Irregular Astigmatism After Corneal Transplantation—Efficacy and Safety of Topography-Guided Treatment

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Purpose: To analyze the efficacy and safety of topography-guided photorefractive keratectomy (TG-PRK) to treat irregular astigmatism after corneal transplantation.

Methods: This was a retrospective observational case series. Eyes with irregular astigmatism after penetrating keratoplasty treated with TG-PRK (Allegretto Wave Eye-Q) with the topography-guided customized ablation treatment protocol were included. All treatments had been planned to correct the topographic irregularities, as well as to reduce the refractive error after neutralizing the induced refractive change. Clinical records, treatment plan, and the examinations performed were reviewed and the following data were collected: corrected and uncorrected distance visual acuities; manifest refraction; topographic parameters, and corneal endothelial cell count.

Results: We included 31 eyes [30 patients; mean age 45.0 ± 13.4 (SD) years]. At the last postoperative follow-up (mean 9.2 ± 8.2 months), we observed a significant improvement in corrected ($P = 0.001$) and uncorrected distance visual acuities ($P < 0.001$). There was a gain of ≥1 uncorrected distance visual acuity line in 96.8% (n = 30) of the eyes. Similarly, the refractive parameters also improved (cylinder $P < 0.001$; spherical equivalent $P = 0.002$). At the last visit, 54.8% (n = 17) of the patients presented a spherical equivalent of ≥1 D. The 3-mm topographic irregularity also decreased significantly ($P < 0.001$). There was no significant variation of the corneal endothelial cell count.

Conclusions: This is the largest case series of TG-PRK to treat irregular astigmatism in postcorneal transplantation eyes. Our results confirm that TG-PRK is an efficient treatment, associated with significant improvements of both visual acuity and refractive parameters.

Corneal transplantation (CT) is one of the most commonly performed transplant procedures throughout the world. Although it is generally successful, patients frequently present with high irregular postoperative astigmatism, which precludes them from achieving satisfactory visual acuity. It can affect up to 40% of the eyes and remains a challenge even for experienced cornea specialists, as spectacles and rigid contact lenses often represent an unsuccessful option for visual rehabilitation.

In recent decades, excimer laser treatment has emerged as an alternative. The conventional ablation procedures account only for lower-order aberrations, such as defocus and regular astigmatism; therefore, their efficacy is widely limited for the highly aberrated post-CT corneas. When the target is irregular astigmatism, customized ablation protocols must be considered. Currently, there are 2 options available: wavefront-guided and topography-guided (TG). Wavefront ablation considers the aberrations of the entire eye and assumes that most, and potentially all, can be corrected by reshaping the cornea. However, mainly because of the limitations of the current wavefront sensors (aberrometers), these measurements are difficult to obtain and are usually not accurate in highly aberrated corneas. Additionally, this treatment protocol does not address their core pathology, as in these cases, higher-order aberrations and irregular astigmatism are mainly attributed to corneal irregularities.

Conversely, TG treatments rely only on topographic corneal height maps and thus can be more suitable. This was highlighted in a recent review, which concluded that, even with reliable wavefront measurements, in the presence of significant corneal irregularities, TG treatments may be superior. TG ablation is planned to reshape the irregular cornea to a symmetric regular surface by fitting it to the best asphere. The main skepticism of this approach is the theoretical lack of predictability of the final refractive outcome because of unknown changes induced by the correction of irregularities. The new treatment protocols already take it into account, performing a final adjustment to
the manifest refractive error, but a second procedure may be required to address it.12

Despite the current evidence that TG ablation treatments are more suitable for highly irregular corneas and therefore may represent the most appropriate option for post-CT eyes, only small limited series have been published, and it is not widely adopted.

To our knowledge, this study presents the largest case series of irregular astigmatism after CT treated with topography-guided photorefractive keratectomy (PRK). Our aim was to evaluate the efficacy and safety of this approach.

**MATERIALS AND METHODS**

This is a retrospective, noncomparative, consecutive case series, conducted at the Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. Before TG surgery, all patients were informed about the risks and benefits of the procedure. All patients signed an informed consent form in accordance with the Declaration of Helsinki, in which they agreed that their clinical data could be included in scientific studies.

