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班会議・班会議議事録

厚生労働省　難治性疾患克服研究事業　「膠様滴状角膜変性症の標準的治療レジメンの確立と新規治療法の創出」　班会議

日時　　平成２５年２月１５日（金曜日）　　15:30～17:00
場所　　青少年研修センター　1F　会議室

班会議場所

学会場

平成 24 年度 厚生労働省科学研究費補助金（難治性疾患克服研究事業）
「膠様滴状角膜変性症の標準的治療レジメンの確立と新規治療法の創出」
第一回研究班会議 議事録

記録：篠宮 克彦

日時：平成 25 年 2 月 15 日 （金）15:30〜16:15
場所：和歌山県白浜町青少年研修センター 1 階会議室
参加者：8 名 （敬称略）

● 川崎 諭（京都府立医科大学）
● 稲富 勉（京都府立医科大学）
● 足立 紘子（京都府立医科大学）
● 篠宮 克彦（京都府立医科大学）
● 辻川 元一（大阪大学）
● 臼井 智彦（東京大学）
● 宮井 尊史（東京大学）
● 松田 彰（順天堂大学）

　はじめに研究代表者の川崎から、配布資料の説明があった。本日の議題は以下のとおりである。

1. 3 年間の実験成果について （川崎より資料を用いて説明）
2. 診断基準について
3. 遺伝子検査について
4. 治療ガイドラインについて
5. SCL について
6. 今後の治療について
7. 報告書について

1. 3 年間の実験成果について
　別資料（PowerPoint）を用いて研究代表者の川崎より概要を説明した。以下、概略を記載する。
　遺伝子治療については in vitro モデル、GDLD 患者由来不死化細胞、HCE-T を用いて実験を行っていたが、いずれも限界があった。遺伝子治療の可能性については SCL をキャリアにする方法、レンチウイルスを用いる方法が考えられるが、不死化 GDLD 細胞にTACSTD2 を遺伝子導入してもバリアはあまり上がらなかった。

2. 診断基準について（以降のセクションは話の内容を時系列で記す）

- 診断基準作成について再度各施設の意見を聞き直したい。
- 診断基準はこのうちどれかを満たせば OK という基準にはしにくい。
- TACSTD2 の遺伝子異常が必ずあるので、検査ができれば確定診断できる。
- あっても症状が出ない場合もあると思われるがその場合はどうすべきか？
- シンプルに遺伝子変異があれば OK とすべきか？
- 遺伝子検査ができる施設の方が少ないと思われるが、検査ができない場合はどうするか?

3. 遺伝子検査について

- 遺伝子検査の意義は?
- 必須にするとできない施設はどうするか?
- 角膜ジストロフィーは遺伝子変異が確定されていることが必須、できない場合は疑いで。
- 厚労省に出す診断基準については、学会が認めたものにしてほしい。学会の中でパブコメを募集するなど。また日本眼科学会にも出せばオーサライズできる。このようにやってほしい。
- 診断基準にもレベルがある。なるべくみんなに広く使ってもらえるものにすべき。
- 確定診断は、遺伝子異常+症状、基準の 1-②、③、3-②で OK では?
- 遺伝子異常が無かったものの扱いはどうするか。無かったらシロではない。完全に弾かれるのはまずい。疑い例は作らざるを得ない。これは注記に入れる。
- 1-①は不要では?
- 基準の 1-②、③、3-②を満たせば確定、臨床症状だけでは疑いとする。わかりやすく改訂して回覧する。
- 遺伝子検査ができない施設をどうするか。施設の倫理委員会の問題、臨床検査会社に依頼するにも例数が少なく、おそらく会社がペイできない。
- 費用は外注なら保険外で、数万円と高額になることが予想される。
  - SRL や三菱に外注検査としてやってもらえるかを聞いてみる。シングルエクソン遺伝子なので、他の遺伝子に比べれば敷居は低いはず。

4. 治療ガイドラインについて

- 疾患概要を省くか？
  - あった方がいい。
- 原則、進行を遅らせるという考え方は疑う余地がない。
- 前眼部 OCT でチェックする。

- 軽症～重症の治療についてエビデンスが必要では？
- エビデンスをしっかり出すというなら SCL 以外は出ていない。
- エビデンスなしでは学会で承認されないかもしれない。
- 希少疾患なので前向き研究は困難。
- 全国調査報告ではダメか?
- 重症のところをもっとシェイプアップした方がいい。
- 全体的に言葉をシェイプアップすべき。

5. SCL について

- 効果が本当にあるのか。
  - 効果があるのは経験的にも一昨年度の検討でも疑う余地はない。
- メカニズムについて。CL の前、後でラクトフェリンの定量をやっている。ラクトフェリンを吸着しやすい素材の SCL がいい。
  - シードがやっている。今年度の報告書に記載する。
- 術後に使用する CL は、これがいいというエビデンスが無い。
  - ハイドロゲル、シリコン、どれかがメディカルユースの治療用 CL として認可を取っている。

6. 今後の治療について

- 現状で十分か、不十分か。
  - 不十分であることは否めない。
- 遺伝子治療について、プラスミドを用いた方法は継続して研究すべきか。
- 安全性ではプラスミド、レンチウイルスの安全性は？
- いずれも TER が上がるという実験結果が無いと説得力に欠ける。
  - 現時点では難しい。
- 根治できない疾患で、眼表面疾患なので遺伝子治療のハードルは他科症例に比べて低いと考えられる。効果があることを確認できれば遺伝子治療の方向性というのは悪い考え方ではない。

7. 報告書について

- 統括研究報告書、総合報告書は 5/31 が期限。
- 川崎が各機関の提出期限を決めて書類を集める。

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研究成果の刊行に関する一覧表

平成 24 年度　成果論文一覧

1. Fukuda R, Usui T, Miyai T, et al. Corneal thickness and volume measurements by swept source anterior segment optical coherence tomography in normal subjects. *Curr Eye Res.* 2013;38(5):531-6 DOI: 10.3109/02713683.2012.745878.

2. Hieda O, Kawasaki S, Wakimasu K, et al. Clinical outcomes of phototherapeutic keratectomy in eyes with Thiel-Behnke corneal dystrophy. *Am J Ophthalmol.* 2013;155(1):66-72 e1 DOI: 10.1016/j.ajo.2012.06.022.

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7. Shinomiya K, Ueta M, Sotozono C, et al. Immunohistochemical analysis of inflammatory limbal conjunctiva adjacent to Mooren's ulcer. *Br J Ophthalmol.* 2013;97(3):362-6 DOI: 10.1136/bjophthalmol-2012-302631.

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研究成果の刊行物・別刷

informa
healthcare

Corneal Thickness and Volume Measurements by Swept Source Anterior Segment Optical Coherence Tomography in Normal Subjects

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ABSTRACT

Purpose: To evaluate central corneal thickness (CCT) and corneal volume (CV) in healthy eyes using swept source anterior segment optical coherence tomography (SS-AS-OCT) and other devices.

