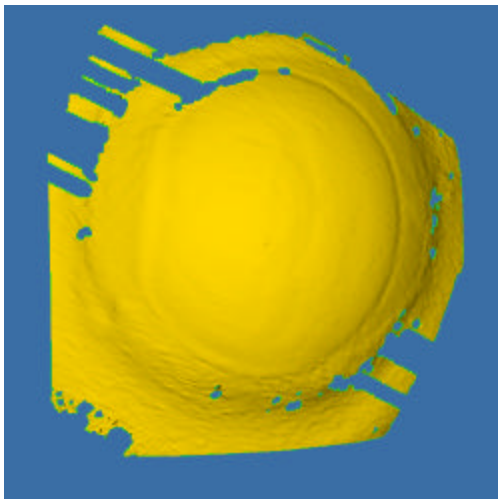
BioShape

New findings and recent developments

with the BioShape ICT



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1 Summery

Alcon has supported clinical research trials conducted by BioShape together with surgeons using the LADARVision platform in Milan and Prague. The aim of the trials was to find out whether BioShape's technology is suited to predict the long term outcome of laser refractive treatments by assessing surface shapes during the ongoing treatments. Results of the trials indicated low predictability of the method in connection with LASIK. The number of PRK patients was too small to draw a final conclusion. It seemed as if PRK was better suited because the far peripheral surface in the region of the limbus remains stable without using any microkeratome as in LASIK. No other results of the trials had been discussed in the final report.

The clinical data was reviewed in order to identify other issues that might be relevant for LASIK or PRK outcomes. This report discusses these issues. First chapter 2 presents a number of beneficial applications of a system adapted and attached to a laser system. A number of research related topics can be examined with such an add-on. It might as well generate profit depending on its design and price. Chapter 3 discusses interesting and new commercial and research applications for a stand alone topographer. Chapter 4 gives an inside view into different aspects of laser treatments that evolved from the clinical study. These aspects have not yet been accounted for due to a lack of public awareness. There is some knowledge with the experts but the issues have obviously not been addressed so far.

Basically there are issues connected with the flap and apparently with the blend zone of the ablation profile that are relevant for the clinical outcome of the treatment. These issues are well documented in this report. We have shown the capability to quantify them. It is absolutely necessary to optimize the treatment and to minimize the effects. BioShape has the required technology to bring the treatment modalities back on track.

As a conclusion neither LASIK nor PRK will be able to provide the currently promoted benefits for the patients without considerable changes. Any form of higher order aberration optimized treatment must fail because of the observed effects. Compared to PRK LASIK has additional bad effects on the outcome. The report shows that it is absolutely necessary to move away from LASIK towards PRK to eliminate flap effects. BioShape strongly suggests to further investigate the findings. We can offer a solution by providing data to optimize the blend zone for each patient individually. This is mandatory as the existing ablation algorithms cannot deliver good quality which is very bad for the future of the market.

2 New ICT applications

When our joint research project did not reveal any direct benefits for using the ICT system as an online monitor during LASIK procedures we have been seeking for alternative fields of application for the technology. Essentially we focus on using it as a superior corneal topographer which is incorporated in or attached to the laser. The following list contains a number of advantages for both the surgeon and the manufacturer.

2.1 Benefits for the surgeon

- Replacement of the conventional topographer. The surgeon does not need his old Placido ring based topographer any more and receives the most recent technology. At the same time he gains some space in his praxis.
- All systems provided by one manufacturer. The topographer provides the surgeon with an integrated solution. Alcon will be the sole partner for all important diagnostic and therapeutic aspects of the treatment.
- One software package. Alcon can deliver a complete software solution for all aspects of the treatment. The surgeon will have just one provider for all his software needs.
- More accurate topographies, wider measuring field. The data provided by the ICT solution is highly superior towards any existing system. Real elevation data show more details with higher accuracy. The large measuring field with lots of data in the periphery even beyond the limbus allows precise registering of data sets from different sessions.
- Difference measurements. Highly accurate difference maps can be generated due to the excellent registration capabilities. This allows to measure very delicate surface feature changes. This enables observing the healing process yielding the whole treatment effect. The ablation rate is accessible intraoperatively.
- Intraoperative 3d control. Local ultrasound pachymetry to control the residual bed thickness is state of the art. A 3d measurement in contrast contains much more information on a much larger area. This is what the surgeon really wants and needs. There are so many variables today that can be eliminated with an accurate 3d measurement.
- Superposition of diagnostic maps. Treatment data, wavefront maps and topographies can be registered using the limbus as a reference. Uncertainties arising from variations in determining the pupil center are eliminated. The surgeon gets the whole picture nicely superimposed.
- 3d flap information. The 3d flap shape is determined by subtracting surface measurements before and after the flap cut. This immediately tells whether the residuals

bed thickness is sufficient for the intended treatment. Intraoperative ultrasound is much less accurate and locally confined.

- Slit lamp function. The fringe projector works nicely as a light source that shows many more tiny surface details. It allows a fast quality check of the repositioned flap immediately after the treatment. It helps easily finding the flap edge for retreatments.
- Epithelial ingrowths nicely visible. The fringe pattern reveals any surface irregularity as its regularly bent lines appear distorted. The distortions give a uniquely clear picture of any ingrowths under a flap. Those are sometimes transparent under the laser microscope and might be left in place. This will not happen when looking at the fringe pattern.
- More confidence in the treatment. ICT's data display a much more complete picture of the whole treatment than ever before. This gives the surgeon more confidence in what he is doing on every single patient rather than relying on statistics. He feels more secure and can do his job much more relaxed.

2.2 Benefits for Alcon

- One manufacturer for all aspects. Alcon is the surgeon's partner for all aspects of the treatment. The customer feels at home with Alcon. The relationship will be reinforced. Alcon can provide an optimum solution instead of justifying differences to other companies' topographers. Hardware and software can be optimized at Alcon's to yield an integrated system with solutions for each aspect of the surgery.
- Innovation, Marketing. Alcon stands for innovative, state-of-the-art products. ICT as an on board solution matches this quality and optimally fits into the product range.
- Simple setup. The optical system can be kept very simple. Alignment and calibration is straight forward. Using the technology will be easy.
- Laser research instrument. The technology allows checking the efficiency of newly developed algorithms. It reveals whether a new shape was really generated on the cornea. Eventually the influence of a potentially variable ablation rate is accessible. Thus it allows checking how real results of software simulations are.
- Flap research tool. The previous clinical trials have shown that flap effects might influence the final outcome even one month after the treatment. Any kind of flap folding, wrinkling or bulging can be monitored with the system.
- Competition advantages. To date no competitor can offer any kind of 3d measurement connected to the laser. On the other hand BioShape has gained lots of experience and know-how during the past five years (partly due to Alcon's support) which

Alcon can now profit of immediately. Thus development cycles can be drastically shortened.

