Role of Percent Tissue Altered on Ectasia After LASIK in Eyes With Suspicious Topography

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ABSTRACT

PURPOSE: To investigate the association of the percent tissue altered (PTA) with the occurrence of ectasia after LASIK in eyes with suspicious preoperative corneal topography.

METHODS: This retrospective comparative case–control study compared associations of reported ectasia risk factors in 129 eyes, including 57 eyes with suspicious preoperative Placido-based corneal topography that developed ectasia after LASIK (suspect ectasia group), 32 eyes with suspicious topography that remained stable for at least 3 years after LASIK (suspect control group), and 30 eyes that developed ectasia with bilateral normal topography (normal topography ectasia group). Groups were subdivided based on topographic asymmetry into high- or low-suspect groups. The PTA, preoperative central corneal thickness (CCT), residual stromal bed (RSB), and age (years) were evaluated in univariate and multivariate analyses.

RESULTS: Average PTA values for normal topography ectasia (45), low-suspect ectasia (39), high-suspect ectasia (36), low-suspect control (32), and high-suspect control (29) were significantly different from one another in all comparisons (P < .003) except high- and low-suspect ectasia groups (P = .033), and presented the highest discriminative capability of all variables evaluated. Age was only significantly different between the high-suspect ectasia and normal topography ectasia groups, and CCT was not significantly different between any groups. Stepwise logistic regression revealed that the PTA as the most significant independent variable (P < .0001), with RSB the next most significant parameter.

CONCLUSIONS: There remains a significant correlation between PTA values and ectasia risk after LASIK, even in eyes with suspicious corneal topography. Less tissue alteration, or a lower PTA value, was necessary to induce ectasia in eyes with more remarkable signs of topographic abnormality, and PTA provided better discriminative capabilities than RSB for all study populations.

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sufficient to induce postoperative ectasia in patients with suspicious corneal topographic patterns.

The purpose of this study was to evaluate PTA values in eyes with suspicious topographic patterns that did and did not develop ectasia after LASIK and compare the relative importance of PTA to other known risk metrics, especially residual stromal bed thickness (RSB).

**PATIENTS AND METHODS**

This retrospective comparative case–control study included eyes that developed ectasia after LASIK for myopia and myopic astigmatism with suspicious preoperative Placido disk-based corneal topography (suspect ectasia group) and a contemporaneous population comprising eyes with suspicious preoperative Placido disk-based corneal topography that underwent uncomplicated LASIK for myopia and myopic astigmatism without developing ectasia with at least 3 years of postoperative follow-up (suspect control group). For comparison, an additional group comprising eyes that developed ectasia with bilateral normal preoperative topography, previously published,7 was also included (normal topography ectasia group). The study was approved by the University of São Paulo and Emory University Institutional Review Boards and adhered to the tenets of the Declaration of Helsinki.

The following preoperative information was obtained for all cases: patient age; gender; preoperative CCT based on ultrasound pachymetry; Placido disk-based color corneal topography; manifest refraction spherical equivalent in diopters (D); and corrected distance visual acuity (CDVA). Perioperative and postoperative information included date of surgery (year), measured LASIK FT, calculated central AD obtained from the excimer laser print outs, and calculated RSB. RSB was derived from the following formula: RSB = CCT – FT – AD. LASIK flap measurements were taken either intraoperatively with ultrasound pachymetry using the subtraction method or postoperatively with optical coherence tomography (OCT) or confocal microscopy.11

The PTA during LASIK was obtained as previously described.7 For this study, preoperative topographic pattern groups were defined based on Placido disk analysis, as follows:

A. Normal (Class 0): regular and symmetric patterns (including round, oval, or symmetric bowtie patterns) or mildly asymmetric steepening < 0.5 D without a skewed radial axis (Figure 1A).

B. Low suspect (Class 1): asymmetric bowtie pattern with ≥ 0.5 D but < 1.0 D asymmetric steepening in any direction without a skewed radial axis (Figure 1B).

C. High suspect (Class 2): Inferior steep/skewed radial axis, including a significant skewed radial axis with or without inferior steepening, or ≥ 1 D of inferior steepening in some areas but an inferior-superior value of < 1.4 or patterns not otherwise consistent with forme fruste keratoconus.9,12,13 (Figure 1C).