Methods: Thirty-three healthy right eyes of 33 subjects were investigated. CCT was measured with SS-AS-OCT, rotating Scheimpflug camera, ultrasonic pachymetry and specular microscopy. CV was determined within a diameter of 10 mm at the center using SS-AS-OCT and Scheimpflug camera.

Results: Mean CCT was 523.5 ± 25.2 μm by SS-AS-OCT, 523.9 ± 26.1 μm by Scheimpflug camera, 532.1 ± 26.6 μm by ultrasonic pachymetry, and 525.5 ± 33.5 μm by specular microscopy. The CCTs measured with SS-AS-OCT, Scheimpflug camera and specular microscopy were significantly thinner than those measured with ultrasonic pachymeter ($p < 0.001$). The mean CV within a diameter of 10 mm at the center was 57.2 ± 3.0 mm^3 by SS-AS-OCT and 59.4 ± 2.9 mm^3 by Scheimpflug camera. Scheimpflug measurements of CV were statistically larger than SS-AS-OCT measurements ($p = 0.0008$). Statistically significant correlation was found between the CCT and CV measurements of each imaging devices ($p < 0.0001$, $r = 0.527$, and $p < 0.0001$, $r = 0.749$, respectively).

Conclusion: SS-AS-OCT enables the measurements of CCT and CV, demonstrating agreement with other devices. CV in addition to CCT measurement may serve as a practical parameter of the corneal endothelial pump function.

Keywords: Central corneal thickness, corneal volume, optical coherence tomography, Scheimpflug camera, ultrasonic pachymetry

INTRODUCTION

Central corneal thickness (CCT) measurement is an essential parameter of corneal endothelial function and serves as a valuable quantitative evaluation for corneal diseases and surgical procedures.[1,2] Traditionally, CCT measurements have been assessed using various devices including ultrasonic pachymetry,[1–19] scanning-slit topography/pachymetry,[4–13,20,21] rotating Scheimpflug camera,[4,7,12,17,20,22] noncontact specular microscopy[8–10,21,22] and optical coherence tomography (OCT).[4–6,12–17,20] In terms of corneal volume (CV), the rotating Scheimpflug camera, Pentacam (Oculus, Wetzlar Germany), used to be the only commercially available modality to automatically calculate CV, within regions of 3, 5, 7 and 10 mm diameter. Previously, CV has been evaluated on eyes with keratoconus,[23–26] after cataract operations,[27,28] laser *in situ* keratomileusis (LASIK)[29] and contact lens wear.[30] A combination of CCT and CV measurements could possibly present a more comprehensive understanding of corneal conditions.

Recently introduced Fourier domain swept source anterior segment OCT (SS-AS-OCT) with a wavelength of 1310 nm (SS-1000 CASIA, Tomey, Japan) can obtain three-dimensional imaging in addition to cross-sectional imaging of the anterior segment of the eyes. This OCT system allows higher speed of data

acquisition, greater imaging depth and wider observable range,[31–33] and has been reported to yield high repeatability and reproducibility of anterior ocular biometric measurements.[34] Further, a newly installed system in SS-1000 enabled CV measurements from 2 mm to 16 mm in diameter via the application of its three-dimensional imaging technique. However, the evaluation of CV by SS-AS-OCT has not yet been reported. Therefore, the aims of the current study were to evaluate the CCT and CV using SS-AS-OCT and to compare these measurements with other principal devices in normal eyes.

MATERIALS AND METHODS

This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Miyata Eye Hospital, Japan. The observational cross-sectional study population constituted 33 healthy right eyes of 33 patients (six males and 27 females). Exclusion criteria were ocular diseases, history of intraocular surgeries including refractive surgeries and contact lens use within two weeks.

All subjects underwent ophthalmic examination, including refractometer and keratometer (ARK530A, Nidek Corp., Japan), SS-AS-OCT, Scheimpflug camera, specular microscopy (SP-2000P, Topcon Corp., Japan) and ultrasonic pachymetry (UP-2000, Nidek Corp., Japan) sequentially. For SS-AS-OCT, CCT measurements were acquired in an anterior segment mode in a dimly lit room. This protocol consists of 128 radial B-scans of 16-mm length centered on the corneal center, with each B-scan including 512-A-scans. The measurement time was 2.4 s per eye. This OCT system applies three-dimensional refractive correction based on the index of the human cornea, 1.389.[35] During the examination, patients were encouraged to open their eyes as widely as possible. When motion or blinking of the eyes hampered accurate examination, the practice was repeated up to three times and the best image was selected for analysis. If necessary, the examiner used fingers to open the patients' eyes wide enough to permit the best possible observations without pressing the eyeballs. Under horizontal image with refractive correction, CCT was automatically determined by the device while scleral spur on both sides was plotted manually by an ophthalmologist (RF). For CV measurements, the same anterior segment mode was selected. After designating a domain of 10-mm diameter on a two-dimensional basis, the area of the cornea was automatically traced. For normal cornea, the program recognizes the appropriate outlines of the cornea and further correction is not necessary. Thirty-two images were analyzed by the program, because an analysis of 32, 64 and 128 images conducted prior

to this study showed no significant difference between image numbers (data not shown). By integrating the area of 32-slice images in the rotational direction, CV was automatically calculated.

Scheimpflug camera uses a blue light-emitting diode with a wavelength of 475 nm, generating 50 slit images in 2 s. During the measurement, subjects were instructed to fixate on a target in a dark room, and CCT was automatically calculated. CV within a diameter of 10 mm centered on the thinnest point was automatically calculated by the reconstruction of elevation points at each slit into three-dimensional data. The SP-2000P is a noncontact specular microscope that projects light onto the cornea and captures the image reflected from the optical interface between the corneal endothelium and the aqueous humor, providing specular images and pachymetry. Measurement was taken once in a dimly lit room. For ultrasonic pachymetry, the cornea was anesthetized with topical 0.4% oxybuprocaine hydrochloride, and a probe that generates ultrasound waves into the cornea and detects reflected ultrasound waves was applied perpendicularly on the central corneal surface of the subjects in a sitting position. Up to 10 sequential measurements were obtained until the value was stabilized, and the most frequent value was adopted.

For statistical analysis, measurements were compared across the four devices using the repeated-measures analysis of variance, and two devices were compared using the paired t-test or t-test with the Bonferroni correction. Agreement between measurements of two devices was evaluated by a Bland-Altman plot with 95% limits of agreement for each comparison. Furthermore, the intra-class correlation (ICC) and slope value of the linear regression line were calculated between CV measurements by SS-AS-OCT and Scheimpflug camera. For bivariate correlation analysis, the Pearson's correlation coefficient was calculated. Data analysis was conducted using Microsoft Excel 2007 (Microsoft Corp., WA, USA) and JMP version 6.0 (SAS Institute Inc. NC, USA).