**Study Design and Population**

Eyes submitted to TG-PRK were identified in our database, and their clinical records were reviewed. Only subjects who fulfilled the following inclusion criteria were considered for this study: (1) TG-PRK performed according to the protocol described below, because of irregular astigmatism caused by CT; (2) Minimum follow-up of 6 months; (3) Availability in the preoperative evaluation and the last appointment of corneal topography and pachymetry obtained with the Orbscan IIz system (Bausch & Lomb, Rochester, NY), and the corneal endothelial cell count obtained with the Topcon specular microscope. Irregular astigmatism was considered as the presence of spectacle corrected distance visual acuity (CDVA) of one or more lines less than the visual acuity with a rigid contact lens or pinhole, coupled with the presence of topographic changes—either unequal slopes of hemimeridians along a single meridian or hemimeridians of an equal slope but not aligned with each other, or a combination of both.16

For this analysis, we excluded patients with a spectacle CDVA inferior to 20/100 (0.70 logMAR) or with a history of other concomitant ocular pathologies (such as retinal, inflammatory, autoimmune, or neuroophthalmic diseases), as well as a history of other ocular surgeries besides CT. In addition, among eyes undergoing CT, we included only subjects treated with penetrating keratoplasty (PK). Other surgical techniques, such as deep anterior lamellar keratoplasty, were excluded from our study because they induce different biomechanical corneal responses and represented a minority of the cases that we have treated with TG-PRK.

For subjects who fulfilled all the eligibility criteria, the following data were collected: age; sex; treated eye; primary diagnosis for CT; clinical data from the baseline visit (before TG treatment) and the last follow-up visit—uncorrected distance visual acuity (UDVA) and CDVA with Snellen charts (converted to logMAR values for analysis), manifest refractive parameters (spherical equivalent, manifest cylinder and sphere), and topography parameters (irregularities at the 3- and 5-mm zones), and central pachymetry (Orbscan IIz system; Bausch & Lomb). Treatment characteristics were also collected, namely the maximum and central ablation treated, as well as the optical and astigmatism zones and the treated refractive error. Duration of follow-up and complications were also registered.

**Surgical Plan and Surgical Technique**

All eyes had been treated with topography-guided customized ablation treatment (T-CAT) PRK with the Allegretto Eye-Q 400-Hz excimer Wavelight (Germany) (wavelength: 193 nm, pulse duration: 12 nanoseconds, repetition rate: 400 Hz). TG-PRK was always performed at least: 12 months after CT; 6 months after the removal of the last sutures—sutures were removed in the steepest meridian when topographic astigmatism (Orbscan IIz system; Bausch & Lomb) was equal or superior to 3 diopters (D). If the astigmatism remained high despite this approach, all sutures were removed; 6 months of confirmed refractive stability, defined as less than 0.50 D change; and adequate corneal thickness.

All surgical plans were performed by the same surgeon (A.M.R.), based on data obtained using the Allegretto Topolyzer (Germany). This is a Placido-based system with 11 rings that generates 22,000 measuring points and has an integrated keratometer. It provides several topographic maps, which should be similar to each other. Up to 8 maps are averaged by the system, and the percentage of the data contained in the chosen optical zone is displayed. Highly irregular corneas after CT, without a specific pattern of astigmatism, were treated as long as more than 90% of their area was acquired (maps with less than 90% of data are excluded automatically) and data were reproducible in 8 topographic maps. Eyes that did not fulfill these criteria were not submitted to this treatment. To perform the surgical plans, the following protocol was followed stepwise:

1. Initially, the surgeon evaluated the treatment plans produced by the Topolyzer without information about manifest refraction. As the correction of the irregularities induces a shift in refraction, manifest refraction should not be initially entered, otherwise it can induce a refractive error.

2. Second, the induced change in sphere and the needed amount of treatment to compensate for it were identified. For example, if more tissue ablation was planned for the periphery than for the center, resembling a hyperopic correction, it would induce myopia (ie, make the central cornea steeper), which must be taken into account. This is performed by adjusting the spherical equivalent (C12) and sphere (C4) until they are similar.