- Combination with aberrometer. Combining different data sets will become more and more important in the future. Especially the registration of wavefront and topography data sounds very promising. BioShape's system with its large measurement area is optimally suited for this task. Alcon would be the first company to use this kind of integrated data sets.
- Add on module. Alcon can offer the technology to every user of the LADARVision technology as an add on system. The manufacturing costs are in the order of a few thousand dollars as the Excimer source is already there. One might even consider using the Alcon PC for the data evaluation sometime in the future by just adding a menu to the existing software. In the beginning a laptop solution will do the job.
- Commercial benefit. A procedure fee might be justified as the safety of the treatment will be improved.

These aspects add to the still existing option of an online control of surface ablations (PRK or LASEK) in the original sense. In some parts of the world surface ablations are still quite popular. The advent of Epi-LASIK and the ever growing rate of all laser procedures might also initiate a renewed interest in ICT for an online control.

3 Stand alone topographer applications

Apart from the issues mentioned above we have identified a number of applications that would benefit from a stand alone topographer based on our technology. Most of them are research related as they require an accuracy which has not been available until today. Actually the awareness of the BioShape technology is quite low in most of these markets as we have not done any marketing so far at all.

Here are some examples of which scleral lenses (3.4) are the most promising:

3.1 Other refractive procedures

A variety of other non laser refractive procedures is based on shape changes of either the corneal surface or the whole eye. These procedures use more or less well established techniques. Nevertheless their outcomes are sometimes not well predictable and their acceptance could be higher. Sometimes the underlying effects are not well understood so that nomograms need to be established and improved regularly. Some of them try to fight presbyopia which sounds like a good idea because of the enormous market.

3.1.1 Conductive Keratoplasty

The company Refratec has received FDA approval for their method of reaching improved near vision by applying radio frequency pulses to the cornea. Changes in the collagen structure of the cornea are supposed to steepen its center resulting in a shift of the cornea's refractive power. The amount of energy deposited in the cornea probably does not always result in the same shape change. It might be a good idea to look more deeply into the changes that are affected short and long term. All this can be done using BioShape's technology which covers the whole cornea even beyond the limbus region.

3.1.2 Intracorneal rings

Intracorneal rings (Intacts) have been on the market for quite some time. Meanwhile the producing company Keravision had to file for chapter 11. Nevertheless intacs are still considered to be an option for certain cases. No study has ever been done about the real shape changes that are induced by inserting those rings into the cornea and whether the procedure is really reversible as claimed. The registration capabilities and the high accuracy of our technology would allow this kind of study.

3.1.3 Treatment of presbyopia

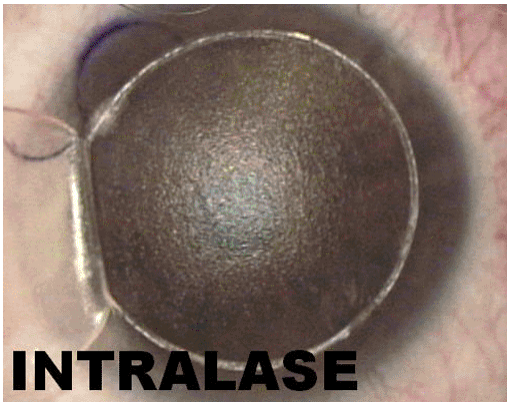
Scleral expansion rings have been claimed to restore the eye's capability to accommodate to fight presbyopia. There are different methods of inserting the rings into the sclera. US companies offering the technology include Surgilight and Refocus (Presby Corp.). The mechanism behind the effect has not yet been well understood. Predictability is low. High resolution measurements of the corneal and scleral surface could reveal in how far the eye's shape is influenced by inserting the PMMA segments.

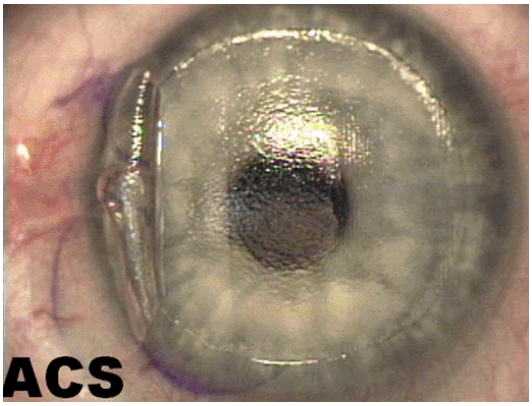
3.2 Microkeratome and flap issues

It is well known that the microkeratome cut has an influence on the corneal structure. Additional aberrations are induced by the cut. In our joint clinical study we found that there sometimes is a hinge effect where the flap does not fully adhere to the underlying bed. This leads to a fold which can compromise vision. It would be interesting to find out which factors influence the size and location of this fold and in how far the patient's vision is deteriorated by the fold.

In addition it is obvious that the flap cannot fit into the bed any more after a treatment. As tissue is taken away by the laser the underlying curved surface is shortened. Hence the flap is too long and too wide after a treatment. Where does the additional tissue go? Will it result in wrinkles and folds or will the flap edge lay on the epithelium outside the crater? The latter would allow epithelial ingrowths.

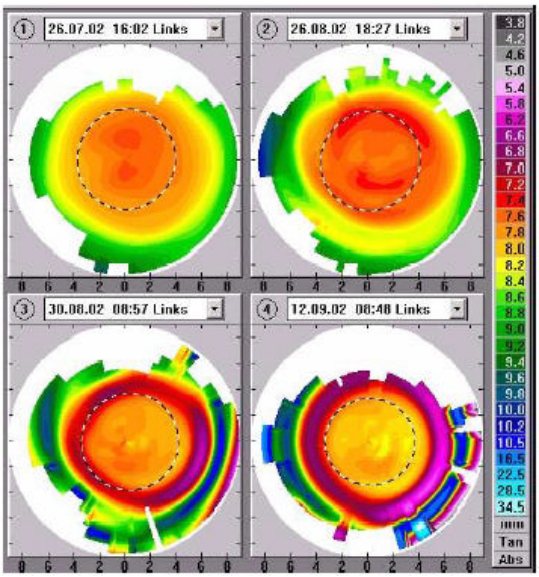
We observed some of these issues in our study. One might consider taking a closer look at them in a controlled study including a femtosecond laser microkeratome.