RESULTS

Subject age ranged from 18 to 53 years with the mean age ± standard deviation (SD) of 37.8 ± 9.8 years. The mean spherical equivalent refraction was −1.28 ± 2.04 D (range: −8.0 D to +2.25 D), with the mean astigmatism of −0.59 ± 0.64 D (range: −2.0 D to +0.75 D). The mean CCT was 523.5 ± 25.2 μm by SS-AS-OCT, 523.9 ± 26.1 μm by Scheimpflug camera, 532.1 ± 26.6 μm by ultrasonic pachymetry and 525.5 ± 33.5 μm by specular microscopy (Table 1). Ultrasonic pachymetry measurements were significantly greater than measurements obtained by OCT, Scheimpflug camera and specular microscopy measurements ($p < 0.001$ in all cases, t-test with the

Bonferroni correction). CCT measurements did not significantly differ across these latter three devices ($p = 0.603$, repeated measures analysis of variance). Statistically significant linear correlation was present among all four devices ($p < 0.0001$ in all cases, $r = 0.90$–0.99). The strongest linear relationship was found between SS-AS-OCT and ultrasonic pachymetry ($p < 0.0001$, $r = 0.990$). Figure 1 demonstrates the

TABLE 1. Central corneal thickness measurements.

	Mean ± SD (μm)	Minimum values (μm)	Maximum values (μm)
SS-AS-OCT	523.5 ± 25.2	469	576
Scheimpflug camera	523.9 ± 26.1	462	587
Ultrasonic pachymetry	532.1 ± 26.6	469	583
Specular microscopy	525.5 ± 33.5	441	594

SS-AS-OCT = Swept source anterior segment optical coherence tomography; SD = standard deviation.

Bland–Altman plots for the different comparisons between each pair of instruments.

The mean CV was $57.2 \pm 3.0\,mm^3$ by SS-AS-OCT and $59.4 \pm 2.9\,mm^3$ by Scheimpflug camera. Scheimpflug measurements of CV were significantly larger than OCT measurements ($p = 0.0008$, paired t-test). CV measurements correlated significantly between the two devices ($p < 0.0001$, $r = 0.863$). ICC for CV measurements was 86.3%, and the slope of the linear regression line was 0.90, indicating very high agreement between OCT and Scheimpflug camera. Furthermore, a statistically significant correlation was found between CCT and CV measurements taken by each imaging devices ($p < 0.0001$, $r = 0.527$, and $p < 0.0001$, $r = 0.749$, respectively). The Bland–Altman plot showed that the limit of agreement between SS-AS-OCT and Scheimpflug measurements of CV was good ($\pm 3.08\,mm^3$, Figure 2). Age, sex and refraction were not correlated with CCT or CV measurements regardless of the device.
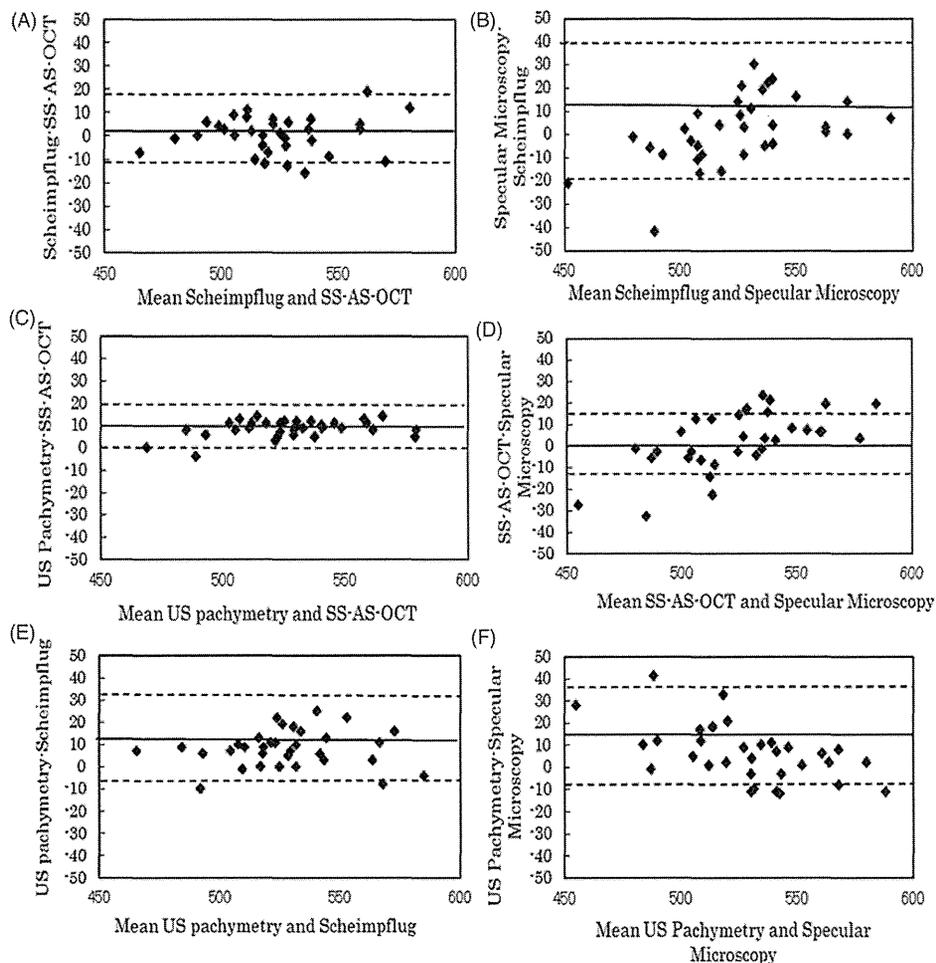

FIGURE 1. Bland–Altman plots of the differences in central corneal thickness measurements (μm) between (A) Scheimpflug camera and swept-source anterior segment optical coherence tomography (SS-AS-OCT), (B) specular microscopy and Scheimpflug camera, (C) ultrasonic (US) pachymetry and SS-AS-OCT, (D) specular microscopy and SS-AS-OCT, (E) US pachymetry and Scheimpflug camera and (F) US pachymetry and specular microscopy. The solid lines represent the mean differences and the dotted lines represent the 95% limits of agreement.
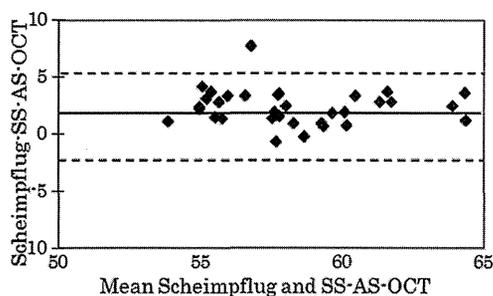
FIGURE 2. Bland–Altman plots of the differences in corneal volume measurements (mm³) within a 10 mm diameter between swept source anterior segment optical coherence tomography (SS-AS-OCT) and Scheimpflug camera. The solid line represents the mean differences and the dotted lines represent the 95% limits of agreement.