3. Finally, the manifest refraction was added to calculate the final treatment.

Treatment was centered on the visual axis. The target asphericity was not adjusted, because previous authors...
suggested that it is usually associated with poor predictability. This system considers all aberrations up to the sixth order as a whole, so no selective treatments based on Zernike terms were applied. The only exception was to tilt, which the software allows to unselect. By definition, tilt is a lower-order aberration that describes a prism error of an eye. Its correction would require a prism-like ablation profile, with maximum ablation on one point of the optical zone and zero ablation at the opposite edge of the optical zone, thus requiring large amounts of tissue removal. Considering this, treating a prism error would increase the central ablation depth without affecting the refractive result, so we selected “Tilt off” in all our treatment plans. No additional modifications of the aberration profile are possible with this software.

Regarding tissue ablation, besides taking into account that the maximum approved treatment for the T-CAT protocol is up to 6 D of astigmatism in the corneal plan, we did not predefine a maximum value, as the other treatment option for these eyes would be to perform a new corneal transplantation. However, the system does not allow any treatments that may result in a minimum residual corneal thickness inferior to 250 μm. For eyes requiring deep ablations (total equal or superior to −10 D), we reduced the ablation area 0.5 to 1.0 mm.

Surgeries were performed by 4 surgeons (A.M.R., C.T., C.L., and M.J.Q.) under topical anesthesia. The corneal epithelium was mechanically removed with a spatula, and then patients were asked to fixate on a target light during corneal ablation, under constant eye-tracking control. Immediately after laser ablation, mitomycin C 0.02% was applied during 40 seconds with a Week sponge, which was placed over the ablated stroma to avoid haze and refractive regression. The corneal surface and the entire conjunctiva were then vigorously irrigated with saline solution. At the end of the procedure, a bandage contact lens was applied and kept until the fourth day after surgery. Topical antibiotic was prescribed in the first 2 weeks, and steroids were administered for 3 months, with a tapered dosing schedule. Subjects with a history of herpetic keratitis were additionally treated with oral acyclovir 400 mg twice per day.

We included 31 eyes of 30 patients [mean age 45.0 ± 13.4 (SD) years]. Of the treated eyes, 18 (58.1%) were right eyes. The main primary diagnosis leading to CT was keratoconus (74.2%). The remaining were corneal central scars due to herpes simplex keratitis (6.5%) or due to other causes (19.4%), including previous trauma. All eyes had been submitted to PK, with the diameters of corneal buttons varying from 8 to 8.5 mm. The baseline characteristics of the included subjects are detailed in Table 1.

Regarding TG-PRK ablation, the maximum treatment applied was 110.4 ± 28.2 μm (range: 60.5–171.9 μm) and the central ablation was 90.4 ± 37.6 μm (range: 13.8–171.5 μm). The mean correction performed in these eyes was −5.86 ± 0.84 D (range: −12.00 to 0.00 D) of sphere and 5.47 ± 0.84 D (range: 3.29–6.00 D). The optical and ablation zones varied between 5.0 to 6.5 mm and 8.0 to 9.0 mm, respectively.

### Postoperative Outcomes

The mean duration of available follow-up was 9.2 ± 8.2 months (range: 6–33 months). At the last visit, CDVA presented a significant improvement (0.14 ± 0.19 logMAR) compared with baseline (0.25 ± 0.15 logMAR, P = 0.001) (Fig. 1A).

### Statistical Analysis

The sample’s demographics and clinical characteristics were summarized with traditional descriptive methods, namely mean ± SD for continuous variables and percentages (%) for nominal or categorical parameters. Assumption of normality was calculated with the Shapiro–Wilk test. Because all the evaluated comparisons related to continuous variables, preoperative and postoperative values were assessed with the paired-sample t test when normality was observed and with the 1-sample sign test when it was not. Statistical analysis was performed with SPSS statistical software, version 20.0 (SPSS Inc, Chicago, IL), and the significance level was set at P ≤ 0.05.