![Illustrative pictures of axial curvature topographic patterns in the study.](image)

**Figure 1.** Illustrative pictures of axial curvature topographic patterns in the study. (A) Normal patterns, including regular and symmetric patterns (including round, oval, or symmetric bowtie patterns) or mildly asymmetric steepening < 0.5 diopters (D) without a skewed radial axis. (B) Low-suspect patterns, with asymmetric bowtie ≥ 0.5 D but < 1.0 D asymmetric steepening in any direction without a skewed radial axis. (C) High-suspect patterns, with inferior steep/skewed radial axis, including a significant skewed radial axis with or without inferior steepening, or ≥ 1 D of inferior steepening in some areas but an inferior-superior value of < 1.4 or patterns not otherwise consistent with forme fruste keratoconus.
LASIK with high-suspect preoperative topography; low-suspect ectasia (eyes developing ectasia after LASIK with low-suspect preoperative topography); and normal topography ectasia (eyes developing ectasia after LASIK with normal preoperative topography).

Postoperative corneal ectasia was defined as progressive inferior steepening, increasing myopia and astigmatism, loss of uncorrected visual acuity, and often loss of CDVA. All patients with ectasia included in the analysis had uneventful surgery with initially good outcomes prior to developing the aforementioned findings.

Patients with ectasia were included if they had all relevant necessary preoperative and perioperative information for analysis. Eyes that had more than one excimer laser refractive surgery or any other ocular surgery were excluded. Patients with a family history of keratoconus were excluded. Ectasia case and control data were collected from cases referred to the authors’ institutions: Universities of Rio de Janeiro and São Paulo, Emory Eye Center, The Cleveland Clinic, and University Center Hospital of Bordeaux. A variety of different Placido imaging devices were used and analyzed. These cases did not have LASIK in our institutions, so although Placido topography images were available for author review in all included cases, the specific devices used to measure ultrasound pachymetry were not available for review.

Statistical analyses were performed using JMP software (version 8.0; SAS Institute, Inc., Cary, NC). Although PTA is a continuous variable, it was also evaluated as a discontinuous risk factor (cut-off) variable based on analysis of receiver operating characteristic (ROC) curve, which revealed specific cut-off values with the maximized sum of sensitivity and specificity for high- and low-suspect topography pattern, respectively. Although not intended to be used as a single metric, this cut-off was investigated to evaluate where the proposed metric (PTA) would stand compared to other recognized risk factors in this patient population and potential differences in sensitivity for the same PTA value when comparing high- and low-suspect topography pattern groups.

Logistic stepwise regression was performed to investigate the significance of risk factors as predictors of the event (ectasia). Normality of data was evaluated with the Kolmogorov–Smirnov test. When parametric analysis was not possible, the non-parametric Wilcoxon analysis was used to compare data between the two groups. The analysis of primary outcome measures was based on a non-normal distribution of the data. When parametric analysis was possible, the Student’s t test was used to compare the outcomes. Categorical variables were compared using either chi-square or Fisher exact test as appropriate. To correct for multiple comparisons performed in this study (approximately 25) using the Bonferroni method, only individual P values less than .003 were considered significant. Continuous data were expressed as mean values ± standard deviation and confidence interval. Categorical variables were expressed as frequency (n) and percent (%). Level of correlation (Spearman’s rho and confidence interval) between PTA and topography pattern was also investigated in the group of eyes that developed ectasia.

RESULTS

The study population included 87 eyes with ectasia (40 high suspect, 17 low suspect, and 30 normal topography), and 32 control eyes (17 high suspect and 15 low suspect). Eighty-one eyes (93%) that developed ectasia had the LASIK flap created by mechanical microkeratome and 6 (7%) by femtosecond laser. Table 1 shows the mean values, range, and confidence interval of the main outcomes. Control groups had significantly lower PTA values, with a tighter data spread, than ectasia groups. PTA increased as topography suspect group decreased (less suspicious) in the ectasia groups (Figure 2). Mean values of RSB were relatively high in the groups that developed ectasia. In the high-suspect group, 34 of 40 eyes (85%) that developed ectasia had RSB of 300 µm or greater, 5 eyes (12.5%) had RSB between 280 and 299 µm, and 1 eye (2.5%) had RSB less than 250 µm, whereas 11 of 17 low-suspect eyes (76%) that developed ectasia presented a RSB of 300 µm or greater and 4 of 17 eyes (24%) had a RSB between 265 and 299 µm.

PATIENT VARIABLES: COMPARISON OF MEANS

Table 2 shows statistical comparisons between groups. PTA was the most significant differentiating variable and was significantly different in all comparisons except high- versus low-suspect ectasia groups. RSB was significantly different in most comparisons except high- versus low-suspect ectasia groups and low-suspect controls and high-suspect ectasia eyes. CCT was not significantly different in any comparison, and age was only significant between the high-suspect ectasia and normal topography ectasia groups.

Spearman’s rho (-0.636), and confidence interval of correlation (-0.722 to -0.450) revealed a statistically significant (P < .0001) inverse correlation between topographic pattern and PTA in the ectasia group (Figure A, available in the online version of this article), whereas no significant correlation was found between age and PTA. There was a wide distribution of age with different PTA values in the ectasia group.
and non-linear correlation (Figure B, available in the online version of this article).