DISCUSSION

Our results showed that CCT measurements determined by SS-AS-OCT were correlated with those determined by Scheimpflug camera, ultrasonic pachymetry and specular microscopy. Although ultrasonic pachymetry has been a gold standard for CCT measurements, it provided consistently higher values than the other three devices. In previous studies, ultrasonic pachymetry provided measurements that were higher than the OCT measurements,[4–6,12,14–17,20] which is consistent with our result. One of the accepted theoretical explanations for this discrepancy is methodological differences.[16] While ultrasonic pachymetry is a contact technique, the other techniques are noncontact. Ultrasonic pachymetry measures CCT by detection of reflected ultrasound waves; however, uncertainty over the posterior corneal reflection point for ultrasound waves, which is considered to be between Descemet's membrane and the anterior chamber, has been pointed out.[9] Manual determination of the center of the cornea[7] and lack of fixation lights for precise control of patient gaze during measurements are additional shortcomings of ultrasonic pachymetry.[14] Although high repeatability of ultrasonic pachymetry has been reported,[3] the operator's skill level and the patient's fixation capability may influence the accuracy of measurements. Furthermore, corneal edema from local anesthesia drops may lead to the overestimation of CCT measurements: Nam et al.[36] demonstrated a 7.7-μm increase in corneal thickness after applying oxybuprocaine.

Previous studies of CCT measurements using SS-OCT were based on a model designed for posterior segment imaging; for anterior segment imaging, primarily Visante OCT has been used (Carl Zeiss Meditec, CA). Li et al.[6] indicated that with an automatic algorithm, the anterior corneal boundary delineated by Visante OCT was positioned slightly below the anterior corneal surface. Although automatic Visante OCT measurements underestimated CCT compared to ultrasonic pachymetry, manual identification of the boundaries yielded OCT measurements that were thicker than those of ultrasonic pachymetry. Meanwhile, a recently developed SS-AS-OCT, the SS-1000 has a measurement speed over 10 times faster than time-domain-OCT.[25] SS-1000 demonstrated the most comparable agreement with ultrasound pachymetry ($r = 0.990$, $p < 0.0001$). Fukuda et al.[34] reported that the SS-1000 produced better repeatability and reproducibility compared to Visante OCT for CCT measurement. They also reported that CCT measurements with SS-1000 were not significantly different from ultrasonic pachymetry or scanning-slit topography, but lower than Scheimpflug camera measurements.[4] On the other hand, our results showed that CCT measurement with SS-1000 was not significantly different from Scheimpflug camera and specular microscopy, but was significantly thinner than ultrasonic pachymetry measurement. A larger study size and manual measurements with the SS-1000 should be considered in future investigations.

CV is gaining attention as an appealing parameter for topographical, morphological and pachymetric changes. The Scheimpflug camera used to be the only means to determine corneal volume automatically. Other studies obtained corneal volume measurements by scanning-slit topography/pachymetry data[37] or the original calculation method using topography and topographic pachymetry data.[38] To the best of our knowledge, this report is the first to measure CV using SS-AS-OCT.

Scheimpflug camera can estimate CV within 3, 5, 7 and 10 mm diameter regions, whereas SS-1000 is able to calculate volume within a 2–16 mm range by every 2 mm, possibly offering more precise information about CV. In this study, Scheimpflug measurements of CV were consistently larger than SS-AS-OCT measurements in the same area (10 mm central region), although CCT measurements by the two instruments did not significantly differ. One possible explanation for this discrepancy may be due to peripheral corneal thickness determination. Ponce et al.[17] reported that Scheimpflug imaging gave approximately 30 μm greater peripheral corneal thickness values than Visante OCT. They also proposed that this discrepancy may be due to the different measurement principles of these two instruments.

CV measurements may contribute to the early detection of complications after cataract operation[27,28] as well as LASIK.[29] Although specular microscopy demonstrates corneal endothelial damage by measuring the change in the endothelial cell number after cataract surgery, it only represents the selected portion of the corneal endothelium. By contrast, CV can be calculated up to 10 mm zones with a Scheimpflug

camera, possibly representing an overall evaluation of corneal endothelium function, since postoperative corneal swelling correlates to corneal endothelial cell loss.[39] Suzuki et al.[27] reported that 10 mm CVs one month after cataract surgery were significantly higher than preoperative values, whereas 3 mm CVs showed no difference. Although CV measurements correlated with CCT measurements, respective values could not be used interchangeably for the evaluation of corneal condition. Moreover, CV measurement has been proposed as a new index to diagnose keratoconus.[23–26] Significant decrease in CV in keratoconus was detected by Scheimpflug camera, especially in central and paracentral areas.[23,24,40] CV measurements may represent a more comprehensive indicator of corneal health. As a next step for future studies, CV should be evaluated using SS-AS-OCT in corneal diseases and perioperative corneas.

In conclusion, the current study evaluated CCT and CV measured by SS-AS-OCT and compared these values with those from other principal instruments in the healthy cornea. CCTs measured with SS-AS-OCT, Scheimpflug camera and specular microscopy were significantly thinner than those measured with ultrasonic pachymetry. SS-AS-OCT and Scheimpflug camera demonstrated comparable agreement between CCT and CV.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Clinical Outcomes of Phototherapeutic Keratectomy in Eyes With Thiel-Behnke Corneal Dystrophy

OSAMU HIEDA, SATOSHI KAWASAKI, KOUICHI WAKIMASU, KENTA YAMASAKI, TSUTOMU INATOMI, AND SHIGERU KINOSHITA

● PURPOSE: To investigate the functional and morphologic midterm outcome of phototherapeutic keratectomy (PTK) for Thiel-Behnke corneal dystrophy diagnosed by gene-mutation analysis.

● DESIGN: Retrospective, single-center clinical study.

● METHODS: Between July 2001 and May 2010, 10 consecutive PTKs were performed in 10 eyes of 5 patients (2 male, 3 female; mean age: 55 ± 13 years) with superficially accentuated opacities caused by Thiel-Behnke corneal dystrophy and were followed up for at least 12 months (range: 12–108 months). Main outcome measures included (1) best-corrected visual acuity (BCVA), (2) uncorrected visual acuity (UCVA), (3) spherical equivalent, and (4) recurrence rate. The probability of recurrence of Thiel-Behnke corneal dystrophy after PTK was calculated using the Kaplan-Meier method for survival analysis.

● RESULTS: The p.Arg555Gln mutation was found within the TGFBI gene in all 5 patients. Average logarithm of minimal angle of resolution (logMAR) BCVA change was −0.55 ± 0.26. Average logarithm UCVA change was −0.54 ± 0.31. In 5 of the 10 eyes, recurrence of central superficial opacification was clinically identified during the follow-up periods, and in 4 of those 5 eyes, the level of the recurrence was so significant that the visual acuity was reduced more than 2 lines. The maximum follow-up period of the 1 eye without significant post-PTK recurrence was 108 months.