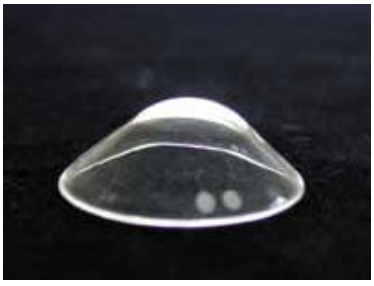
3.3 Orthokeratology

Recently a new contact lens has been introduced in the market (Paragon in the US). It can cure low to moderate nearsightedness over night. This is achieved by remodeling the epithelium using local pressure on the tissue while sleeping. The technology works for up to -4 diopters and seems to be completely reversible as only the epithelium is altered. Until now it is not well understood how the remodeling is affected. Results have only been observed with conventional topographers that do not cover the whole area influenced by the lens. Our technology would allow taking a look at the changes beyond the edge of the lens that might influence the central shape. The picture shows an example of a cornea of which the curvature (measured by a Placido ring system) was changed by orthokeratology.

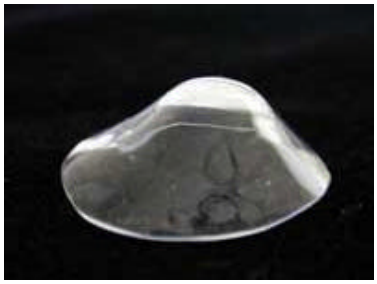


3.4 Scleral lenses

There are corneal diseases having a large visual influence that cannot be overcome with conventional vision aids. These diseases include keratoconus and bad refractive laser surgery outcomes. Most of these patients can be treated with good success using scleral lenses (Boston scleral lens in the US). The lenses are more than 20mm in diameter and fit on the sclera. There is no contact with the cornea. Instead the volume between the lens and the cornea is filled with liquid. Scleral lenses fit on the sclera which requires a good knowledge of the sclera's shape. To date there is no technology to measure the sclera sufficiently accurate. Instead a set of fitting lenses is provided by the company which makes the process complicated and long. It also requires an expert in the field to do the fitting. There are only few experts left as scleral lenses are not very common any more. With our technology at hand fitting those lenses would be straight forward as we collect highly accurate data from the sclera. Multiple measurements with the eye looking in different directions allow us to cover a range of more than 20mm in diameter after registering the sin-



gle measurements. This is the basis for manufacturing an extremely well fitting lens. The diagnosis is much faster than today and does not require an experienced lens fitter. There is a huge and even growing market for scleral lenses, especially as long as laser surgeries are still popular and their outcomes so unpredictable.



3.5 Customized contact lenses

The US company Ophthonix offers an aberrometer which they claim to use for building individual wavefront optimized glasses. They have established a partnership with Optical Connection to offer individual wavefront optimized contact lenses. It seems to make sense to have a good knowledge of the underlying surface of the contact lens to guarantee its position on the eye. Otherwise higher order aberration cannot be corrected efficiently. This highly accurate surface shape information can be provided with BioShape's technology.

4 Clinical data reviewed

We have taken another look at the clinical data as we have further improved our software to display more details. Our main focus was to understand how the flap influences the peripheral surface shape even more than 30 days after the treatment. These effects were not in the scope of the first report which focused on the intraoperative measurements. Some of the effects can be seen in the yellow 3d models using special illumination. The effects become very obvious when looking at curvature maps that were generated from the height data.

The colored maps show the local curvature derived from the height data by calculating the mean between maximum and minimum slope within a 1.5mm diameter. Curvature values are given in diopters. The white bar on the lower left represents 1mm. Control pictures were taken at least 30 days after the treatment as a stable situation had been assumed by then.

We were interested in whether the effects found in LASIK eyes differed from what the PRK outcomes looked like. Surprisingly also PRK eyes in some fields showed similar effects. This lead to the following conclusions:

1. The flap generation has an influence on the surface shape that might can extend well into the optical zone.
2. The flap effect is larger for deeper ablations
3. PRK treatments also show effects in the periphery.
4. The blend zone seems to play an important role in this context.
5. Precise knowledge of the pre op surface shape might allows to generate an individually optimized blend zone for each patient.

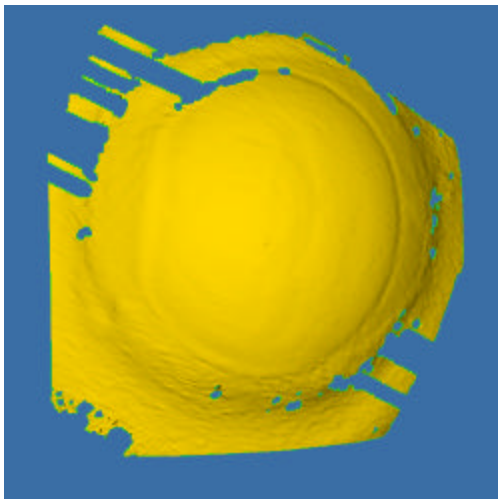
4.1 LASIK patients

Nearly all of the LASIK eyes show some peripheral bulging of the surface toward the flap's edge. The bulging is more pronounced with deeper ablations. This indicated a correlation which can be explained with the difference of the areas on the inside of the flap and in the treated bed. After the treatment the flap does not fit any more. The surgeon usually makes sure that the flap adheres well in the center. The residual tissue is then piling up towards the bed's edge. The following patients give some examples.