### RESULTS

We included 31 eyes of 30 patients [mean age 45.0 ± 13.4 (SD) years]. Of the treated eyes, 18 (58.1%) were right eyes. The main primary diagnosis leading to CT was keratoconus (74.2%). The remaining were corneal central scars due to herpes simplex keratitis (6.5%) or due to other causes (19.4%), including previous trauma. All eyes had been submitted to PK, with the diameters of corneal buttons varying from 8 to 8.5 mm. The baseline characteristics of the included subjects are detailed in Table 1.

### TABLE 1. Clinical and Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Sample Eyes/Patients, n</th>
<th>31/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>Mean ± SD 45.0 ± 13.4</td>
</tr>
<tr>
<td>Range</td>
<td>23 to 83</td>
</tr>
<tr>
<td>Sex, male/female, no. patients</td>
<td>20/11</td>
</tr>
<tr>
<td>Eye, right/left, n</td>
<td>18/13</td>
</tr>
<tr>
<td>Primary diagnosis, eyes, n (%)</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Central scar due to herpetic keratitis</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Central scar due to other causes</td>
<td>0.00 to 0.70</td>
</tr>
<tr>
<td>UDVA, logMAR</td>
<td>0.95 ± 0.27</td>
</tr>
<tr>
<td>Range</td>
<td>0.52 to 1.30</td>
</tr>
<tr>
<td>CDVA, logMAR</td>
<td>0.25 ± 0.15</td>
</tr>
<tr>
<td>Range</td>
<td>0.00 to 0.70</td>
</tr>
<tr>
<td>Manifest spherical equivalent, D</td>
<td>−3.36 ± 3.68</td>
</tr>
<tr>
<td>Range</td>
<td>−16.00 to 3.00</td>
</tr>
<tr>
<td>Manifest cylinder, D</td>
<td>6.35 ± 2.21</td>
</tr>
<tr>
<td>Range</td>
<td>3.00 to 11.00</td>
</tr>
<tr>
<td>Central pachymetry, μm</td>
<td>546.3 ± 81.7</td>
</tr>
<tr>
<td>Range</td>
<td>313 to 733</td>
</tr>
<tr>
<td>3-mm irregularity, D</td>
<td>3.80 ± 1.39</td>
</tr>
<tr>
<td>Range</td>
<td>2.00 to 8.80</td>
</tr>
<tr>
<td>5-mm irregularity, D</td>
<td>6.27 ± 2.56</td>
</tr>
<tr>
<td>Range</td>
<td>2.90 to 13.30</td>
</tr>
</tbody>
</table>
Most of the eyes (n = 23, 74.2%) gained at least 1 line of CDVA, and 12.9% (n = 4) presented a gain of 5 or more lines, as presented in Figure 1B. In 2 cases, the opposite was observed, with loss of 1 and 3 lines of CDVA, respectively. The first case developed postoperative grade 3 central haze. The second was due to recurrence of herpetic keratitis with further development of a central corneal scar. The mean gain of CDVA lines was 1.85 ± 1.32 (range: loss of 3 to gain of 6 lines).

A similar pattern of improvement was observed in UDVA (Fig. 1A). UDVA increased from 0.95 ± 0.27 logMAR to 0.38 ± 0.30 logMAR, P < 0.001. At the last follow-up, all but 1 eye (96.8%) had gained lines of UDVA (Fig. 1C). Interestingly, a high percentage of eyes gained at least 5 lines of UDVA (42.0%), with a mean gain of UDVA lines of 4.55 ± 3.04 (range: 0–9).

Regarding manifest refraction, there was a significant reduction in both spherical equivalent (−3.36 ± 3.68 to −1.11 ± 1.63 D, P = 0.002) and cylinder (6.35 ± 2.21 D preoperative to 1.96 ± 1.14 D, P < 0.001). Figure 1D presents the comparison before and after TG-PRK.