● CONCLUSIONS: PTK is a successful therapy for Thiel-Behnke corneal dystrophy, and results in midterm stable visual acuity and corneal transparency. Unlike in Reis-Bücklers corneal dystrophy cases, PTK delays the need for more invasive surgical intervention in Thiel-Behnke corneal dystrophy. (Am J Ophthalmol 2013;155: 66–72. © 2013 by Elsevier Inc. All rights reserved.)

T HIEL-BEHNKE CORNEAL DYSTROPHY,[1] ALSO KNOWN as "honeycomb" corneal dystrophy,[2] is an autosomal dominant inheritable disease and was described as corneal dystrophy of the Bowman layer and superficial stroma type II (CDB II, OMIM#602082) in a report by Küchle and associates.[3] Recent molecular biological analysis has revealed that this dystrophy is caused by the missense mutation (p.Arg555Gln) of the human transforming growth factor beta–induced (TGFBI) gene.[2,4–7]

Characteristic bilateral, subepithelial corneal opacities, frequently accompanied by recurrent corneal erosions, normally appear in Thiel-Behnke corneal dystrophy patients between the ages of 10 and 20 years. This disease runs a slow progressive course, with painful erosive episodes and gradual deterioration of vision.[2–4] The treatment modalities for this disease include superficial keratectomy, lamellar keratoplasty,[3] penetrating keratoplasty (PKP),[8] and phototherapeutic keratectomy (PTK).[9–12]

In Japan, the Ministry of Health, Labour and Welfare approved the medical use of 193-nm argon-fluoride excimer laser devices for PTK procedures in 2000. Since then, PTK has been applied for the treatment of various types of corneal diseases, including inheritable corneal dystrophies,[2,12–17] band keratopathy,[10,18–20] recurrent corneal erosion,[15,21,22] certain types of degenerative corneal diseases (eg, Salzmann's degeneration),[10,20,23] and bullous keratopathy.[24,25] The PTK procedure is generally thought to produce the best results when it is used for the ablation of corneal opacity restricted to the anterior stroma of the cornea. When PTK is performed on patients who have passed strict diagnostic criteria, the satisfaction level in relation to the results of this procedure is reportedly very high.[26]

The purpose of this retrospective, single-center clinical study was to investigate the functional and morphologic midterm outcome of PTK performed in multiple Thiel-Behnke corneal dystrophy patients who were strictly diagnosed through the use of gene mutation analysis.

METHODS

● STUDY POPULATION: This study involved 10 consecutive PTKs performed in 10 eyes (5 right eyes and 5 left eyes) of 5 patients (2 male and 3 female) to treat superficially accentuated opacities that were clinically and
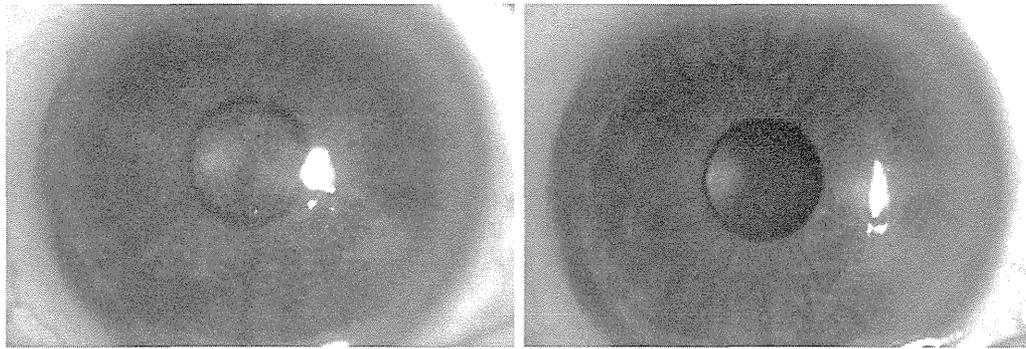
FIGURE 1. Slit-lamp microscopy images of the left eye of a 57-year-old woman with Thiel-Behnke corneal dystrophy (Patient 1) (Left) before and (Right) 1 month after undergoing phototherapeutic keratectomy surgery. Note that the superficial corneal opacities visible around the axial area of the cornea in the left-hand image (presurgery) are no longer visible in the right-hand image (postsurgery).

TABLE. Summarized Clinical Information of Eyes With Thiel-Behnke Corneal Dystrophy Before and After Phototherapeutic Keratectomy

Patient[a]	Age (y)	Sex	Eye	BCVA (logMAR) Preoperative	BCVA (logMAR) Postoperative[b]	Calculated Ablation (μm)	(Month) T1	(Month) T2
1	57	F	R	0.52	−0.18	113	1	108
1	65	F	L	0.70	0.10	100	12	12
2	32	M	R	0.22	−0.08	100	3	108
2	32	M	L	0.15	−0.08	110	3	108
3	57	F	R	0.52	0.05	114	24	96
3	57	F	L	1.22	0.15	120	3	96
4	66	M	R	0.70	−0.08	120	12	18
4	66	M	L	0.70	0.22	121	12	18
5	61	F	R	0.52	0.15	140	6	18
5	61	F	L	0.52	0.10	125	3	18

BCVA = best-corrected visual acuity; F = female; L = left; logMAR = logarithm of minimal angle of resolution; M = male; R = right; T1 = mean time before achieving the best overall BCVA after surgery; T2 = follow-up period.
[a]Patients 2, 3, and 5 were blood relatives.
[b]Postoperative BCVA denotes the best overall BCVA after surgery.

genetically diagnosed as Thiel-Behnke corneal dystrophy between July 13, 2001 and May 14, 2010. Only the patients who were followed up for at least 12 months after the PTK surgery were enrolled in this study. The mean age of the patients was 55 ± 13 years (range: 32–66 years). None of the enrolled patients had any previous history of corneal surgery. The PTK surgery was performed for the patient's visual rehabilitation at the time when the patient complained of decreased vision or when the patient's best-corrected visual acuity (BCVA) had become worse than logMAR 0.15. Each of the 5 patients had experienced painful erosive episodes prior to undergoing the surgery. Three of the 5 patients were members of the same pedigree.