**LOGISTIC STEPWISE REGRESSION AND ROC CURVE**

Using a stepwise logistic regression analysis, PTA and RSB were independent significant variables ($P < .0001$), with PTA having higher discriminative capabilities than RSB. The other factors investigated were not significant independent predictors of ectasia. ROC curve revealed cut-off PTA values to differentiate between eyes with high and low risk of ectasia of 30% in the group with more topographic irregularity (high suspect), and 32% in the group with less topographic irregularity (low suspect). The ROC curve also revealed that, for similar values of PTA, the sensitivity in determining high ectasia risk was lower in eyes with more remarkable signs of topographic abnormality. In the high-suspect group, PTA (>$30\%$) would have considered 93% of eyes at high risk compared to only 13% based on RSB ($<300\ \mu m$), whereas in the low-suspect group, PTA (>$32\%$) would have considered 94% of eyes at high risk compared to 24% based on RSB ($<300\ \mu m$) (Figure 3).

**DISCUSSION**

This aggregate analysis provides evidence that PTA is a significant factor in the development of ectasia after LASIK in eyes with suspicious preoperative Placido-based corneal topography. Although PTA was high (45%) for eyes that developed ectasia with normal topographic patterns, this value decreased significantly in eyes that developed ectasia with more suspicious topographic patterns (36% to 39%).

Abnormal corneal topography has been shown to be the most robust risk factor for postoperative ectasia.$^{8-10}$ Using these suspicious topographic patterns and relative asymmetry as a surrogate for corneal strength measurements, these findings signify that less tissue alteration was necessary to induce ectasia in eyes with less biomechanically stable corneas. Further, our results demonstrate that in eyes with suspicious topographic patterns, eyes submitted to less biomechanical alteration (lower PTA values) were able to be more stable over time.

These findings are in some ways intuitive; the more a cornea is altered surgically, the greater its risk for ectasia. Given the depth-dependent nature of corneal tensile strength, PTA represents the most relevant part of the anterior corneal stroma that is ablated, resulting in corneal weakening in increasing proportion.$^{2,3,6,7,14,15}$ However, the specific relationship between PTA and suspicious topography has not previously been directly explored.
In multivariate analysis, PTA was a more significant factor than RSB for many group comparisons, and was a more significant factor than CCT or age for all group comparisons (Table 2). When matching for topography suspect level (similar suspect pattern), RSB was a robust factor, meaning that increasing RSB still reduced ectasia risk. Age was most significant for patients with normal topographic findings, reinforcing the relationship between age in interpreting subtle topographic asymmetry findings and the importance of using age in screening algorithms for these patients. It seems likely that some combination of PTA, RSB, and age may yield the most robust screening metric to model the biomechanical effects of photorefractive keratectomy (PRK) and LASIK.

Interestingly, because PTA addresses the anterior corneal stroma in a depth-dependent manner, it may only indirectly apply to small incision lenticule extraction (SMILE), in which the anterior-most fibers are maintained. We are not aware of any cases of ectasia that have been reported after SMILE to date; however, the findings of lower PTA values in eyes with more suspicious topographies indicate that caution is warranted when considering SMILE in eyes with clear topographic abnormalities until or unless it can be determined that these eyes may safely undergo this procedure.

Although PTA average values were distinguishable between groups in patients with suspicious topography...
phies, there was significantly greater overlap in PTA ranges than between normal topography ectasia eyes and controls (Figure 2). The immediate consequences of the presence of biomechanical weakening, represented by a suspicious topographic pattern, is that the sensitivity of any other risk factor will have its importance reduced; therefore, it is notably more difficult to determine a cut-off limit for PTA after which the risk of ectasia increases in these eyes, despite the higher discriminative capability compared to RSB. The analysis of ROC curve is in agreement with this, because for a similar value of cut-off point the high-suspect topography pattern group derives a lower sensitivity (80%) value compared to the low-suspect topography pattern group (95%).

It should be clear that these results do not indicate that is safe to perform LASIK in eyes with suspicious topographic patterns simply by respecting a low PTA limit. These findings merely demonstrate that lower PTA values are associated with increased corneal stability and therefore reduced ectasia risk even in eyes with suspicious preoperative topography.

We defined suspicious topographic patterns as clearly and unambiguously as possible for this study. However, we believe that other patterns also warrant additional consideration, even though they are less amenable to be clearly quantified or classified. These patterns include significant between-eye topographic asymmetry, even if neither eye’s topographic pattern is in itself decidedly abnormal, and young patients with against-the-rule astigmatism.

