform cannot substitute for CP altogether. In order to accomplish the full steps of lens removal surgery, a phacoemulsification and irrigation/aspiration device is required; that is, for aspirating the lens material and further polishing of the capsular bag. Some attempts have been made to reduce the need of phacoemulsification machines in the context of low-grade cataract or refractive clear lens surgery^{158,179}; such endeavor is understandable, taken that FLALS may be beneficial in such cases, by enabling higher precision and customization to capsulotomy and its impact on premium IOL positioning.

Our research led us to establish the benefits of femtosecond laser assisted lens surgery. It is apparent that the low-energy concept stands at a higher level compared to the high-energy pattern, when it comes to the rate of adverse effects, namely pupil behavior and, presumably, capsular events. This impacts strongly on the feasibility of premium lens surgery (MIOLs, in particular), as it requires an almost ideal capsulotomy and optimized

pupil conditions for IOL centration. Furthermore, due to its high precision and customization, FSL capsulotomy, in general, stands ahead CP for the purpose of refractive correction. For that matter, effectiveness of capsulotomy centration reflects on higher standards of aberrometry correction.

Ultimately, the features mentioned above, together with the strengthened evidence of long-term stability and unveiled low incidence of complications, pull femtosecond laser assisted lens surgery (FLALS) particularly low energy based, into the future.

6. Conclusions and Future Directions for Research

The present research highlights the contribution of low energy femtosecond laser for lens surgery.

It is our belief, along our research's path, that the expression of femtosecond laser assisted lens surgery (FLALS) is more appropriate than FLACS. The acronym FLALS was preferably employed in this thesis. The inclusive expression FLALS stands for clear lens or cataract surgical procedure, as it addresses crystalline lens removal.

The need for better postoperative refractive results supports, itself, the refractive nature of cataract surgery. This refractive driven concern clearly dilutes the old dichotomy between cataract removal and the so-called refractive lens surgery and has thrust the investment in technology regarding new techniques and IOLs, creating an unsurprisingly high status of expectation and demand from patients. Rather than a clear separation between pure cataract removal and refractive lens surgery, the indications are better set in a continuous spectrum of patients-based needs, as the surgical steps are the same. The electiveness of refractive lens surgery will stand on the farthest point of such a spectrum, in which autonomy of spectacles is the patient's highest desire. Expectation and deliverance, like most of all human activities, are the turn wheels of cataract surgery's evolution.

The advent of femtosecond laser aimed to give birth to a new standard in cataract surgery, intended to overmatch the paradigm of conventional phacoemulsification. Femtosecond laser assisted lens surgery enables a higher level of reproducibility, precision, accuracy, and customization when performing the several steps involved in lens removal. These features of FLALS assume high relevance, especially when considering the implantation of premium intraocular lenses, such as toric, enhanced depth-of-focus or multifocal lenses.

The behavioral difference between different low and energy FS pulses is currently being unveiled, although seldom published. An increased knowledge of the spectrum of differences regarding FSL technologies allows better judgment and appraisal upon surgical option's planning. This is translated into a lower incidence of anterior capsule complications and adverse events such as pupil constriction with low-energy pulse devices. By avoiding those drawbacks, the way for uneventful presbyopia correction with MIOLs is widened. In this set, and as a result of our research, candidates for MIOL implantation with shallow chambers, such as high hyperopes, with this regard, may be

proposed to FLALS instead of CP. Likewise, the gathered evidence regarding customization of capsulotomy centration (this research introducing a novel marking procedure), fast postoperative visual recovery, high SE accuracy and long-term stability, enables FSL surgery to compare better to CP. These features are most relevant in the realm of premium lens surgery.

Some evidence has been gathered of FLACS indication for special cases over CP, as cataractous patients with associated ocular conditions, such as endothelial pathology or zonular instability.

As FLALS levels up with CP in terms of the complications rate (and even better in certain contexts, as mentioned above), its performance on the ground of visual outcomes is still on the run to declare an unequivocal superiority over CP's. The ultimate potential benefit in visual and refractive outcomes with FLALS as compared to CP still remains uncertain, mostly due to the global appraisal reports that concern cataract surgery rather than refractive lens exchange (with premium IOLs).

The paradigm for cataract removal remains conventional phacoemulsification, primarily based on economic reasons and a lesser standard regarding refractive concerns. However, the compass of cataract surgery is changing, pointing towards a higher performance regarding refractive correction and, ultimately, emmetropia. For this matter, femtosecond laser may be advantageous in premium lens surgery, inherent to the expanding universe of premium IOLs.

Also, looking further into the future, developments of this attractive and promising technology may enable, through incremented pulse and lens fragmentation patterns, to extend the abolition of any ultrasound energy (already feasible for clear lens surgery), in the removal of denser cataracts, broadening the use of this technique.

In this context, FSL platforms must be self-sufficient in terms of surgical machinery, dispensing the use of phacoemulsification devices. To this aspect, technological improvements are necessary, such as full lens treatment with laser covering all grades of cataract, with no need for additional energy sources, such as ultrasound. This feature is liable to be accomplished by developing fragmentation patterns to near-infinitesimal scale. An aspirating system would then be incorporated in the platform, enabling the lens material removal.

To these improvements, portability should be stressed as a favorable feature, and it has been object to a strong investment by the industry. Some recent developments of already existing platforms, such as ALLY (LensAR, Inc.), the next generation of LensAR's FS

device, have evolved in the direction of modified energy pulse patterns and portability, aiming to better performance. A similar effort, in the pursuit of surgical steps' optimization, has been taken by other companies, such as Alcon's LensX with ASCEND™ Technology, which incorporates Artificial Intelligence. Likewise, FemtoMatrix (Keranova, Inc.), although a high energy FSL platform, was introduced as a mobile FS device.

Another direction to explore, reducing the intervention's invasiveness, would be the reduction of hydric requirements and avoid the overhydrated status of the eye during standard surgery; in addition, it would diminish other risks of an open globe (such as infectious). For that matter, as all-FS laser surgery is performed in a closed globe, it may set the path for "dry" surgery. We believe that this is an endeavor to undertake regarding the future of lens surgery.

Also, with the aid of imaging supporting technology, FSL platforms may elevate customization of new IOLs' implantation to unseen levels. In that line of course, the Ziemer platform has evolved to a new version, the Femto LDV Z8 NEO, with, among other features (slim arm), an improved OCT with faster scanning and better recognition of intraocular structures.

Regarding cost-effectiveness, it is evident that FLALS cannot currently compete with CP, the main difference residing in the high cost of the laser equipment and consumables. Therefore, CP keeps the crown of the standard technique of lens surgery, limiting the use of FLALS as an option, mainly for the above indications. This latter choice has inherent additional expenses, usually charged to the patient. However, and taken the attractive grounds of laser-based techniques, this high-cost scenery is liable to change, subject to the old laws of offer and demand; for this matter, further developments on the delivery outcomes are on the wait.

In summary, FLALS has evolved technically since its dawn, namely with the development of different types of pulse energy levels and broader surgical step coverage and refinement. The low energy concept is liable to present itself as a step forward into the future. Like other surgical techniques in its youth, indications have been simultaneously widened and fine-tuned. Still, further improvements in this technique should be expected, together with larger studies approaching the different laser systems in general, and low energy pulse devices in particular.