• MOLECULAR ANALYSIS: Peripheral blood samples were collected from all 5 patients after they had received a complete, detailed explanation of the study protocols. DNA was extracted from the peripheral blood lymphocytes using a commercially available kit (DNeasy Blood & Tissue Kit; QIAGEN GmbH, Hilden, Germany). Exons 4, 11, 12, and 13 of the TGFBI gene, as well as their flanking introns, were amplified by polymerase chain reaction (PCR) and directly sequenced on both strands using previously published primers.[27]

• INTERVENTIONAL PROCEDURE: PTK was performed by the use of 1 of 3 commercially available 193-nm excimer laser devices, each produced by a different company. Five eyes were treated using the EC-5000 excimer laser (NIDEK Co Ltd, Gamagori, Japan), 3 eyes were treated using the VISX S4IR excimer laser (Abbott Medical Optics Inc, Abbot Park, Illinois, USA), and the remaining 2 eyes were treated using the Technolas T-217z Zyoptix laser system (Bausch & Lomb, Rochester, New York, USA). In all 10 eyes, the epithelium was removed directly by the excimer laser, and the ablation continued
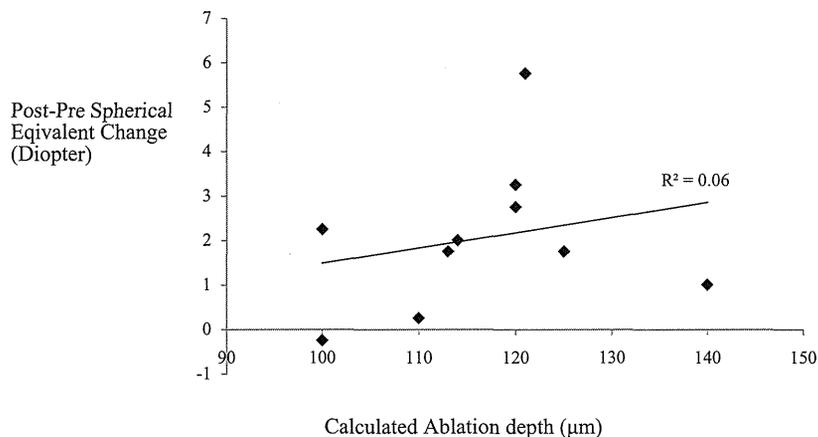
FIGURE 2. A scattergram demonstrating the relationship between the spherical equivalent changes (between preoperative and postoperative) and the calculated ablation depth of phototherapeutic keratectomy surgery in eyes with Thiel-Behnke corneal dystrophy. Although the spherical equivalent change seems to have a tendency to increase with the increase of ablation depth, no statistically significant ($R^2 = 0.06$) association was found between the spherical equivalent changes and the calculated ablation depth.

into the corneal stroma until approximately 50 μm of the stromal ablation was performed. During the surgery, the cornea of each eye was examined by use of the microscope equipped in the excimer laser devices under sclerotic scattering illumination using a vitrectomy-endoillumina-tor placed on the limbus.[28] When deemed necessary, additional ablations were performed to remove the bulk of the pathologic opacity from the visual axis. For all 10 eyes, the ablation was performed until the majority of opacities were removed, thus resulting in a mean calculated total ablation depth (including epithelium and stroma) of 116 ± 12 μm (range: 100–140 μm). Masking fluid was not used. Postoperatively, all 5 patients were initially administrated 0.1% fluorometholone (FLUMETHOLON; Santen Pharmaceutical Co, Ltd, Osaka, Japan) and 1.5% levofloxacin hydrate (CRAVIT; Santen Pharmaceutical Co, Ltd) 4 times daily, with a tapering-off of the dosage over 12 weeks. Each patient was instructed to continually wear a soft contact lens on the operated cornea until the epithelial defect had closed.

● MAIN OUTCOME MEASURES: In this present study, main outcome measures including BCVA, uncorrected visual acuity (UCVA), spherical equivalent (SE), and recurrence of Thiel-Behnke corneal dystrophy were assessed.

● CLINICAL DEFINITION FOR RECURRENCE OF THIEL-BEHNKE CORNEAL DYSTORPHY POST–PHOTOTHERAPEU-TIC KERATECTOMY: The recurrence of Thiel-Behnke corneal dystrophy was considered significant when slit-lamp examination showed signs of increased central opacification of the superficial cornea that were also associated with significant visual loss (a 2-line or more loss of BCVA) according to the previous study.[15] The probability of recurrence of Thiel-Behnke corneal dystrophy after PTK

surgery was calculated using the Kaplan-Meier method for survival analysis.[12,14,15,17]

● STATISTICAL ANALYSIS: For analysis of the results, Excel Tokei 2002 statistics software (SSRI Co Ltd, Tokyo, Japan) was used. Differences between paired samples were analyzed with the paired t test. A probability value of <.05 was considered statistically significant.

RESULTS

THE P.ARG555GLN MUTATION WAS FOUND WITHIN THE *TGFBI* gene in all 5 patients. In all 5 patients, the superficial corneal opacities were successfully removed from the corneal visual axis (Figure 1). In all 10 eyes, epithelial defects closed within 3 to 5 days and visual acuity gradually improved in 3 to 24 months after the surgery (Table.). The mean follow-up period was 60 ± 46 months (range: 12–108 months). Postoperatively, all 5 patients requested to have PTK surgery performed to their contralateral eyes, thus indicating that they were satisfied with the results of the initial PTK surgery.

A 2-line or more increase in BCVA was found in all of the 10 enrolled eyes after the PTK surgery. The mean logMAR BCVA improved from 0.57 ± 0.29 preoperatively to the overall best of 0.04 ± 0.13 postoperatively, which was statistically significant ($P < .001$). The mean UCVA also significantly improved, from logMAR 0.84 ± 0.34 preoperatively to the overall best of logMAR 0.30 ± 0.26 postoperatively ($P < .01$). The average logMAR UCVA change was −0.54 ± 0.31.

