Guest Editorial

Multimodal imaging for refractive surgery: *Quo vadis?*

The emergence and the popularization of elective refractive surgery have boosted a major scientific evolution in ophthalmology. The elective essence of such procedures typically performed in patients with no ocular pathology but refractive errors determined the fundamental need to continuously striving for higher standards of safety and efficiency. Besides the innovations and improvements in the industry of lasers, intraocular lenses, and other surgical devices, major scientific advances are recognized in the understanding of the biological wound healing response after these procedures.[1] Such knowledge opened the horizon for advances in genetic and molecular biology that are promising to preventing complications such as corneal haze.[2] Furthermore, we have witnessed a continuously evolving revolution on diagnostic/imaging tools for characterizing different aspects of the cornea, lens, and the whole optics of the eye.[3]

Refractive surgery has also impacted the management of corneal conditions, such as keratoconus and ectatic diseases.[4] In addition, the need for advancing the field of therapeutic techniques to manage the reasonably infrequent complications after refractive procedures has been recognized.[5] Nevertheless, the distinction from elective refractive procedures aiming for patient satisfaction through the reduction or elimination of the need for refractive correction and the therapeutic procedures for visual rehabilitation became of relevance, considering such different goals and success threshold levels.[6]

"If you know the enemy and you know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle" Sun Tzu (孫子 ĭ ; The Art of War).

The classic ancient military-strategic wisdom from Sun Tzu that dates the sixth century B.C. is a metaphor for the understanding of the why's and the how's which the refractive surgeon should operate to prevent complications and optimize outcomes. Table 1 refers to some of the most important complications, considering the conditions that are to be detected, and the available technologies.

The nomenclature for the different diagnostic test became a major consideration for standardizing scientific communication. For example, front surface Placido's disk reflection-based corneal topography is distinguished from corneal tomography, which provides three-dimensional characterization with front and back surfaces elevation and thickness mapping.[17] In addition, the ability to depict layers of the cornea such as the epithelium merits for further differentiation, as segmental or layered tomography.[9] Furthermore, besides epithelial thickness mapping, the ability of high-resolution OCT for characterizing Bowman's roughness,[18] and also calculating the virtual curvature of the anterior stroma/Bowman's surface after mathematically eliminating the epithelium were shown.[19]

Considering clinical interpretation of the data from diagnostic devices, there is significant inter-observer variability in the subjective classifications using the same scale, and also significant intra-observer variability between color-coded scales.[20] Thereby, the need for considering objective metrics based on accuracy testing is indisputable.[8] Also, artificial intelligence (AI) has been found to augment the clinical applications of diagnostic data, including the ability for detecting mild forms of ectasia.[19,21]

The need for depicting the innate susceptibility of each individual cornea for ectasia progression was recognized,[22] leading to the quest of going beyond and not over classic tests such as computerized topography and central corneal thickness.[7] In fact, the characterization of corneal biomechanical properties has been a significant area for research and development.[23] There are two instruments commercially available, the Ocular Response Analyzer (ORA- Reichert Ophthalmic Instruments, Depew, New York) and the Corvis ST (OCULUS Optikgeräte GmbH, Wetzlar, Germany).[23] In addition, Brillouin technology has also shown clinical utility by showing focal biomechanical disturbance within the protrusion area in ectatic eyes, which endorses the concept that biomechanical failure initiates with a focal decompensation.[24]

The integration of corneal shape and biomechanics has been shown to further enhance the ability for screening cases at risk for ectasia after laser vision correction.[25] The Tomographic and Biomechanical Index (TBI)[26] was generated by AI, combining Scheimpflug-based corneal tomography and biomechanical assessments from Oculus Pentacam HR and Corvis ST. The original TBI study included 94 eyes with normal topography (NT) based on objective data, from very asymmetric ectasia (VAE) patients, in which clinical diagnosis of ectasia was confirmed in the fellow eye.[26] Such cases with highly asymmetric ectasia were used in different approaches for developing and testing different diagnostic approaches to enhance ectasia diagnosis.[27,28] The TBI was shown to provide greater accuracy for detecting for detecting mild forms of ectasia among eyes with than other variables, including Belin/Ambrósio Enhanced Ectasia Final Deviation (BAD-D) and Corneal Biomechanical Index (CBI).[23,26] The optimized cutoff of 0.29 for TBI would lead to 90.4% of sensitivity for the VAE-NT cases, with less than 5% "false-positive" results.[26] Interestingly, such normal eyes with high TBI may be the actual cases that we need to detect with high risk for ectasia progression, whereas the VAE-NT cases with low TBI may represent true unilateral ectasia cases, which is in agreement with the global consensus that true unilateral keratoconus does not exist, but secondary ectasia induced by a mechanical process may occur unilaterally.[29] The current understanding is that the integration of the diagnostic data epitomizes the inherent predisposition or susceptibility for biomechanical decompensation and ectasia progression. As for any AI algorithm, external validation is mandatory, even if the training set had included adequate internal validation strategies such as the leave one out cross-validation (LOOCV) used in the TBI.[26] Although the initial external validation tests were in high agreement with the original study, there are reports of lower accuracy for the TBI among VAE cases.[23] These cases elude to the possibility for optimization of the algorithm through reinforced learning, which is a major advantage of AI. Thereby,