7. References

1. Strickland D, Mourou G. Compression of amplified chirped optical pulses. *Opt Commun* 1985
2. Ali MH, Javaid M, Jamal S, Butt NH. Femtosecond laser assisted cataract surgery, beginning of a new era in cataract surgery. *Oman J Ophthalmol* 2015; 8(3): 141–146
3. Vogel A, Busch S, Jungnickel K, Birngruber R. Mechanisms of intraocular photodisruption with picosecond and nanosecond laser pulses. *Lasers Surg Med* 1994; 15: 32–43
4. Heisterkamp A, Ripken T, Mamom T, et al. Nonlinear side effects of fs pulses inside corneal tissue during photodisruption. *Appl Phys B* 2002; 74: 419–25
5. Loesel FH, Tien A-C, Backus SJ, et al. Effect of reduction of laser pulse width from 100 ps to 20 fs on the plasma-mediated ablation of hard and soft tissue. In: *Thermal therapy, laser welding, and tissue interaction*. Proc SPIE; 1999: 3565
6. Cook C. E. Pulse Compression-Key to More Efficient Radar Transmission. *Proceedings of the IRE* 1960; 48(3): 310-316
7. Pepose J, Lubatschowski, H. Comparing femtosecond lasers. *Cataract & Refractive Surgery Today* 2008; 10: 45-51
8. Asshauer T, Latz C, Mirshahi A, et al. Femtosecond lasers for eye surgery applications: historical overview and modern low pulse energy concepts. *Adv Opt Technol* 2021; 10(6): 393-408
9. Latz C, Asshauer T, Rathjen C, Mirshahi A. Femtosecond-Laser Assisted Surgery of the Eye: Overview and Impact of the Low-Energy Concept. *Micromachines (Basel)* 2021; 12(2): 122
10. Lin, H Y, Chuang Y J, Lin P J. Surgical outcomes with high and low pulse energy femtosecond laser systems for cataract surgery. *Sci. Rep* 2021; 11: 9525
11. Chang J S, Chen I N, Chan W M, et al. Initial evaluation of a femtosecond laser system in cataract surgery. *J. Cataract Refract Surg* 2014; 40(1): 29–36
12. Bonnet C, Al-Hashimi S, Brézin A, et al. Femto Laser-Assisted Cataract Surgery. In: Alireza Z, Michele L, editors. *Eyesight and Imaging*. Rijeka: IntechOpen 2020; p. Ch. 2

13. Doors M, Berendschot T T, de Brabander J, et al. Value of optical coherence tomography for anterior segment surgery. *J Cataract Refract Surg* 2010; 36(7): 1213-1229
14. Talamo JH, Gooding P, Angeley D, et al. Optical patient interface in femtosecond laser-assisted cataract surgery: contact corneal appplanation versus liquid immersion. *J Cataract Refract Surg* 2013; 39(4): 501-10
15. Al Harthi K, Al Shahwan S, Al Towerki A, et al. Comparison of the anterior capsulotomy edge created by manual capsulorhexis and 2 femtosecond laser platforms: scanning electron microscopy study. *J Cataract Refract Surg* 2014; 40: 2106–12
16. Feldman BH. Femtosecond laser will not be a standard method for cataract extraction 10 years from now. *Surv Ophthalmol* 2015; 60: 360–5
17. Bali SJ, Hodge C, Lawless M, et al. Early experience with the femtosecond laser for cataract surgery. *Ophthalmology* 2012; 119: 891– 9.
18. Nagy ZZ, Takacs AI, Filkorn T, et al. Complications of femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2014; 40: 20–8
19. Manning S, Barry P, Henry Y, et al. Femtosecond laser-assisted cataract surgery vs. standard phacoemulsification cataract surgery: study from the European registry of quality outcomes for cataract and refractive surgery. *J Cataract Refract Surg* 2016; 42: 1779–90
20. Zhang X, Yu Y, Zhang G, et al. Performance of femtosecond laser-assisted cataract surgery in Chinese patients with cataract: a prospective, multicenter, registry study. *BMC Ophthalmol* 2019; 19: 77
21. Ambrosio R, Valbon B F, Faria-Correia F, et al. Scheimpflug imaging for laser refractive surgery. *Curr. Opin. Ophthalmol* 2013; 24(4): 310-320
22. Grewal DS, Schultz T, Basti S, Dick HB. Femtosecond laser– assisted cataract surgery—current status and future directions. *Surv Ophthalmol* 2016; 61(2): 103–131
23. Sun H, Fritz A, Dröge G, et al. Femtosecond-laser assisted cataract surgery (FLACS). In: Bille JF, ed. *High Resolution Imaging in Microscopy and Ophthalmology*. Springer International Publishing 2019: 301–317
24. Sanders DR, Higginbotham RW, Opatowsky IE, et al. Hyperopic shift in refraction associated with implantation of the single-piece Collamer intraocular lens. *J Cataract Refract Surg* 2006; 32(12): 2110-2

25. Baumeister M, Bühren J, Kohnen T. Tilt and decentration of spherical and aspheric intraocular lenses: effect on higher-order aberrations. *J Cataract Refract Surg* 2009; 35(6): 1006-12
26. Friedman NJ, Palanker DV, Schuele G, et al. Femtosecond laser capsulotomy. *J Cataract Refract Surg* 2011; 37: 1189– 98
27. Kránitz K, Miháltz K, Sándor GL, et al. Intraocular lens tilt and decentration measured by Scheimpflug camera following manual or femtosecond laser-created continuous circular capsulotomy. *J Refract Surg* 2012; 28(4): 259-63
28. Kránitz K, Takacs A, Miháltz K, et al. Femtosecond laser capsulotomy and manual continuous curvilinear capsulorrhexis parameters and their effects on intraocular lens centration. *J Refract Surg* 2011; 27(8): 558-63
29. Holland D, Rüfer F. Neue Intraokularlinsendesigns für die Femtosekundenlaser-assistierte Kataraktoperation : Chancen und Nutzen [New intraocular lens designs for femtosecond laser-assisted cataract operations : Chances and benefits]. *Ophthalmologe* 2020; 117(5): 424-430
30. Abouzeid H, Ferrini W. Femtosecond-laser assisted cataract surgery: a review. *Acta Ophthalmol* 2014; 92(7): 597-603
31. Mastropasqua L, Toto L, Calienno R, et al. Scanning electron microscopy evaluation of capsulorrhexis in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2013; 39: 1581–6
32. Adams M, Diakonis, V, Weinstock, R. Argentinian Flag Sign and Its Management during Femtosecond Laser-Assisted Cataract Surgery in a Case with Intumescent Cataracts. *Case Rep Ophthalmol* 2021; 12(1): 129-133
33. Zhu Y, Chen X, Chen P, Xu W, Shentu X, Yu Y, et al. Lens capsule-related complications of femtosecond laser–assisted capsulotomy versus manual capsulorrhexis for white cataracts. *Journal of Cataract & Refractive Surgery*. 2019;45(3):337-42
34. Edlmayr AS, Pomberger LJ, Hermann P, et al. Prospective comparison of apex-centered vs standard pupil-centered femtosecond laser-assisted capsulotomy in cataract surgery. *J Cataract Refract Surg* 2021; 47(5): 606-611
35. Kovacs I, Kranitz K, Sandor GL, et al. The effect of femtosecond laser capsulotomy on the development of posterior capsule opacification. *J Refract Surg* 2014; 30: 154–158