There are case reports where PTA With Ectasia After LASIK/Santhiago et al (in this last case ≥ 20%) had a PTA of 34, which corresponds to 16-20% of their patients had available preoperative topographies, and most of those (75%) had abnormal topographies, and most of those (75%) had abnormal topographies. Further, most of their patients had assumed rather than measured flap thickness and/or ablation depth values. Nevertheless, their findings were in general agreement with ours, with the corneal ratio (PTA) having a higher correlation with ectasia than RSB. The PTA was a more prevalent risk factor compared to RSB in eyes that developed ectasia.

Recently Bühren et al. demonstrated in a series of ectasia cases that other asymmetric patterns, not classic keratoconus suspect patterns, were significantly different from the normal stable population and should also be considered suspicious. In their group of 10 eyes that developed ectasia, the mean PTA value was greater than 40 (mean: 47%, range: 34% to 53%), with 80% having a PTA of 45% or greater, high enough to cause ectasia in eyes without topographic abnormalities, whereas 20% had a PTA of 34, which corresponds to the values sufficient to alter a cornea with suspicious topographic patterns in our study.

Brenner et al. investigated a group of eyes that developed ectasia and discussed a similar concept to PTA they termed the “corneal ratio” (ratio of the sum of flap and ablation depths and pachymetry). Only 80% of their patients had available preoperative topographies, and most of those (75%) had abnormal topography. Further, most of their patients had assumed rather than measured flap thickness and/or ablation depth values. Nevertheless, their findings were in general agreement with ours, with the corneal ratio (PTA) having a higher correlation with ectasia than RSB. They also found that a corneal ratio (PTA) greater than 37% was associated with a higher ectasia risk and also with the severity of ectasia, and the corneal ratio (PTA) threshold for ectasia was lower in eyes with less suspicious topographies. They also showed the group that presented the most significant vision loss had a mean CCT of 538 µm and a mean RSB of 306 µm with a corneal ratio (PTA) of 43%, again corroborating our findings that the more individualized measurement (PTA)
is more representative of the ectasia risk than specific cut-off values for CCT or RSB.7,14

It would be ideal to be able to better quantify topographic patterns deemed suspicious in this study, even assigning them specific numeric values to use in modeling. However attractive that may be, that has proved challenging for any diagnostic modality to do. Most quantified scoring approaches to date have found significant overlap even between known control and abnormal (keratoconus) populations.22-24 It is also attractive to use automated screening metrics when interpreting topography or tomography, but this has also proven challenging. In a recent study by Bae et al.,25 advanced tomographic screening metrics were unable to differentiate between the less affected eyes in patients with keratoconus and normal control eyes. In that study, anterior curvature was the most robust differentiating feature.

There are limitations to this study, predominantly based on its retrospective design. As a retrospective study, the data available were limited, which limited the number of cases that could be analyzed. Further, epithelial thickness measurements were not obtained to give a completely accurate analysis of stromal tissue altered. Epithelial thickness variability may play a small role in PTA measurements in addition to its potential role in topographic interpretation and patient screening.20-28 Epithelial thickness does not vary significantly by overall corneal thickness, so the relative stroma altered in any PTA measurement will increase slightly (generally less than 1%) with increasing corneal thickness. However, differences in epithelial thickness among the eyes included in the study would likely not be enough to have a significant impact on the PTA comparisons. Further, additional tomographic information was not available and was therefore not analyzed. This was not the purpose of this study; however, future work with a data set containing both data to determine PTA in addition to other proposed screening metrics could further elucidate the importance of PTA in screening. LASIK flap thicknesses were derived using different strategies (subtraction pachymetry or OCT analysis); however, these measures have been found to be reliably close to one another30,31 so we do not view this as a significant issue in our analysis.

Our results demonstrate that PTA was significantly associated with the development of ectasia in eyes with suspicious topography. In eyes that developed ectasia, those with less suspicious topographic patterns had higher PTA values than those with more suspicious patterns. For stable control eyes, PTA values were significantly lower than those for eyes developing ectasia with comparable topographic patterns.

### Author Contributions

Study concept and design (MRS, SEW, JBR); data collection (MRS, DS, RRK, MLRM, JBR); analysis and interpretation of data (MRS, JBR); writing the manuscript (MRS, SEW, JBR); critical revision of the manuscript (MRS, DS, SEW, RRK, MLRM, JBR); statistical expertise (MRS, DS, SEW, MLRM, JBR); supervision (MRS, JBR)

### References


Figure A. Spearman’s rho (-0.636), and confidence interval of correlation (-0.722 to -0.450) revealed a statistically significant ($P < .0001$) inverse correlation between topographic pattern and percent tissue altered (PTA) in the ectasia group.

Figure B. There was a wide distribution of age with different percent tissue altered (PTA) values in the ectasia group and non-linear correlation. No significant correlation was found between age and PTA.