The mean SE significantly increased from −1.63 ± 2.74 diopters (D) preoperatively to 0.43 ± 2.13 D postoperatively, which was statistically significant ($P < .01$). The
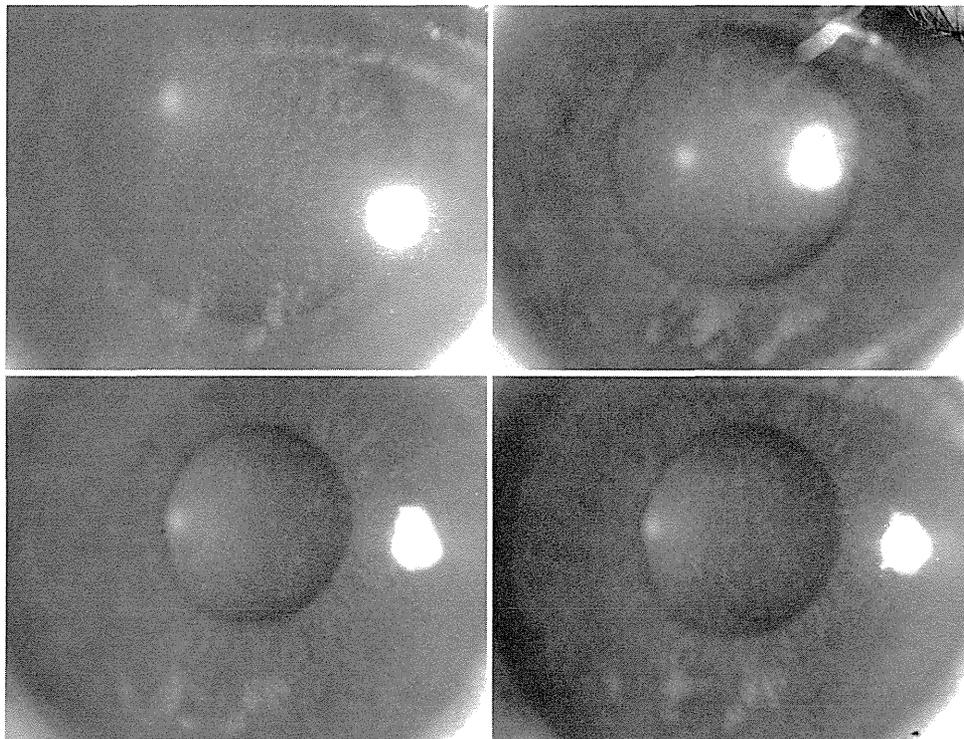
FIGURE 3. Slit-lamp microscopy images of the right eye of 32-year-old man with Thiel-Behnke corneal dystrophy (Patient 2) (Top left) before phototherapeutic keratectomy, (Top right), 3 years after phototherapeutic keratectomy, (Bottom left) 5 years after phototherapeutic keratectomy, and (Bottom right) 8.5 years after phototherapeutic keratectomy. The degree of the opacification at the final follow-up visit (Bottom right) is almost the same as that at 3 years after the phototherapeutic keratectomy surgery (Top right).
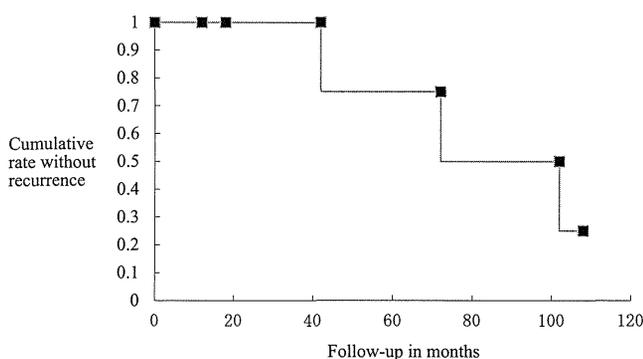
FIGURE 4. Line chart demonstrating the cumulative survival rate for the recurrence of Thiel-Behnke corneal dystrophy after phototherapeutic keratectomy analyzed by Kaplan-Meier survival analysis. The recurrence of Thiel-Behnke corneal dystrophy was defined by significant visual decrease with a 2-line or more loss of best-corrected visual acuity (BCVA) caused by the increased corneal opacification resulting from Thiel-Behnke corneal dystrophy.

average refractive change was +2.05 ± 1.68 D (range: −0.25 to +5.75 D). There was no apparent difference in the SE changes in relation to the type of excimer laser device used or to the calculated ablation depths (Figure 2).

Postoperative complications such as infection, delay in epithelial healing, or stromal haze were not noticed in any of the 10 eyes, and none of the patients experienced any postoperative painful erosive episode. During the follow-up period, 5 of the 10 eyes experienced recurrence of the central superficial opacification. One of those 5 eyes (the right eye of Patient 2) had only a 1-line decrease of visual acuity at 108 months postoperatively (Figure 3). However, in 4 of those 5 eyes, the degree of recurrence was significant enough to lead to a decrease in visual acuity of more than 2 lines, yet none of those patients requested a PTK reoperation at their final follow-up visit. The earliest significant recurrence (the right eye of Patient 3) was observed after 42 months (Figures 4 and 5). The remaining 5 of the 10 eyes exhibited no apparent signs of recurrence, possibly because the follow-up period for those eyes was not very long.

DISCUSSION

IN THE PRESENT STUDY, PTK SURGERY FOR THIEL-BEHNKE corneal dystrophy was found to result in the significant midterm improvement of visual acuity for all patients. During the follow-up period, a gradual recurrence of central superficial opacification was observed, yet the level of the opacification was not severe enough to lead to a significant decrease in visual acuity for at least 42 months after surgery.
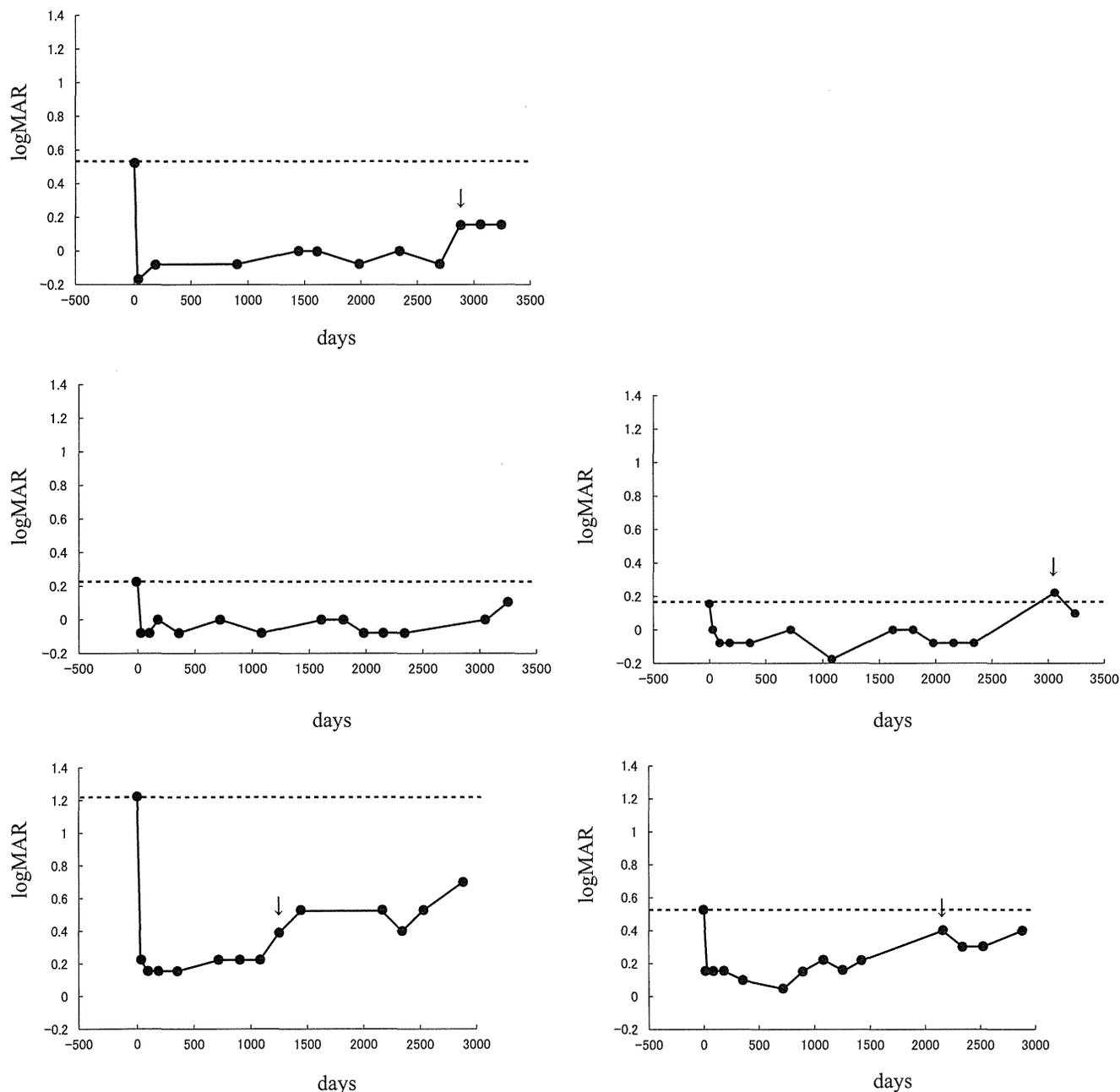
FIGURE 5. Polygonal line graphs denoting the time course of logMAR best-corrected visual acuity (BCVA) in 5 eyes of 3 Thiel-Behnke corneal dystrophy patients followed up for over 96 months after phototherapeutic keratectomy surgery. (Top) Right eye of a 57-year-old woman (Patient 1). (Middle left) Right eye of a 32-year-old man (Patient 2). (Middle right) Left eye of a 32-year-old man (Patient 2). (Bottom left) Right eye of a 57-year-old woman (Patient 3). (Bottom right) Left eye of a 57-year-old woman (Patient 3). Solid circles indicate the time points of the patients' follow-up visits. Arrows indicate the time points when significant recurrences were observed. Broken lines indicate the preoperative logMAR best-corrected visual acuity (BCVA). The recurrence of Thiel-Behnke corneal dystrophy was defined by significant visual decrease with a 2-line or more loss of BCVA caused by increased corneal opacification resulting from Thiel-Behnke corneal dystrophy. logMAR = logarithm of minimal angle of resolution.