36. Schultz T, Tsiampalis N, Dick HB. Laser-assisted capsulotomy centration: a prospective trial comparing pupil versus OCT-based scanned capsule centration. *J Refract Surg* 2017; 33(2): 74–78
37. O'Neill BP, Diakonis VF, Tsaousis KT, Weinstock RJ. Outcomes of toric IOL implantation guided by iris-registered femtosecond laser capsulotomy markings. *Int Ophthalmol*. 2021;41(12):4009-15
38. Agarwal K, Hatch K. Femtosecond Laser Assisted Cataract Surgery: A Review. *Semin Ophthalmol* 2021; 36(8): 618-627
39. Diakonis VF, Yesilirmak N, Sayed-Ahmed IO, et al. Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms. *J Refract Surg* 2016; 32(2): 84–88
40. Wu BM, Williams GP, Tan A, et al. Comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol* 2015; 2015: 616478
41. Roberts TV, Lawless M, Bali SJ, et al. Surgical Outcomes and safety of femtosecond laser cataract surgery. *Ophthalmol* 2013; 120(2): 227–233
42. Malyugin BE. Recent advances in small pupil cataract surgery. *Curr Opin Ophthalmol* 2018; 29(1): 40–47
43. Reyes Lua M, Oertle P, Camenzind L, et al. Superior rim stability of the lens capsule following manual over femtosecond laser capsulotomy. *Invest Ophthalmol Vis Sci* 2016; 57: 2839–49
44. Williams G, George B, Wong Y R, et al. The effects of a low-energy, high frequency liquid optic interface femtosecond laser system on lens capsulotomy. *Scientific Reports* 2016; 6: 24352
45. Kolb C M, Shajari M, Mathys L, et al. Comparison of femtosecond laser-assisted cataract surgery and conventional cataract surgery: a meta-analysis and systematic review. *J Cataract Refract Surg* 2020; 46(8): 1075-1085
46. Salgado R, Torres P, Marinho A. Femtosecond Laser-assisted Lens Surgery with Low-energy Pulse versus Conventional Phacoemulsification for Presbyopia Correction: An Intraindividual Study. *The Open Ophthalmology Journal* 2021;15(1), 43-53
47. Bethke W. Femtosecond Cataract: dodge the Pitfalls. *Rev Ophthalmol* 2016
48. Packer M, Teuma EV, Glasser A, Bott S. Defining the ideal femtosecond laser capsulotomy. *Br J Ophthalmol*. 2015; 99(8): 1137–1142

49. Nagy ZZ, McAlinden C. Femtosecond laser cataract surgery Nagy ZZ, McAlinden C. Femtosecond laser cataract surgery. *Eye Vis Lond Engl* 2015; 2:11
50. Aristeidou A, Taniguchi EV, Tsatsos M. et al. The evolution of corneal and refractive surgery with the femtosecond laser. *Eye Vis Lond Engl*. 2015; 2: 12
51. Kaur M, Titiyal JS, Surve A, et al. Effect of lens fragmentation patterns on phacoemulsification parameters and postoperative inflammation in femtosecond laser-assisted cataract surgery. *Curr Eye Res* 2018; 43: 1228–32
52. Chung SH, Mazur E. Surgical applications of femtosecond lasers. *J Biophotonics* 2009; 2: 557–72
53. Lin H-Y, Kao S-T, Chuang Y-J, Chen S, Lin P-J. Comparison of cumulative dispersed energy between conventional phacoemulsification and femtosecond laser-assisted cataract surgery with two different lens fragmentation patterns. *Lasers in Medical Science*. 2022;37(2):843-8
54. Roberts TV, Sutton G, Lawless MA, et al. Capsular block syndrome associated with femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2011; 37(11): 2068–2070
55. Palanker DV, Blumenkranz MS, Andersen D, et al. Femtosecond laser-assisted cataract surgery with integrated optical coherence tomography. *Sci Transl Med* 2010; 2(58): 58-85
56. Masket S, Sarayba M, Ignacio T, Fram N. Femtosecond laser-assisted cataract incisions: architectural stability and reproducibility. *J Cataract Refract Surg* 2010; 36(6): 1048-9
57. Alio JL, Abdou AA, Soria F, et al. Femtosecond laser cataract incision morphology and corneal higher-order aberration analysis. *J Refract Surg* 2013; 29: 590–5
58. Uy HS, Shah S, Packer M. Comparison of Wound Sealability Between Femtosecond Laser-Constructed and Manual Clear Corneal Incisions in Patients Undergoing Cataract Surgery: A Pilot Study. *J Refract Surg* 2017; 33(11): 744-748
59. Mastropasqua L, Toto L, Mastropasqua A, et al. Femtosecond laser versus manual clear corneal incision in cataract surgery. *J Refract Surg* 2014; 30(1): 27–33
60. Ranjini H, Murthy PR, Murthy GJ, et al. Femtosecond laser-assisted cataract surgery versus 2.2 mm clear corneal phacoemulsification. *Indian J Ophthalmol* 2017; 65(10): 942–948

61. Mirshahi A, Latz C. Astigmatische Keratotomien mit dem Femtosekundenlaser [Femtosecond laser-assisted astigmatic keratotomy]. *Ophthalmologe* 2020 May; 117(5): 415-423
62. Stanojic N, Roberts HW, Wagh VK, Li JO, Naderi K, O'Brart DP. A randomised controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: 12-month results. *Br J Ophthalmol*. 2021;105(5):631-8
63. Roberts HW, Day AC, O'Brart DP. Femtosecond laser-assisted cataract surgery: a review. *Eur J Ophthalmol* 2020; 30(3): 417–429
64. Awdeh R, Hanafie H, Canto A-P. Using a laser for arcuate incisions. *Cataract Refract Surg Today* 2011
65. Desai N, McCabe C, Tauber S, Visco D, Whitman J. Laser arcs for astigmatic correction. *Cataract Refract Surg Today* 2015
66. Cao D, Xu Y, Wang Y. Comparison of Toric Intraocular Lens Alignment Between Femtosecond Laser–Assisted Capsular Marking and Manual Corneal Marking. *J Refract Surg* 2020; 36: 536-542
67. Roberts HW, Wagh VK, Sullivan DL, et al. Refractive outcomes after limbal relaxing incisions or femtosecond laser arcuate keratotomy to manage corneal astigmatism at the time of cataract surgery. *J Cataract Refract Surg* 2018; 44: 955–63
68. Vickers LA, Gupta PK. Femtosecond laser-assisted keratotomy. *Curr Opin Ophthalmol* 2016; 27: 277–84
69. Visco DM, Bedi R, Packer M. Femtosecond laser-assisted arcuate keratotomy at the time of cataract surgery for the management of preexisting astigmatism. *J Cataract Refract Surg* 2019; 45: 1762–9
70. Yoo A, Yun S, Kim JY, et al. Femtosecond Laser-assisted Arcuate Keratotomy Versus Toric IOL Implantation for Correcting Astigmatism. *J Refract Surg* 2015; 31(9): 574-8
71. Lin HY, Chen S, Chuang YJ, Zhang S, Chang SW, Lin PJ, et al. Effectiveness of reducing corneal astigmatism after combined high-frequency LDV Z8 femtosecond laser-assisted phacoemulsification and arcuate keratotomy. *Front Cell Dev Biol*. 2022;10:1036469