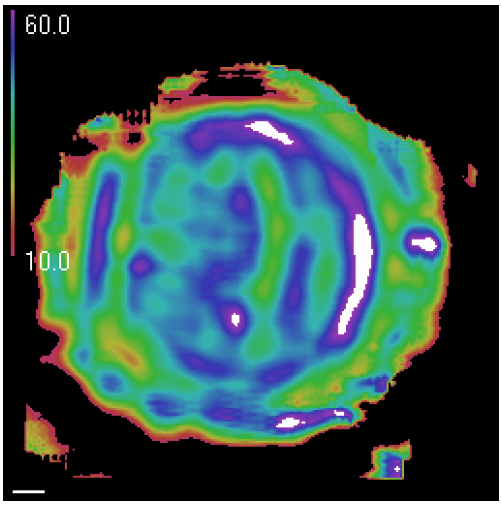
4.1.1 Patient 1 : -6.5D -0.5D x 20°

The following measurements were taken from Vladimir Horak's left eye. He was treated on May 15th 2003 in Prague for -6.5D -0.5D x 20° with a 7mm treatment zone. The Amadeus microkeratome was supposed to cut a 140µm flap.

Here are the 3d model and the curvature map after closing the flap:



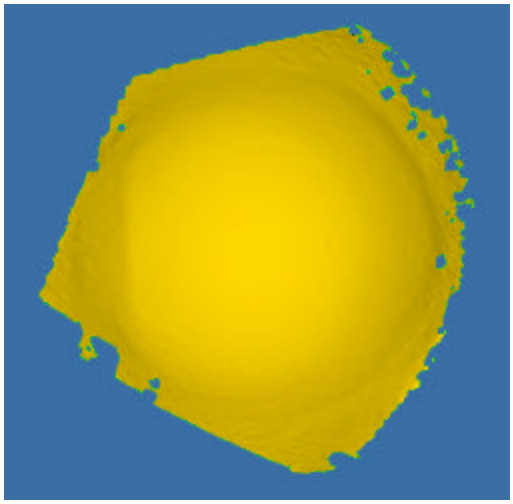
Horak OD: 3d model…



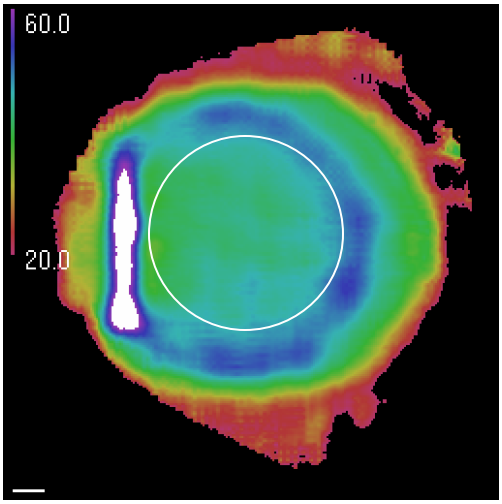
…and curvature map after flap closing.

The surface shows severe irregularities after the flap was closed. In the center there are many wrinkles partly with large amplitudes. The flap edge is bulging in the region from 12 to 4 o'clock (white colours are curved by more than 60D). At the hinge there is a fold which is well visible even in the 3d model. We assume that some of these folds result from the way the flap was opened. Also there is insufficient space in the bed for the flap after the laser has taken away the tissue. The appearance of the closed flap of this patient looks similar to many others.

Here are the corresponding pictures at 40 days after the treatment:

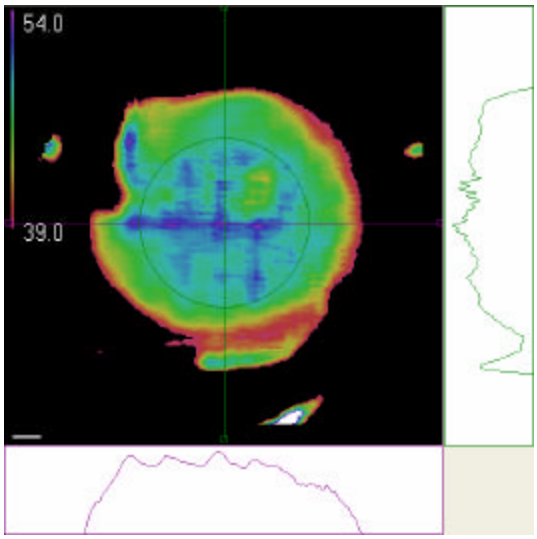


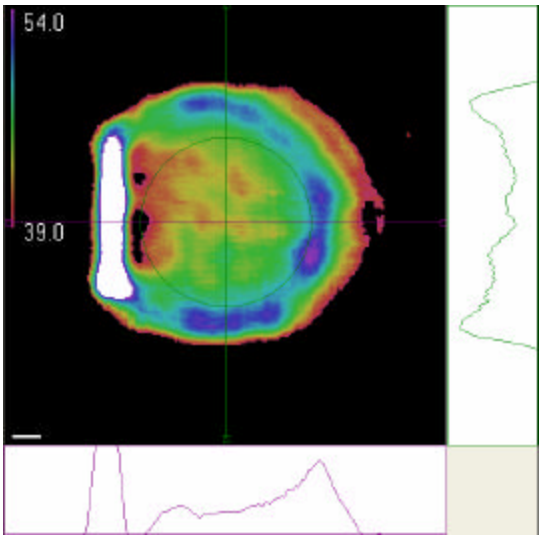
Horak OD: 3d model…



…and curvature map 40 days post op.

The 3d model still shows the fold at the hinge quite clearly. This fold is even better visible in the curvature map. Most of the wrinkles have disappeared as the flap relaxed and adhered nicely in the center of the cornea. It can be assumed that the flap edge fits nicely in the bed border. AS a consequence there is tissue left in the center that piles up inside the bed's border. This appears as the blue bulge which extends well into the 6mm zone.
The following two maps compare the curvature before (left) and 40 days after the treatment (right) on a 15 diopters colour range. Linear scans using the same scale along the lines in the maps are displayed next to them. The green circle has a diameter of 6mm.





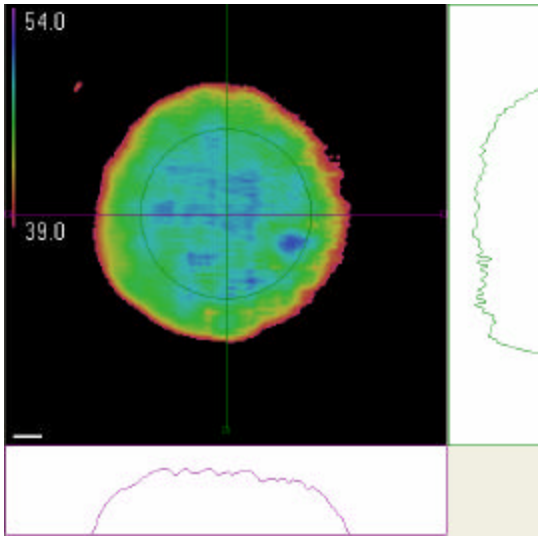
Horak OD: curvature pre… … and 40 days post op.