At the last visit, 54.8% (n = 17) of the eyes presented a manifest spherical equivalent of ±1.00 D (range −4.75 to 1.75 D). All treated subjects presented at that time a manifest cylinder ≤4 D (range: 0–4 D), with 29.0% (n = 9) of them within 1 D and 61.3% (n = 19) up to 2 D. Among the eyes with less than 6.5 D of preoperative manifest cylinder (6 D in the corneal plane, n = 18), 36.8% presented less than 1 D of postoperative refractive astigmatism.

The topographic irregularities also improved significantly in the central 3 mm (P < 0.001) but not in the central 5 mm. There was no significant decrease in the corneal endothelial cell count (1123 ± 756 cells/mm² to 1027 ± 330 cells/mm², P = 0.799). Mean final pachymetry was 443.7 ± 103.1 μm (range: 260–667 μm). Six eyes (19.4%) developed haze, within an average time of 52.0 ± 29.0 days (range: 11–90 days). In all but one case, referred to above, haze was classified as grade 1 and was successfully treated with topical steroids. There were no other postoperative complications registered during the follow-up. Thirty-two percent (32.3%, n = 10) of the eyes were followed for at least 1 year, and no cases of postoperative ectasia were described. Figure 2 presents an example of a case successfully treated with TG-PRK.

**DISCUSSION**

We present a retrospective case series of 31 eyes with irregular astigmatism after PK treated with TG-PRK. Our data reveal that this treatment was associated with a significant improvement in both CDVA (P = 0.001) and UDVA (P < 0.001). At the last follow-up visit, 74.2% of the eyes (n = 23) had gained CDVA lines and a gain of UDVA was also observed in 96.8% (n = 30). This was accompanied by an improvement of manifest refraction (cylinder, P < 0.001; spherical equivalent, P = 0.002), without significant postoperative complications.

Besides the relevance of the observed UDVA improvement, the CDVA increase is particularly critical for patients. It represents an opportunity of returning to useful and tolerable spectacles or soft contact lens wear, which is usually not possible in highly irregular corneas, as observed after CT. Other published studies in this field suggested similar results. For example, Rajan et al published the largest complete series available so far (n = 16 eyes, with TG laser-assisted subepithelial keratectomy) and also observed significant CDVA and UDVA improvements. Regarding TG-PRK, Lin...
et al\textsuperscript{15} evaluated its efficacy to treat several causes of irregular astigmatism, including 27 eyes with a history of CT. However, the authors did not independently characterize this population at baseline and did not mention any preoperative requirements, such as time after the first surgery, so we cannot compare the data. Interestingly, it was recently described\textsuperscript{13} that eyes after CT can present higher UDVA gains than eyes with other diagnoses (such as decentered optic zone, among others), but that the gain of CDVA can present an opposite trend.\textsuperscript{8} Actually, Allan and Hassan\textsuperscript{8} observed that CDVA gain was lower in patients with irregular astigmatism after CT than after previous refractive surgery, describing a median gain of 0 lines for CT eyes. The authors justified these outcomes by the development of severe haze in a significant number of cases. In this study, MMC was not used, which is probably linked with these results. As detailed, all our eyes were treated with MMC, and we registered 6 cases (19.4\%) of haze. All but one resolved with topical steroids, and there was no significant decrease in corneal endothelial cell density associated with this procedure, which suggests that higher duration of MMC exposure might need to be considered in some cases in the future. Interestingly, a higher incidence of haze after CT has been described also with conventional excimer ablation treatments,\textsuperscript{23} and other authors\textsuperscript{4,14,24} had already emphasized that patients previously submitted to corneal transplantation should always receive MMC with TG-PRK ablations. Besides the described occurrence of haze, we observed no other postoperative complications except 1 case.