72. Noh H, Yoo YS, Shin KY, et al. Comparison of penetrating femtosecond laser-assisted astigmatic keratotomy and toric intraocular lens implantation for correction of astigmatism in cataract surgery. *Sci Rep* 2021; 11: 7340
73. Hernandez R, Almenara C, Soriano D, et al. Toric intraocular lens implantation vs. femtosecond laser-assisted arcuate keratotomy for correction of moderate astigmatism in cataract surgery. *J Cataract Refract Surg* 2022; 48: 887–93
74. Wortz G, Gupta PK, Goernert P. et al. Outcomes of femtosecond laser arcuate incisions in the treatment of low corneal astigmatism. *Clin Ophthalmol* 2020; 14: 2229–2236
75. Baharozian CJ, Song C, Hatch K, et al. A novel nomogram for the treatment of astigmatism with femtosecond-laser arcuate incisions at the time of cataract surgery. *Clin Ophthalmol* 2017; 11: 1841–1848
76. Roberts HW, Wagh VK, Sullivan DL, et al. A randomized controlled trial comparing femtosecond laser-assisted cataract surgery vs. conventional phacoemulsification surgery. *J Cataract Refract Surg* 2019; 45: 11–20
77. Ang RET, Quinto MMS, Cruz EM, Rivera MCR, Martinez GHA. Comparison of clinical outcomes between femtosecond laser-assisted versus conventional phacoemulsification. *Eye Vis (Lond)*. 2018;5:8
78. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery vs. phacoemulsification cataract surgery (FACT): a randomized noninferiority trial. *Ophthalmology* 2020; 127: 1012– 9
79. Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery vs. standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev* 2016;7:CD010735
80. Song X, Li L, Zhang X, Ma J. Comparing the efficacy and safety between femtosecond laser-assisted cataract surgery and conventional phacoemulsification cataract surgery: systematic review and meta-analysis. *Can J Ophthalmol*. 2024
81. Dick HB, Conrad-Hengerer I, Schultz T. Intraindividual capsular bag shrinkage comparing standard and laser-assisted cataract surgery. *J Refract Surg* 2014; 30: 228–233
82. Liu Q, Zhang S, Wang X, Liu J, Zhou G, Yuan X. Effects of intraocular lens anterior edge design on anterior capsule morphology changes following femtosecond laser-assisted capsulotomy. *BMC Ophthalmology*. 2022;22(1)

83. Wang Y, Wang W, Zhu Y, Xu J, Luo C, Yao K. Comparison Study of Anterior Capsule Contraction of Hydrophilic and Hydrophobic Intraocular Lenses Under the Same Size Capsulotomy. *Transl Vis Sci Technol*. 2022;11(1):24
84. Donmez O, Asena BS, Aydin Akova Y. Subjective and objective clinical outcomes of a new trifocal toric intraocular lens and effect of femtosecond laser cataract surgery. *European Journal of Ophthalmology*. 2022;32(4):2225-33
85. Reddy KP, Kandulla J, Auffarth GU. Effectiveness and safety of femtosecond laser-assisted lens fragmentation and anterior capsulotomy versus the manual technique in cataract surgery. *J Cataract Refract Surg* 2013; 39: 1297–1306
86. Zhong Y, Zhu Y, Wang W, Wang K, Liu X, Yao K. Femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: comparison of internal aberrations and visual quality. *Graefes Archive for Clinical and Experimental Ophthalmology*. 2022;260(3):901-11
87. Lundstrom M, Dickman M, Henry Y, et al. Femtosecond laser-assisted cataract surgeries reported to the European Registry of quality outcomes for cataract and refractive surgery: baseline characteristics, surgical procedure, and outcomes. *J Cataract Refract Surg* 2017; 43: 1549–56
88. Toto L, Calienno R, Curcio C, et al. Induced inflammation and apoptosis in femtosecond laser-assisted capsulotomies and manual capsulorhexis: an immunohistochemical study. *J Refract Surg* 2015; 31: 290–4
89. Pisciotta A, De Maria M, Verdina T, et al. Anterior capsule of the lens: comparison of morphological properties and apoptosis induction following FLACS and standard phacoemulsification surgery. *Biomed Res Int* 2018: 7242837
90. Sun W, Liu J, Li J, et al. Human lens epithelial cell apoptosis and epithelial to mesenchymal transition in femtosecond laser-assisted cataract surgery. *Int J Ophthalmol* 2018; 11: 401–7
91. Rabinovich M, Niegowski LJ, Bovet J, Aramburu del Boz A, Baumgartner JM, Gillmann K. Comparison of posterior capsule opacification rates between femtosecond laser-assisted and micro-incision cataract surgery over 24 months. *Spektrum der Augenheilkunde*. 2021;35(6):241-5
92. Kulikov IV, Spirin AE, Mullakhmetov BA, Kulikova IL. Secondary cataract in patients after traditional phacoemulsification in comparison with femtolaser extraction. *Ophthalmology Journal*. 2023;16(4):7-13

93. Popovic M, Campos-Moller X, Schlenker MB, et al. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology* 2016; 123: 2113–2126
94. Connell BJ, Kane JX, Vajpayee RB. A comparison of refractive accuracy between conventional and femtosecond laser cataract surgery techniques using modern iol formulas. *Clinical Ophthalmology*. 2021;15:899-907
95. Nagy ZZ, Dunai A, Kranitz K, et al. Evaluation of femtosecond laser-assisted and manual clear corneal incisions and their effect on surgically induced astigmatism and higher-order aberrations. *J Refract Surg* 2014; 30: 522–525
96. Kohnen T, Löffler F, Herzog M, Petermann K, Böhm M. Tomographic analysis of anterior and posterior surgically induced astigmatism after 2.2 mm temporal clear corneal incisions in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2019;45(11):1602-11
97. Fernandez J, Rodríguez-Vallejo M, Martinez J, et al. Prediction of surgically induced astigmatism in manual and femtosecond laser-assisted clear corneal incisions. *Eur J Ophthalmol* 2018; 28: 398–405
98. Pereira A, Somani S, Tam ES, Chiu H, Maini R. Comparison of Surgically Induced Astigmatism and Corneal Morphological Features Between Femtosecond Laser and Manual Clear Corneal Incisions. *J Refract Surg*. 2019;35(12):796-802.
99. Diakonis VF, Yesilirmak N, Cabot F, Kankariya VP, Kounis GA, Warren D, et al. Comparison of surgically induced astigmatism between femtosecond laser and manual clear corneal incisions for cataract surgery. *J Cataract Refract Surg*. 2015;41(10):2075-80
100. Chen X, Chen K, He J, et al. Comparing the curative effects between femtosecond laser-assisted cataract surgery and conventional phacoemulsification surgery: a meta-analysis. *PLoS One* 2016; 11: e0152088
101. Ferreira TB, Ribeiro FJ, Pinheiro J, et al. Comparison of surgically induced astigmatism and morphologic features resulting from femtosecond laser and manual clear corneal incisions for cataract surgery. *J Refract Surg* 2018; 34: 322–329
102. Chen X, Xiao W, Ye S, et al. Efficacy and safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: a meta-analysis of randomized controlled trials. *Sci Rep* 2015; 5: 13123