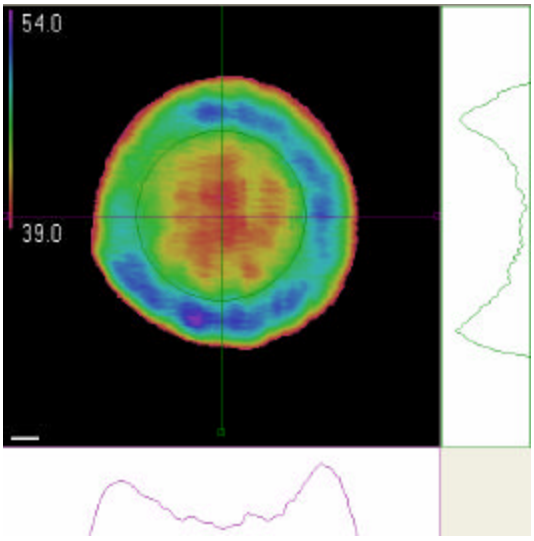
The juvenile cornea shows the expected pattern of a quite spherical central cornea with a constant curvature. The aim of a treatment is to constantly lower this curvature. The original structure can be recognized on the right hand side. Nevertheless the intended aim was not achieved at all. Instead there is a linear increase of the curvature starting at low values at the hinge and rising about 10 diopters within 6mm towards the opposite side. In the vertical direction the bulging of the flap is even more obvious than in the first map.
The patient is one of many examples showing that an increase of the treatment zone to 7mm or more does not automatically help achieving good night vision with a large pupil. Instead a larger flap diameter would be necessary to overcome the bulging problems at the bed edge. In this case the linear decay of the curvature towards the hinge is an additional problem.

4.1.2 Patient 2 : -7.5D

The next example is the right eye of Dagmar Havlickova who was operated on May 20th 2003 in Prague for -7.5D (OZ 7mm). The Amadeus microkeratome was used to cut a 140µm flap.

The following pictures show curvature maps before (left) and 31 days post op (right) again with a total colour range of 15 diopters. Horizontal and vertical line scans are displayed on their corresponding sides. The green circle has a diameter of 6mm. The line scans of the pre op map have a rather flat top out to about 8mm. Those of the post op map are only constant within the central 4mm at most.





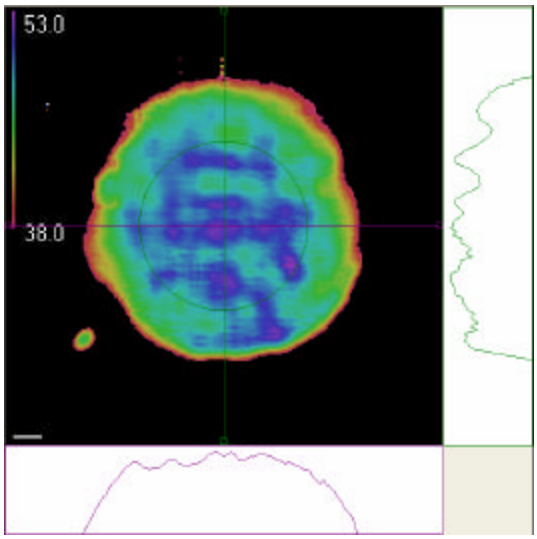
Havlickova OD: curvature pre… … and 31 days post op.

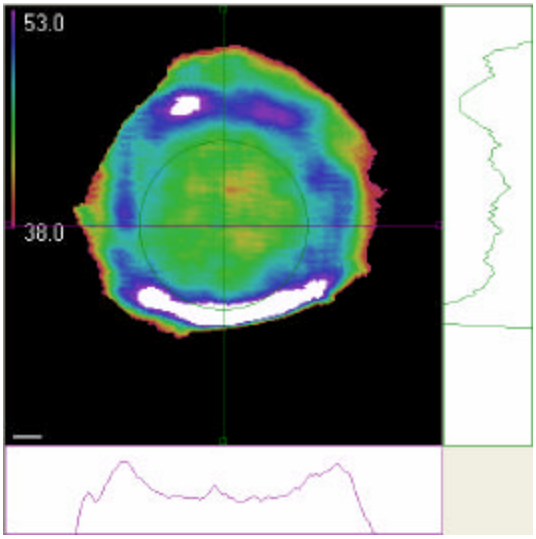
Although this eye does not show the hinge artefact there is considerable bulging of the surface starting clearly within the 6mm zone. The post op curvature map is certainly nothing a surgeon or manufacturer intends to deliver as an outcome after a LASIK procedure. This is certainly not what was programmed into the laser. It is always the aim to generate a sufficiently large optical zone.

It appears doubtful if this aim can be reached by increasing the treatment zone. This goes along with a deeper ablation and hence an even worse fitting flap with more bulging at the bed edge.

4.1.3 Patient 3 : -5.75D

These pictures are from Jitka Lohbergerova, treated on May 14th 2003 for -5.75D (7mm OZ) on her right eye. The microkeratome used was the Beckson Dickinson (130µm flap).