![Figure 2](https://example.com/figure2.png)

**FIGURE 2.** We present a case of a 66 year-old man, with a history of PK in the left eye, which was performed 6 years before because of keratoconus. The patient presented a CDVA of 20/50, with a manifest refraction of $-6.50 \times 15$ degrees. A, Preoperative Topolyzer topography map. As defined in our protocol, 8 of these maps were averaged to obtain the initial treatment plan, which is shown in (B). In this initial plan, the required cilindrical correction would be approximately 9 D (white box). However, it can be safely performed only up to 6 D, so refractive correction was added to sphere. Then, a balance between it (C4, sphere) and spherical equivalent (C12) was guaranteed, achieving the final treatment plan. C, The white box highlights the initial treatment plan and the plan after the described adjustments. In D, we present the Topolyzer map, 3 months after TG-PRK, with an evident improvement compared with the obtained preoperatively (A). In the last visit, the patient presented a CDVA of 20/20, with a correction of $-3.0 \times 140$ degrees.
of herpetic keratitis recurrence. This happened despite oral acyclovir prophylactic treatment, thus suggesting that these eyes should be carefully monitored after this type of laser treatment.

Regarding the refractive outcomes, they were also successful in this study and are particularly relevant to discuss as one of the main skepticisms regarding TG ablation is the theoretical unpredictability of the refraction obtained finally.\textsuperscript{12} Any corneal topographic change leads to an accompanying change in refraction.\textsuperscript{22} However, as described, current surgical TG plans account for it. This results in satisfactory refractive correction, as shown in the present case series. Actually, our results are particularly satisfactory considering the complexity of these eyes and their preoperative extremely high manifest cylinders, ranging from 3 to 11 D. Considering that the maximum approved treatment for the T-CAT protocol is up to 6 D of astigmatism in the corneal plan,\textsuperscript{7} undercorrection was planned for a high percentage of these eyes, which probably precluded even better results. In fact, when we considered only eyes with astigmatism within the treatable range, the postoperative refractive cylinder was lower (36.1% within 1 D, compared with 29.0% considering all the included study population). Vector analysis methods\textsuperscript{25} for the evaluation of surgically induced refractive correction are commonly used to evaluate astigmatic outcomes, but they assume a regular toric corneal surface, so they were not applied here.

These excellent refractive outcomes are also corroborated by the other small published series including eyes with previous CT,\textsuperscript{4,13,14,26,27} all consistently describing significant postoperative improvements of ametropias. Satisfactory results were also reported by Alió et al.,\textsuperscript{28,29} in 2 large prospective case series of highly aberrated corneas after refractive surgery treated with excimer ablations based on corneal wavefront topography. Despite this, the nature of TG ablations should always be taken into account and subjects should be informed that a second procedure to address the refractive error may be necessary.\textsuperscript{7} Patients’ expectations are often high, so they must be informed that TG treatments can help, but present some limitations and thus future refinements may be necessary. In this study, treated eyes presented a trend to a myopic outcome, which was deliberate. Undercorrection is generally recommended for TG-PRK, as significant irregular astigmatism can preclude an appropriate evaluation of manifest refraction, and differential ablation rates may contribute to additional uncertainty.\textsuperscript{8,10}

Altogether, our results and the remaining available small series suggest that TG-PRK offers a valuable option for irregular astigmatism in eyes post-CT. Ablating only the localized defects removes less tissue than correcting a similar amount of regular astigmatism. This sparing of corneal tissue allows treatment of high levels of irregular astigmatism, simultaneously achieving a regular smooth surface. Thus, TG-PRK is particularly well suited for highly aberrated eyes, which wavefront-guided ablation is unable to treat or treats with suboptimal results.\textsuperscript{10}

The main limitation of this study relies in its retrospective nature. A prospective analysis of this case series, presenting its serial evolution in different time points, would be interesting. Additionally, despite not being our aim, it would also be interesting to compare TG with wavefront-guided ablations. The current evidence\textsuperscript{7,10,22} suggests that the former are theoretically more appropriate for highly aberrated eyes, such as post-CT eyes. However, a prospective comparative study could provide important inputs to achieve definite conclusions in this field. Another limitation refers to our eligibility criteria of a minimum spectacle CDVA of 20/100 (0.70 logMAR) that can induce selection bias and may influence our results.

In conclusion, this large case series demonstrated that TG ablations are an efficient treatment of irregular astigmatism after corneal transplantation. The successful visual and refractive results are probably linked with the performed smoothing of the anterior cornea, thus removing its irregular surface shape, which is frequently the cause of the irregular astigmatism and higher aberrations observed in transplanted eyes.

REFERENCES