103. Hatch KM, Schultz T, Talamo JH, et al. Femtosecond laser-assisted compared with standard cataract surgery for removal of advanced cataracts. *J Cataract Refract Surg* 2015; 41: 1833–1838
104. Hida WT, Tzelikis PF, Vilar C, et al. Outcomes study between femtosecond laser-assisted cataract surgery and conventional phacoemulsification surgery using an active fluidics system. *Clin Ophthalmol* 2017; 11: 1735–1739
105. Panthier C, Costantini F, Rigal-Sastourne JC, et al. Change of capsulotomy over 1 year in femtosecond laser assisted cataract surgery and its impact on visual quality. *J Refract Surg* 2017; 33: 44–4997
106. Schultz T, Joachim SC, Tischoff I, et al. Histologic evaluation of in vivo femtosecond laser-generated capsulotomies reveals a potential cause for radial capsular tears. *Eur J Ophthalmol* 2015; 25: 112–118
107. Charles Crozaon P, Bouchet C, Zignani M, Griner R, Foster SD, Zou M, et al. Comparison of real-world treatment outcomes of femtosecond laser-assisted cataract surgery and phacoemulsification cataract surgery: A retrospective, observational study from an outpatient clinic in France. *European Journal of Ophthalmology*. 2021;31(4):1809-16.
108. Pichardo-Loera NS, Corredor-Ortega C, Castro-Monreal MA, Massaro-Corredor MG, Pérez-Vázquez JF, Gonzalez-Salinas R. Femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: A meta-analysis of randomized controlled trials. *Eur J Ophthalmol*. 2024;34(5):1458-68
109. Norrby S. Sources of error in intraocular lens power calculation. *J Cataract Refract Surg* 2008; 34: 368–76
110. Lawu T, Mukai K, Matsushima H, et al. Effects of decentration and tilt on the optical performance of 6 aspheric intraocular lens designs in a model eye. *J Cataract Refract Surg* 2019; 45: 662–668
111. Wang J, Su F, Wang Y, Chen Y, Chen Q, Li F. Intra and post-operative complications observed with femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):177
112. Levitz LM, Dick HB, Scott W, Hodge C, Reich JA. The Latest Evidence with Regards to Femtosecond Laser-Assisted Cataract Surgery and Its Use Post 2020. *Clinical Ophthalmology*. 2021;15:1357-63

113. Narayan A, Evans J R, O'Brart D, et al. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database of Systematic Reviews* (6); 2023
114. Xu J, Chen X, Wang H, et al. Safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: A meta-analysis and systematic review. *Adv Ophthalmol Pract Res* 2022; 2(1): 100027
115. Abell RG, Davies PE, Phelan D, Goemann K, McPherson ZE, Vote BJ. Anterior capsulotomy integrity after femtosecond laser-assisted cataract surgery. *Ophthalmology* 2014; 121: 17–24
116. Day AC, Gartry DS, Maurino V, et al. Efficacy of anterior capsulotomy creation in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2014; 40: 2031–4
117. Piñero A, Kanclerz P, Barraquer RI, Maldonado MJ, Alió JL. Evaluation of femtosecond laser-assisted cataract surgery after 10 years of clinical application. *Arch Soc Esp Oftalmol (Engl Ed)*. 2020;95(11):528-37
118. Larco P, Larco C, Borroni D, Godin F, Piñero DP, Rocha-de-Lossada C, et al. Efficacy of femtosecond laser for anterior capsulotomy in complex white cataracts. *J Fr Ophthalmol*. 2023;46(5):501-9
119. Koenig LR, Duong AT, Yuan M, Van Tassel SH. Adverse events associated with femtosecond laser-assisted cataract surgery reported to the MAUDE database. *J Cataract Refract Surg*. 2022;48(2):168-72
120. Wang W, Chen X, Liu X, Zhang X, Lyu D, Yao K. Lens capsule-related complications in femtosecond laser-assisted cataract surgery: a study based on video analysis. *Br J Ophthalmol*. 2023;107(7):906-11
121. Keci, M., & Schweitzer, C. Femtosecond laser-assisted cataract surgery: Update and perspectives [Mini Review]. *Front Med* 2023; 10
122. Kanclerz P, Alio JL. The benefits and drawbacks of femtosecond laser-assisted cataract surgery. *Eur J Ophthalmol*. 2021;31(3):1021-30
123. Pajic B, Pajic-Eggspuehler B, Rathjen C, et al. Why Use Ultrashort Pulses in Ophthalmology and Which Factors Affect Cut Quality. *Medicina (Kaunas)*. 2021; 57(7): 700

124. Song C, Baharozian CJ, Hatch KM, et al. Rate of unplanned vitrectomies in femtosecond laser-assisted cataract surgery compared to conventional phacoemulsification. *J Refract Surg* 2018; 34: 610–614
125. Riemey J, Latz C, Mirshahi A. Intraoperative complications of cataract surgery using a low-energy femtosecond laser: Results from a real-world high-volume setting. *PLOS ONE* 2022; 17(12): e0279023
126. Popiela MZ, Young-Zvandasara T, Nidamanuri P, et al. Factors influencing pupil behaviour during femtosecond laser assisted cataract surgery. *Contact Lens Anterior Eye* 2019; 42(3): 295–298
127. Schultz T, Joachim SC, Kuehn M, et al. Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery. *J Refract Surg* 2013; 29: 742–7
128. Schultz T, Joachim SC, Stellbogen M, et al. Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. *J Refract Surg* 2015; 31: 78–81
129. Stewart S, Liu YC, Setiawan M, Lin MT, Lee IXY, Sim N, et al. The Effects of High Energy Capsulotomy on Aqueous Cytokine Profiles and Pupil Size During Femtosecond Laser-Assisted Cataract Surgery. *J Refract Surg*. 2022;38(9):587-94
130. Schultz T, Joachim SC, Szuler M, et al. NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. *J Refract Surg* 2015; 31: 791–4
131. Bethke W. Femtosecond Cataract: dodge the Pitfalls. *Rev Ophthalmol* 2016
132. Kent C. Femto laser cataract: avoiding complications. *Rev Ophthalmol* 2014
133. Jun JH, Hwang KY, Chang SD, et al. Pupil-size alterations induced by photodisruption during femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2015; 41: 278–85
134. Mirshahi A, Schneider A, Latz C, et al. Perioperative pupil size in low-energy femtosecond laser-assisted cataract surgery. *PLOS ONE* 2021;16(5): e0251549
135. Salgado R, Torres PF, Marinho A. Pupil Status with Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification: An Intraindividual Comparative Study. *Clin Ophthalmol* 2023; 17: 331-339

136. Schweitzer C, Brezin A, Cochener B, et al. Femtosecond laser-assisted vs. phacoemulsification cataract surgery (FEMCAT): a multicentre participant-masked randomised superiority and cost-effectiveness trial. *Lancet* 2020; 395: 212–24
137. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery compared with phacoemulsification cataract surgery: randomized noninferiority trial with 1-year outcomes. *J Cataract Refract Surg* 2020; 46: 1360–7
138. Bascaran L, Alberdi T, Martinez-Sorola I, et al. Differences in energy and corneal endothelium between femtosecond laser-assisted and conventional cataract surgeries: prospective, intraindividual, randomized controlled trial. *Int J Ophthalmol* 2018; 11: 1308–16
139. Dzhaber D, Mustafa O, Alsaleh F, et al. Comparison of changes in corneal endothelial cell density and central corneal thickness between conventional and femtosecond laser-assisted cataract surgery: a randomised, controlled clinical trial. *Br J Ophthalmol* 2020; 104: 225–9
140. Lin CC, Rose-Nussbaumer JR, Al-Mohtaseb ZN, et al. Femtosecond laser-assisted cataract surgery: a report by the American academy of ophthalmology. *Ophthalmology* 2022; 129: 946–54
141. Ye Z, Li Z, He S. A meta-analysis comparing postoperative complications and outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract. *J Ophthalmol* 2017; 2017: 3849152
142. Kang KH, Song MY, Kim KY, Hwang KY, Kwon YA, Koh K. Corneal Endothelial Cell Changes After Femtosecond Laser-Assisted Cataract Surgery in Diabetic and Nondiabetic Patients. *Eye and Contact Lens*. 2021;47(12):664-9
143. Wang H, Chen X, Xu J, Yao K. Comparison of femtosecond laser-assisted cataract surgery and conventional phacoemulsification on corneal impact: A meta-analysis and systematic review. *PLoS One*. 2023;18(4):e0284181
144. Liu YC, Setiawan M, Chin JY, et al. Randomized Controlled Trial Comparing 1-Year Outcomes of Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification. *Front Med (Lausanne)* 2021; 8: 811093
145. Fan W, Yan H, Zhang G. Femtosecond laser-assisted cataract surgery in Fuchs endothelial corneal dystrophy: long-term outcomes. *J Cataract Refract Surg* 2018; 44: 864–870