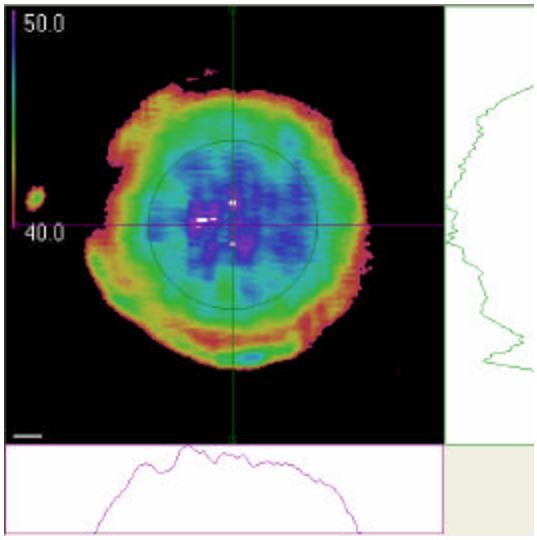


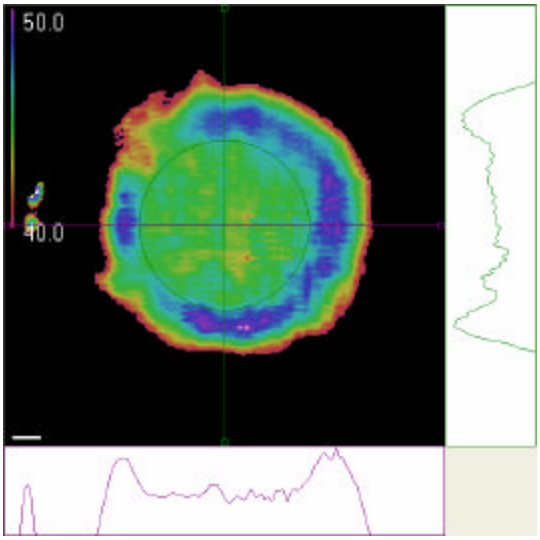
Lohbergerova OD: pre laser… …and 33 days post op.

Again the cornea is rather spherical before the treatment. It appears irregularly surrounded by the bulging flap tissue on day 33 after LASIK. As the treatment itself was symmetric the effects seem to be more strongly related to the flap than to the ablation.

4.1.4 Patient 4: -3.5D -0.5 x 180°

These pictures are from Richard Karlik's right eye. He was treated on May 22nd 2003 for -3.5D -0.5 x 180° (7mm OZ, Amadeus 140µm).



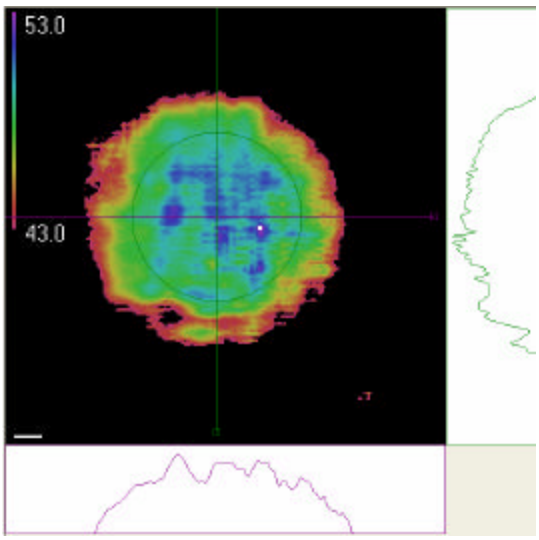


Karlik OD: pre op… …and 33 days post op (range 10D!).

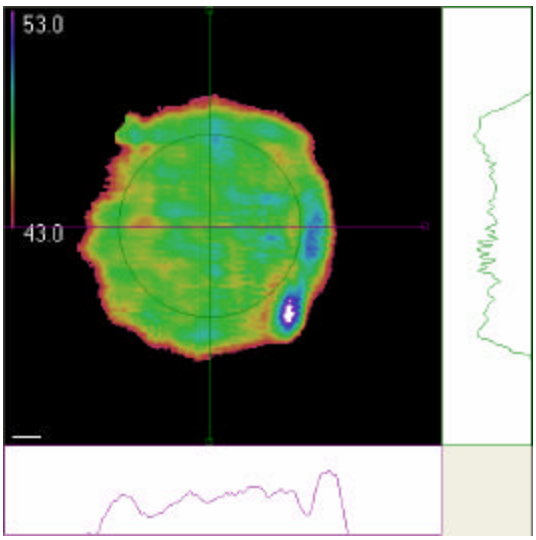
Here the bulging is lower and the spherical region is wider. Still the surface is not looking as intended beyond the 6mm zone. The difference is about 5 diopters.

4.1.5 Patient 5: -2.5D

Jan Pesan's left eye was treated for just -2.5D on May 14th 2003 (7.5mm OZ, BD 130µm). Here are his maps (10 diopters range):



Pesan OS: pre op…

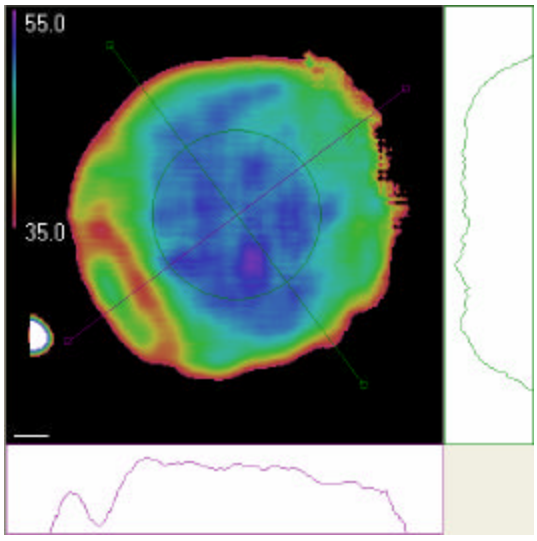


…and 33 days post op (range 10D!).

Even at -2.5D there is still some slight bulging left. It seems as if that should not matter too much though, at least compared to the previous examples.

4.1.6 Patient 6: retreatment

This patient, Simone Roche, received a retreatment of her right eye for -0.5D -0.75D x 150° after her flap was lifted on February 26th 2003 in Milan. Hence she was not included in the original study. This is a curvature map of her eye before the treatment:



Roche OD before flap lift.

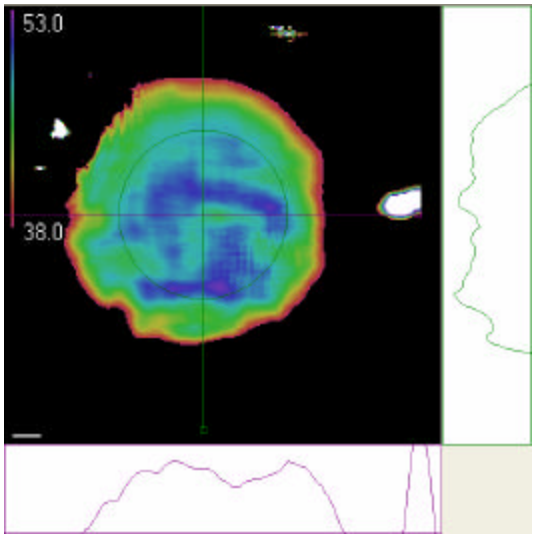
Again the hinge artifact is well visible. It seems to be quite far away from the optical zone though. Nevertheless the picture shows that even after much longer than one month there remains an unforeseen und potentially problematic side effect from the flap cutting.