To date, 3 previous studies have reported a successful clinical outcome in Thiel-Behnke corneal dystrophy patients after undergoing PTK surgery. The first study enrolled 6 eyes of 5 patients who were diagnosed with Thiel-Behnke corneal dystrophy just from the clinical appearance of their corneas and not by genetic analysis.[9] The second study enrolled 8 eyes of 4 patients who were

clinically diagnosed with Thiel-Behnke corneal dystrophy but who had a genomic linkage to chromosome 10, which is therefore thought to be a distinct pathologic entity of the typical Thiel-Behnke corneal dystrophy bearing the p.Arg555Gln mutation within the TGFBI gene.[11] The third study enrolled 1 eye of 1 patient who had the p.Arg555Gln mutation within the TGFBI gene and who

underwent the PTK procedure on a grafted cornea that had undergone PKP.[12]

Reis-Bücklers corneal dystrophy[29] is a bilateral and autosomal dominant inheritable disease. This disease is clinically characterized by corneal opacities in a "geographic" pattern at the level of the Bowman layer, frequently associated with the episode of recurrent painful corneal erosion,[2] and has been referred to as corneal dystrophy of the Bowman layer and the superficial stroma type I (CDB1, OMIM#60847).[3] Because of the similarity of opacity pattern and opacity depth observed in Thiel-Behnke corneal dystrophy and Reis-Bücklers corneal dystrophy, considerable clinical confusion may still exist in distinguishing between these 2 diseases. Although the opacity pattern of Thiel-Behnke corneal dystrophy is reported to be apparently different from that of Reis-Bücklers corneal dystrophy, the opacity patterns of the 2 corneal dystrophies can appear to ordinary ophthalmologists to be quite similar, thus possibly resulting in considerable clinical confusion in discriminating between these 2 dystrophies. In the 1980s, Thiel-Behnke corneal dystrophy was considered to be a special type of Reis-Bücklers corneal dystrophy. These 2 corneal dystrophies of the Bowman layer were reported to be distinguishable through electron microscopy examination of the patient's corneal tissue. However, since a patient's corneal tissue is normally unavailable, it is often difficult to distinguish between these 2 dystrophies.[30] The only clinically identifiable difference between Thiel-Behnke corneal dystrophy and Reis-Bücklers corneal dystrophy is that Reis-Bücklers corneal dystrophy is clinically characterized by disease onset occurring in the patient at a younger age, the severe degree of corneal opacity, and a worse deterioration of vision compared to Thiel-Behnke corneal dystrophy.[2-4] Recent molecular biological analysis has revealed that Reis-Bücklers corneal dystrophy is caused by a mutation (p.Arg124Leu)[7] of the TGFBI gene that is distinct from that in Thiel-Behnke corneal dystrophy.

It should be noted that the early reports[19,20] of PTK for Reis-Bücklers corneal dystrophy possibly included Thiel-Behnke corneal dystrophy cases. In general, there is almost always a recurrence of Reis-Bücklers corneal dystrophy after PTK,[15] and even after PKP,[8] and the recurrence occurs earlier and with a more severe degree of disease compared with other TGFBI-related corneal dystrophies.

However, despite the prominent similarities in several clinical attributes found in Thiel-Behnke corneal dystrophy and Reis-Bücklers corneal dystrophy, Thiel-Behnke corneal dystrophy patients demonstrated a relatively slow postoperative rate of recurrence after undergoing PTK surgery, as is shown in the findings of this present study. This finding may be the result of the difference in the molecular character of the TGFBI proteins that reflect each distinct mutation site. Thus, the simple PTK procedure appears to be an insufficient treatment for Reis-Bücklers corneal dystrophy. In a previous clinical trial, the usefulness of a topical administration of mitomycin C was assessed in Reis-Bücklers corneal dystrophy patients, and it was found to have a beneficial effect on preventing recurrence after PTK surgery.[31] Thus, it is very important to perform gene mutation analysis against the TGBFI gene to definitively discriminate Thiel-Behnke corneal dystrophy from Reis-Bücklers corneal dystrophy in order to make a more precise prediction of postoperative prognosis, as well as to consider the possible additional treatments, such as the administration of mitomycin C, that will be needed when patients are diagnosed as having Reis-Bücklers corneal dystrophy.

In conclusion, the findings of the present study show that PTK is a successful therapy for Thiel-Behnke corneal dystrophy. It should be noted that this study was retrospective and that the sample size was not very large. In addition, TGFBI corneal dystrophies sometimes demonstrate varying degrees of severity even with the same gene mutation. Thus, it is difficult to make a generalized statement as to the efficacy of PTK surgery for Thiel-Behnke corneal dystrophies from the limited results presented in this study. However, and to the best of our knowledge, this is the first report to demonstrate the midterm clinical outcome of PTK surgery for Thiel-Behnke corneal dystrophy patients who were diagnosed strictly by gene mutation analysis to have the p.Arg555Gln mutation and who had not undergone any surgery to their corneas prior to the PTK surgery. We hope that a randomized controlled trial will be conducted in the future in order to better understand the more precise clinical course of Thiel-Behnke corneal dystrophy after PTK surgery.