146. Wei Dayna YW, Hui-Chen Charmaine C, Liang S, et al. Comparing outcomes of phacoemulsification with femtosecond laser assisted cataract surgery in patients with Fuchs endothelial dystrophy. *Am J Ophthalmol* 2018; 196: 173–180
147. Zhu DC, Shah P, Feuer WJ, et al. Outcomes of conventional phacoemulsification versus femtosecond laser-assisted cataract surgery in eyes with Fuchs endothelial corneal dystrophy. *J Cataract Refract Surg* 2018; 44: 534–540
148. Van Nuffel S, Claeys MF, Claeys MH. Cystoid Macular Edema Following Cataract Surgery with Low-Energy Femtosecond Laser versus Conventional Phacoemulsification. *Clin Ophthalmol*. 2020;14:2873-8
149. Asena BS, Karahan E, Kaskaloglu M. Retinal and choroidal thickness after femtosecond laser-assisted and standard phacoemulsification. *Clin Ophthalmol* 2017; 11: 1541–1547
150. Conrad-Hengerer I, Hengerer FH, Al Juburi M, et al. Femtosecond laser-induced macular changes and anterior segment inflammation in cataract surgery. *J Refract Surg* 2014; 30: 222–226
151. Nagy ZZ, Ecsedy M, Kovacs I, et al. Macular morphology assessed by optical coherence tomography image segmentation after femtosecond laser-assisted and standard cataract surgery. *J Cataract Refract Surg* 2012; 38: 941–946
152. Enz TJ, Faes L, Bachmann LM, et al. Comparison of macular parameters after femtosecond laser-assisted and conventional cataract surgery in age-related macular degeneration. *J Cataract Refract Surg* 2018; 44: 23–27
153. Ma LY, Rong A, Jiang Y, Deng SY. Effects of Femtosecond Laser-Assisted Cataract Surgery on Macular and Choroidal Thickness in Diabetic Patients. *Ophthalmology and Therapy*. 2021;10(1):137-50
154. Abell RG, Allen PL, Vote BJ. Anterior chamber flare after femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2013; 39: 1321–1326
155. Cioana M, Patodia Y, Tong L, Chiu HH, Tam ES, Somani S. Anterior chamber cytokine production and postoperative macular edema in patients with diabetes undergoing FLACS. *Journal of Cataract & Refractive Surgery*. 2024;50(2):160-6
156. Schwarzenbacher L, Schartmüller D, Leydolt C, Menapace R. Intraindividual comparison of cytokine and prostaglandin levels with and without low-energy, high-frequency femtosecond laser cataract pretreatment after single-dose topical NSAID application. *J Cataract Refract Surg*. 2020;46(8):1086-91

157. Poyales F, Poyales B, Medel D, López-Brea I, López-Artero E, Garzón N. The influence of surgeons and technicians on the learning curve of femtosecond-laser cataract surgery. *J Optom.* 2020;13(4):242-8
158. Dick HB, Schultz T. On the way to zero phaco. *J Cataract Refract Surg* 2013; 39: 1442–1444
159. Zhang X, Xu W, Shentu X, Chen P, Yu Y, Lai K, et al. Incidence and analysis of intraoperative complications in femtosecond laser-assisted cataract surgery: a large-scale cohort study to establish the learning curve. *Br J Ophthalmol.* 2024
160. Xu J, Li W, Xu Z, Zhao B, Zhong Y, Wang K, et al. Comparative visual outcomes of EDOF intraocular lens with FLACS vs conventional phacoemulsification. *J Cataract Refract Surg.* 2023;49(1):55-61
161. Lee YW, Cho KS, Hyon JY, Han SB. Application of Femtosecond Laser in Challenging Cataract Cases. *Asia Pac J Ophthalmol (Phila).* 2023;12(5):477-85
162. Holland D, Rüfer F. [New intraocular lens designs for femtosecond laser-assisted cataract operations: Chances and benefits]. *Ophthalmologe.* 2020;117(5):424-30
163. Auffarth GU, Friedmann E, Breyer D, Kaymak H, Holland D, Dick B, et al. Stability and Visual Outcomes of the Capsulotomy-Fixated FEMTIS-IOL After Automated Femtosecond Laser-Assisted Anterior Capsulotomy. *Am J Ophthalmol.* 2021;225:27-37
164. Sandhu U, Osborn AR, Dang DH, Murphy DA, Langenbucher A, Wendelstein JA, et al. Refractive Astigmatism Outcomes of Femtosecond Laser-Assisted Arcuate Keratotomies Combined with Femtosecond Laser-Assisted Cataract Surgery: Two-Year Results. *Curr Eye Res.* 2024;49(9):961-71
165. Ou Y, Wang Y, Wu T. Comparison of ultrasound energy consumption between low-energy femtosecond laser-assisted cataract surgery and conventional phacoemulsification cataract surgery in patients with different cataract densities *Eur J Ophthalmol* 2023; 33(3): 1373-1379
166. Han SB, Liu YC, Setiawan M, Lee IXY, Patil M, Ong HS, et al. Effects of Different Capsulotomy and Fragmentation Energy Levels on the Generation of Oxidative Stress Following Femtosecond Laser-Assisted Cataract Surgery. *Biomolecules.* 2024;14(3)
167. Mathalone N, Ben-Shaul O, Podkovyrin O, Lux C, Geyer O. The Impact of Femtosecond Laser on Intraocular Pressure with Cataract Surgery in Healthy Eyes. *Journal of Glaucoma.* 2024