4.2 PRK patients

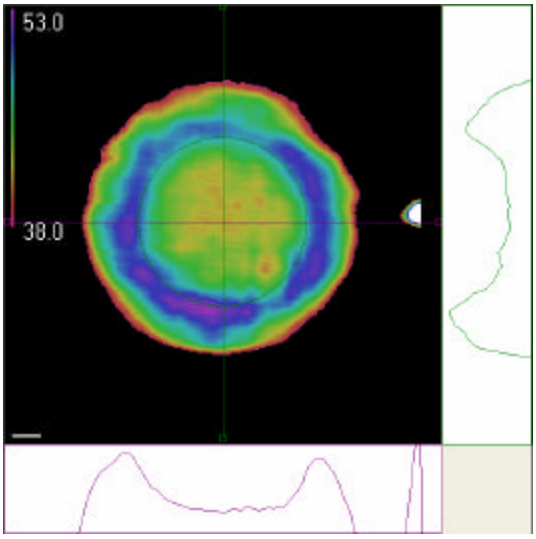
If the flap artifact was only problematic for large corrections one might consider PRK treatments the better option to prevent the effect. Unfortunately the few PRK eyes that were included in the study also show some similar effects. They are more regular and symmetric. This leaves the treatment itself and more specifically the blend zone as the only explanation for bulging effects. It might seems to be reasonable to adapt the blend zone to the specific needs of the patient's cornea. This would requires an exact measurement of the peripheral shape that could then be accounted for in an optimized individual blend zone.

4.2.1 Patient 1: -6.25D 0.75D x 145°, TZ 7mm

Mauricia Ghiradelli's left eye was treated in Milan for -6.25D 0.75D x 145°(7mm OZ) on March 11th 2003. Here are her pre op and control curvature maps with 15 dioptersrange:



Ghiradelli OS: pre op…

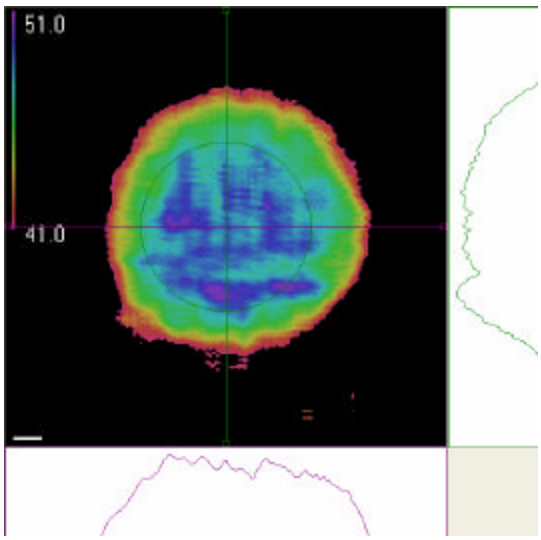


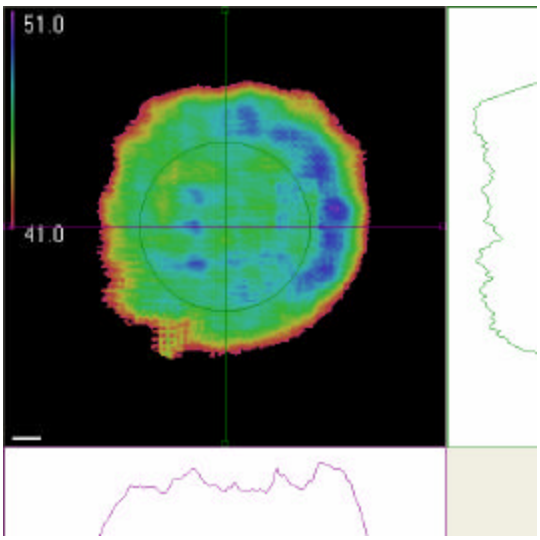
…and 23 days post op.

Again the pre op map shows a quite regular curvature. The post op map displays a similar pattern as the LASIK patients. It is more symmetric about the center. The central curvature was reduced as intended. But starting at about 5mm there is an increase in curvature well above pre op level.

4.2.2 Patient 2 : -1.6D, TZ 7.5mm

Eva Stepanova's right eye was treated on May 22nd 2003 in Prague for just 1.6D. Here are her maps:



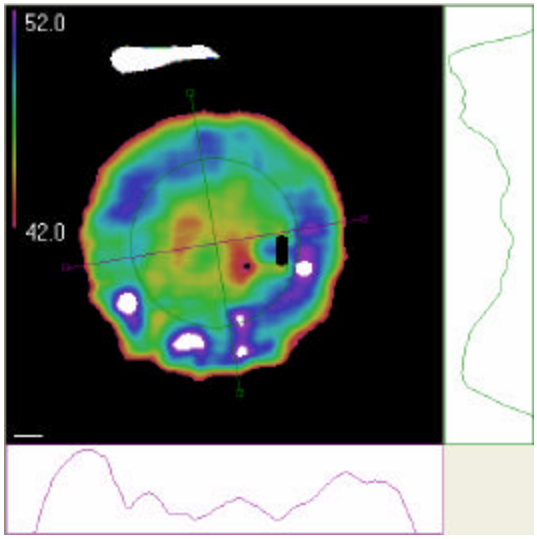


Stepanova OD: pre op… …and 26 days post op.

This patient is an example for a rather small ablation which nevertheless shows some effects in the periphery. In this case the elevated curvature is restricted to the 12 – 4 o'clock area just along the 6mm zone.