Table 1: Rationale the strategies on using refractive imaging for preventing complications

Complication	What are we screening for preoperatively	How to screen for it
Progressive keratectasia	Detect mild forms of keratoconus, ectasia susceptibility, considering the refractive treatment and the impact on the cornea	Placido-disk corneal topography,[7] Scheimpflug tomography,[8] OCT (or VHF US) segmental tomography,[9] and biomechanical assessments.[10] Integration with the impact on the cornea by LVC[11]
Tear dysfunction and dry eye	Characterize contact lens intolerance, dry eye preoperatively; poor ocular surface health	Questionnaires, tear film osmolarity and inflammation biomarker, tear film stability and optical regularity, membomian gland visualization with infrared.[12]
Ocular pain/dysesthesia	Assess tear dysfunction syndrome[12,13]; systemic neuropathy; low vitamin B_{12}[14] or D	Confocal microscopy Esthesiometry[12,13]
Epithelialization of the interface (SmILE and LASIK)	Detect occult corneal basement membrane dystrophy	High-resolution OCT for the evaluation of the basement epithelial layer.[15]
Severe quality of vision symptoms	Assess preoperative visual performance	Mesopic/scotopic pupil size, corneal/ocular wavefront[16]

a novel optimized version of the TBI has been development with significantly higher accuracy than the first version of the algorithm which was already the best individual parameter for ectasia detection (unpublished data, 2020).

Besides corneal analysis, ocular aberrometry has been widely applied in refractive surgery for the investigation of low and higher-order aberrations, particularly for designing wavefront-guided refractive surgery.[30] The dysfunctional lens index (DLI) derives from integrated whole eye ray-tracing and corneal aberrometry, which showed a high negative linear correlation with the subjective biomicroscopy derived LOCS III and Scheimpflug derived nuclear opalescence score, which facilitates the clinical decision if cataract surgery is indicated.[31]

Although we contemplate the advances on corneal and refractive imaging, this is predictable that molecular biology will play a higher role. For example, in the characterization of keratoconus, considering the molecular and cellular changes associated with the pathogenesis of ectasia, including extracellular matrix degeneration. an up-regulation of degradative enzymes, oxidative stress and inflammation may further enhance the ability for ectasia characterizafion[32,33] In fact, the future is bright for refractive surgery and imaging technologies.

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Prof. Renato Ambrósio trained in Ophthalmology at the Instituto de Oftalmologia Tadeu Cvintal (São Paulo) in 1999, followed by a fellowship in Refractive Surgery and Cornea at the University of Washington (Seattle, WA) in October 2002, and PhD at the Faculdade de Medicina da Universidade de São Paulo in May 2004.

In 2006, he was elected the President of the Brazilian Society of Administration in Ophthalmology, being in this position until July 2010. From 2012 until 2014, he was the last president of the Brazilian Society of Refractive Surgery before the incorporation with the Brazilian Society of Cataract and Implants for the creation of BRASCRS. He was also the vice-president of the Brazilian Council of Ophthalmology from 2013 until 2015 and is the current president of the International Society of Refractive Surgery (ISRS; 2020-22).

In 2007, he founded The Rio de Janeiro Corneal Tomography and Biomechanics Study Group, from which over one hundred publications have originated. He is an affiliate professor of the Federal University of São Paulo (stricto sensu) and Adjunct Professor of the Federal University of the State of Rio de Janeiro (UNIRIO).

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