168. Dryjski O, Awidi A, Daoud YJ. Femtosecond laser-assisted cataract surgery in patients with zonular weakness. *Am J Ophthalmol Case Rep.* 2019;15:100483
169. Teshigawara T, Meguro A, Sanjo S, Hata S, Mizuki N. The advantages of femtosecond laser-assisted cataract surgery for zonulopathy. *International Medical Case Reports Journal.* 2019;12:109-16
170. Sachdev MS, Malik R, Gupta H, Sachdev R, Sachdev GS. Femtosecond laser-integrated anterior segment optical coherence tomography to detect preexisting posterior capsular dehiscence and increase safety in posterior polar cataracts. *J Cataract Refract Surg.* 2020;46(2):235-40
171. Elghobaier MGE, Ibrahiem MFK, Abdelhalim AS, Eid AM, Murad KAS. Clinical and surgical outcomes of femtosecond laser-assisted cataract surgery (Flacs) on hard cataracts in the egyptian population. *Clinical Ophthalmology.* 2020;14:1383-9
172. Chen X, Yu Y, Song X, Zhu Y, Wang W, Yao K. Clinical outcomes of femtosecond laser-assisted cataract surgery vs. conventional phacoemulsification surgery for hard nuclear cataracts. *J Cataract Refract Surg* 2017; 43: 486– 91
173. Salgado R, Torres P, Marinho A, Ribeiro FJ. Cataract Grade and Pupil: Comparison Between Conventional Phacoemulsification and Low-Energy Femtosecond Laser Assisted Cataract Surgery. *Clin Ophthalmol* 2023; 17: 2193-2200
174. Vasavada VA, Vasavada S, Vasavada AR, et al. Comparative evaluation of femtosecond laser-assisted cataract surgery and conventional phacoemulsification in eyes with a shallow anterior chamber. *J Cataract Refract Surg* 2019; 45: 547–52
175. Yong WWD, Chai HC, Shen L, et al. Comparing outcomes of phacoemulsification with femtosecond laser-assisted cataract surgery in patients with Fuchs endothelial dystrophy. *Am J Ophthalmol* 2018; 196: 173– 80
176. Verdina T, Peppoloni C, Barbieri L, Carbotti MR, Battaglia B, Mastropasqua R, et al. Long-Term Evaluation of Capsulotomy Shape and Posterior Capsule Opacification after Low-Energy Bimanual Femtosecond Laser-Assisted Cataract Surgery. *J Ophthalmol.* 2020;2020:6431314
177. Gerten G, Schultz M, Oberheide U. Treating capsule contraction syndrome with a femtosecond laser. *J Cataract Refract Surg* 2016; 42(9): 1255–1261
178. Wu BM, Williams GP, Tan A, Mehta JSA. Comparison of different operating systems for femtosecond lasers in cataract surgery. *J Ophthalmol* 2015; 2015: 616478

179. Dick HB, Schultz TA. Review of laser-assisted versus traditional phacoemulsification cataract surgery. *Ophthalmol Ther* 2017; 6 (1): 7–18
180. Trinh T, Solomon B, Mimouni M, Cohen E, Gouvea L, Santaella G, et al. Outcomes of femtosecond laser-assisted cataract and refractive lens surgery in patients with prior radial keratotomy. *J Cataract Refract Surg*. 2022;48(4):449-55
181. Friehmann A, Assia EI. Femtosecond Laser Capsulotomy in Previous Radial Keratotomy. *Cornea*. 2023;42(6):699-701
182. Masket S, Belani S. Combined preoperative topical atropine sulfate 1% and intracameral nonpreserved epinephrine hydrochloride 1:2500 for management of intraoperative floppy-iris syndrome. *J Cataract Refract Surg* 2007; 33(4): 580–582
183. Anisimova NS, Arbisser LB, Petrovski G, et al. Effect of NSAIDs on pupil diameter and expression of aqueous humor cytokines in FLACS versus conventional phacoemulsification. *J Refract Surg* 2018; 34(10): 646–652
184. Kiss HJ, Takacs AI, Kranitz K, et al. One-day use of preoperative topical nonsteroidal anti-inflammatory drug prevents intraoperative prostaglandin level elevation during femtosecond laser-assisted cataract surgery. *Curr Eye Res* 2015; 41: 1–4
185. Jirasková N, Rozsival P and Lešták L. Use of Malyugin pupil expansion ring in femtosecond laser-assisted cataract surgery. *J Clin Exp Ophthalmol* 2013; 4: 6
186. Shajari M, Khalil S, Mayer WJ, et al. Comparison of 2 laser fragmentation patterns used in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg* 2017; 43(12): 1571-1574
187. Chee SP, Chan NS, Yang Y, Ti SE. Femtosecond laser-assisted cataract surgery for the white cataract. *Br J Ophthalmol*. 2019;103(4):544-50
188. Conrad-Hengerer I, Hengerer FH, Joachim SC, et al. Femtosecond laser–assisted cataract surgery in intumescent white cataracts. *J Cataract Refract Surg*. 2014; 40 (1): 44–50
189. Issa M, Tong L, Somani S. Argentinian flag sign during refractive laser-assisted cataract surgery - A case report. *Am J Ophthalmol Case Rep*. 2023;29:101764
190. Chee S-P, Chan NS-W, Yang Y, et al. Femtosecond laser-assisted cataract surgery for the white cataract. *Br J Ophthalmol* 2019; 103 (4): 544–550

191. Coelho RP, Neumann RZ, Vieira Messias AM. Comparison between FLACS and Nd:YAG laser in preventing the Argentinian flag sign in intumescent white cataracts. *J Cataract Refract Surg*. 2023;49(2):213-4
192. Huang P-W, Huang W-H, Tai Y-C, et al. Femtosecond laser-assisted cataract surgery in a patient with traumatic cataract and corneal opacity after LASIK: a case report. *BMC Ophthalmol* 2020; 20(1): 218
193. Noecker R. Laser cataract surgery in the glaucoma patient. *Ophthalmol Manag*. 2017; 21: 8–10
194. Wang YH, He YZ, Chiang MH, Lee CY, Wu CL. Association between Ocular Parameters and Intraocular Pressure Elevation during Femtosecond Laser-Assisted Cataract Surgery in Open-Angle Glaucoma and Nonglaucoma Individuals. *Journal of Personalized Medicine*. 2022;12(2)
195. Abell RG, Darian-Smith E, Kan JB, et al. Femtosecond laser-assisted cataract surgery versus standard phacoemulsification cataract surgery: Outcomes and safety in more than 4000 cases at a single center. *J Cataract Refract Surg* 2015; 41(1): 47-52
196. Day AC, Burr JM, Bennett K, et al. Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT noninferiority RCT. *Health Technol Asses* 2021; 25:1–68
197. Shaheen MS, AbouSamra A, Helaly HA, et al. Comparison between refractive outcomes of femtosecond laser assisted cataract surgery and standard phacoemulsification. *BMC Ophthalmol* 2020; 20(1): 1
198. Koch DD, Kohnen T, Obstbaum SA, Rosen ES. Format for reporting refractive surgical data. *J Cataract Refract Surg*. 1998;24(3):285-7
199. Alió JL, Mulet ME. Presbyopia correction with an anterior chamber phakic multifocal intraocular lens. *Ophthalmology*. 2005;112(8):1368-74
200. Fernández-Vega L, Alfonso JF, Rodríguez PP, Montés-Micó R. Clear lens extraction with multifocal apodized diffractive intraocular lens implantation. *Ophthalmology*. 2007;114(8):1491-8
201. Brenner LF, Gjerdrum B, Aakre BM, Lundmark PO, Nistad K. Presbyopic refractive lens exchange with trifocal intraocular lens implantation after corneal laser vision correction: Refractive results and biometry analysis. *Journal of Cataract & Refractive Surgery*. 2019;45(10):1404-15

202. Pérez-Santonja JJ, Alió JL, Jiménez-Alfaro I, Zato MA. Surgical correction of severe myopia with an angle-supported phakic intraocular lens. *Journal of Cataract & Refractive Surgery*. 2000;26(9):1288-302
203. Gomel N, Negari S, Frucht-Pery J, Wajnsztajn D, Strassman E, Solomon A. Predictive factors for efficacy and safety in refractive surgery for myopia. *PLoS One*. 2018;13(12):e0208608
204. Monteiro T, Correia FF, Franqueira N, Mendes JC, Pinto C, Vaz F. Long-term efficacy and safety results after iris-fixated foldable phakic intraocular lens for myopia and astigmatism: 6-year follow-up. *Journal of Cataract & Refractive Surgery*. 2021;47(2):211-20
205. van Rijn GA, Gaurisankar ZS, Saxena R, Gibbes D, Jongman HP, Haasnoot GW, et al. Implantation of an iris-fixated phakic intraocular lens for the correction of hyperopia: 15-year follow-up. *Journal of Cataract & Refractive Surgery*. 2021;47(6):748-58
206. Reinstein DZ, Archer TJ, Srinivasan S, Mamalis N, Kohnen T, Dupps WJ, Jr., et al. Standard for reporting refractive outcomes of intraocular lens-based refractive surgery. *J Cataract Refract Surg*. 2017;43(4):435-9
207. Bo L, Wenjuan D. Efficacy of FLACS and conventional CPS in the treatment of cataract: a Meta-analysis. *Revista de Psiquiatria Clinica*. 2023;50(6):244-53
208. Ashena Z, Maqsood S, Ahmed SN, Nanavatya MA. Effect of Intraocular Lens Tilt and Decentration on Visual Acuity, Dysphotopsia and Wavefront Aberrations. *Vision*. 2020;4(3):41
209. Lawu T, Mukai K, Matsushima H, Senoo T. Effects of decentration and tilt on the optical performance of 6 aspheric intraocular lens designs in a model eye. *J Cataract Refract Surg*. 2019;45(5):662-8
210. Chen XY, Wang YC, Zhao TY, Wang ZZ, Wang W. Tilt and decentration with various intraocular lenses: A narrative review. *World J Clin Cases*. 2022;10(12):3639-46
211. Pérez-Merino P, Marcos S. Effect of intraocular lens decentration on image quality tested in a custom model eye. *J Cataract Refract Surg*. 2018;44(7):889-96
212. Akaishi M, Teshigawara T, Hata S, Meguro A, Mizuki N. Multiple linear regression model for improving accuracy of capsulorhexis size calculation in femtosecond laser-assisted cataract surgery for adults: a retrospective single-center study. *BMC Ophthalmology*. 2023;23(1)

213. Cornaggia A, Clerici LM, Felizietti M, Rossi T, Pandolfi A. A numerical model of capsulorhexis to assess the relevance of size and position of the rhexis on the IOL decentering and tilt. *Journal of the Mechanical Behavior of Biomedical Materials*. 2021;114:104170
214. Montrimas A, Žemaitienė R, Yao K, Grzybowski A. Chord mu and chord alpha as postoperative predictors in multifocal intraocular lens implantation. *Graefes Arch Clin Exp Ophthalmol*. 2023
215. Pérez-Gracia J, Varea A, Ares J, Vallés JA, Remón L. Evaluation of the optical performance for aspheric intraocular lenses in relation with tilt and decenter errors. *PLoS One*. 2020;15(5):e0232546
216. Wang R, Long T, Gu X, Ma T. Changes in angle kappa and angle alpha before and after cataract surgery. *J Cataract Refract Surg*. 2020;46(3):365-71.
217. Assia EI, Wong JXH, Shochot Y. The Effect on Post-Operative Intraocular Lens Centration by Manual Intraoperative Centration versus Auto-Centration. *Clin Ophthalmol*. 2020;14:3475-80
218. Mirshahi A, K AP. Changes in Pupil Area during Low-energy Femtosecond Laser-assisted Cataract Surgery. *J Ophthalmic Vis Res*. 2019;14(3):251-6
219. Germano CS, Germano RAS, Cid FB, Germano FAS, Carricondo PC, Germano JE. Comparison of pupillary diameter variation between conventional phacoemulsification versus femtosecond laser-assisted cataract surgery. *Arquivos Brasileiros de Oftalmologia*. 2022;85(1):25-9
220. Grzybowski A, Kanclerz P. Methods for achieving adequate pupil size in cataract surgery. *Curr Opin Ophthalmol*. 2020;31(1):33-42
221. Lazar R, Degen J, Fiechter AS, Monticelli A, Spitschan M. Regulation of pupil size in natural vision across the human lifespan. *R Soc Open Sci*. 2024;11(6):191613
222. Plainis S, Panagopoulou S, Charman WN. Longitudinal changes in objective accommodative response, pupil size and spherical aberration: A case study. *Ophthalmic Physiol Opt*. 2024;44(1):168-76
223. Boden KT, Julich-Haertel H, Rickmann A, Szurman P, Januschowski K, Seitz B, et al. Efficacy of a new fragmentation pattern in femtosecond laser-assisted cataract surgery with the Ziemer FEMTO LDV Z8. *International Ophthalmology*. 2023;43(7):2237-45

224. Ou Y, Wang Y, Wu T. Comparison of ultrasound energy consumption between low-energy femtosecond laser-assisted cataract surgery and conventional phacoemulsification cataract surgery in patients with different cataract densities. *Eur J Ophthalmol*. 2023;33(3):1373-9
225. Lin HY, Kao ST, Chuang YJ, Chen S, Lin PJ. Comparison of cumulative dispersed energy between conventional phacoemulsification and femtosecond laser-assisted cataract surgery with two different lens fragmentation patterns. *Lasers in Medical Science*. 2022;37(2):843-8
226. Medhi S, Senthil Prasad R, Pai A, et al. Clinical outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification: A retrospective study in a tertiary eye care center in South India. *Indian J Ophthalmol* 2022; 70(12): 4300-4305
227. Lin HY, Chuang YJ, Lin PJ. Surgical outcomes with high and low pulse energy femtosecond laser systems for cataract surgery. *Sci Rep*. 2021;11(1):9525
228. Slezak F, Thumann G, Kropp M, Cvejic Z, De Clerck EEB, Bravetti GE, et al. Comparison of Conventional and Femtosecond Laser-Assisted Cataract Surgery Regarding Macula Behavior and Thickness. *Medicina (Kaunas)*. 2023;59(4)
229. Alvarez-Ascencio D, Prado-Larrea C, Jimenez-Roman J, Castañeda-Diez R. Long-term visual field changes after femtosecond laser-assisted cataract surgery in glaucoma patients, case series. *American Journal of Ophthalmology Case Reports*. 2021;23
230. Devience EX, Awidi A, Kalarn S, DeVience S, Bui B, Munir WM, et al. Predictors of intraocular pressure reduction after femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: a prospective trial. *International Ophthalmology*. 2023;43(1):285-92
231. Chen DZ, Chee S-P. Femtosecond laser-assisted cataract surgery for complex cataracts – A review. *Indian Journal of Ophthalmology*. 2024;72(5):629-36
232. Roberts HW, Wagh VK, Mullens IJM, Borsci S, Ni MZ, O'Brart DPS. Evaluation of a hub-and-spoke model for the delivery of femtosecond laser-assisted cataract surgery within the context of a large randomised controlled trial. *Br J Ophthalmol*. 2018;102(11):1556-63
233. Villavilla-Castillo J, Pérez-Casaseca C, Espejo-de-Los-Riscos E, Fernández-Baca-Vaca G, Fernández-Baca-Casares I, Piñero-Llorens DP, et al. Study of the efficiency and

workflow of femtosecond laser-assisted cataract surgery in a Spanish public hospital. J Fr Ophtalmol. 2021;44(8):1190-201

234. Li L, Zhang Y, Li M, Zhang Z, Dang Y, Yang Y. Current Application and Progress of Laser Technology in Ophthalmology. Zhongguo Jiguang/Chinese Journal of Lasers. 2022;49(5)

235. Vasquez-Perez A, Simpson A, Nanavaty MA. Femtosecond laser-assisted cataract surgery in a public teaching hospital setting. BMC Ophthalmol 2018; 18: 26

236. Bartlett JD, Miller KM. The economics of femtosecond laser-assisted cataract surgery. Curr Opin Ophthalmol (2016) 27:76–81