4.2.3 Patient 3: retreatment

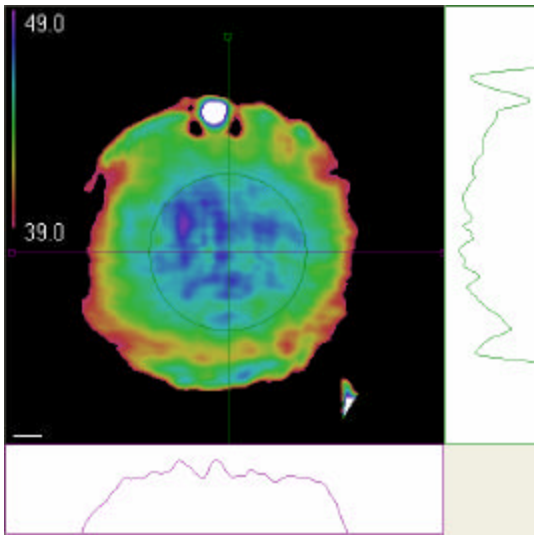
This patient, Patrizia Zamperioli, received a PRK retreatment of -2.3D -0.1 x 70° (6.5mm OZ) on February 25th 2003 in Milan. Here is the map of the eye before the retreatment:

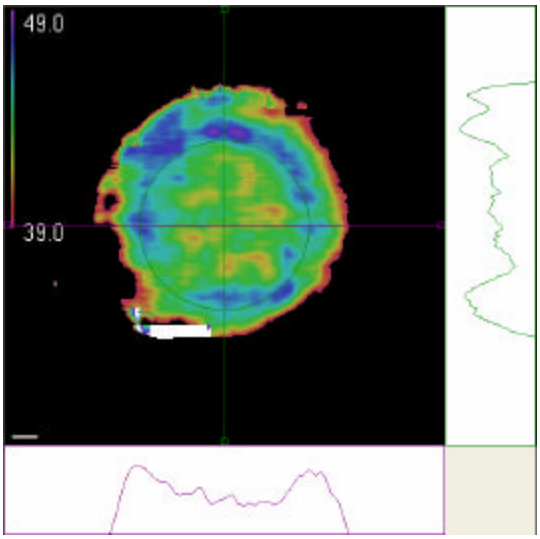


The bulging effect in the periphery was present before the retreatment. There is no control measurement of this patient so we cannot tell how it changed after the retreatment.

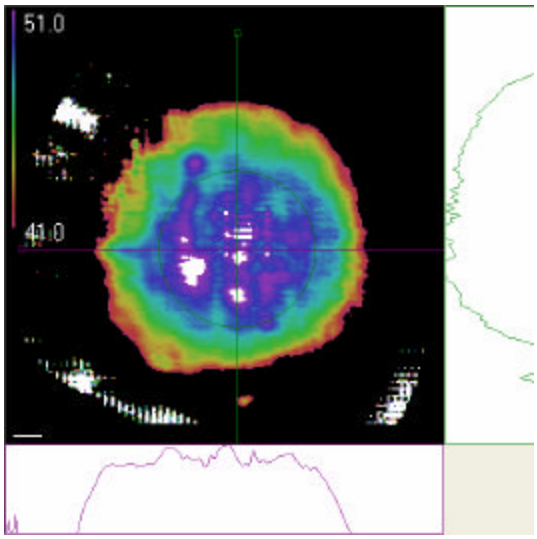
On the following pages there are another 6 PRK eyes that all show similar patterns.

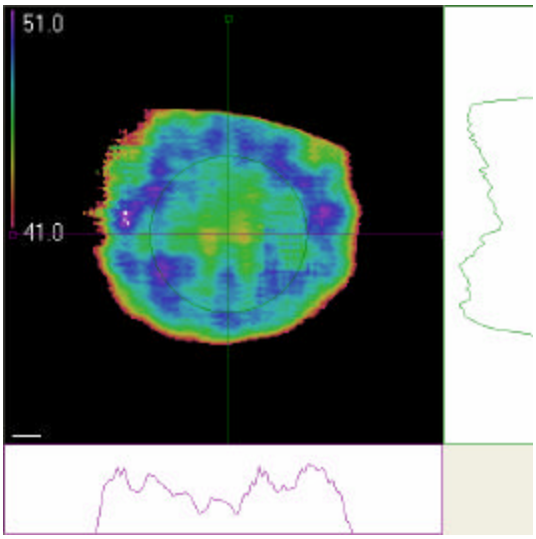
Vrba OD: -3D, TZ 7mm, BZ 0(?)



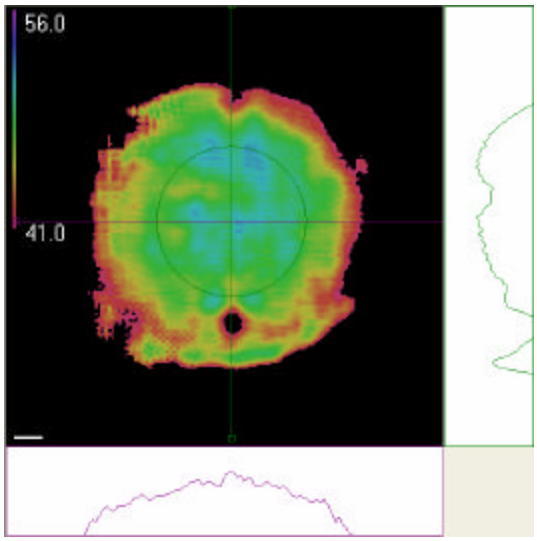


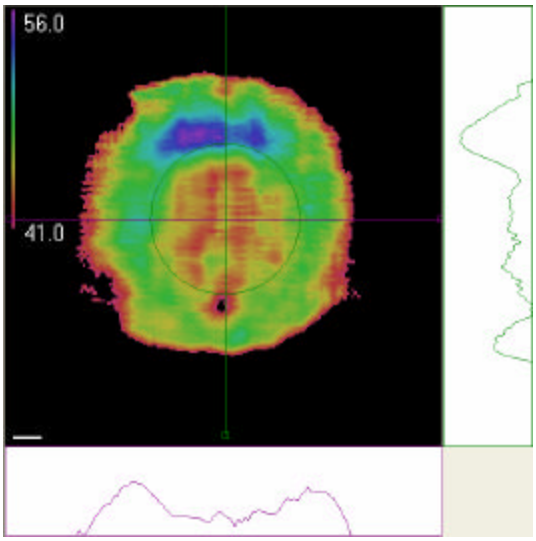
Machyan OS: -3.5D, TZ 6.5mm, BZ 0 (?)



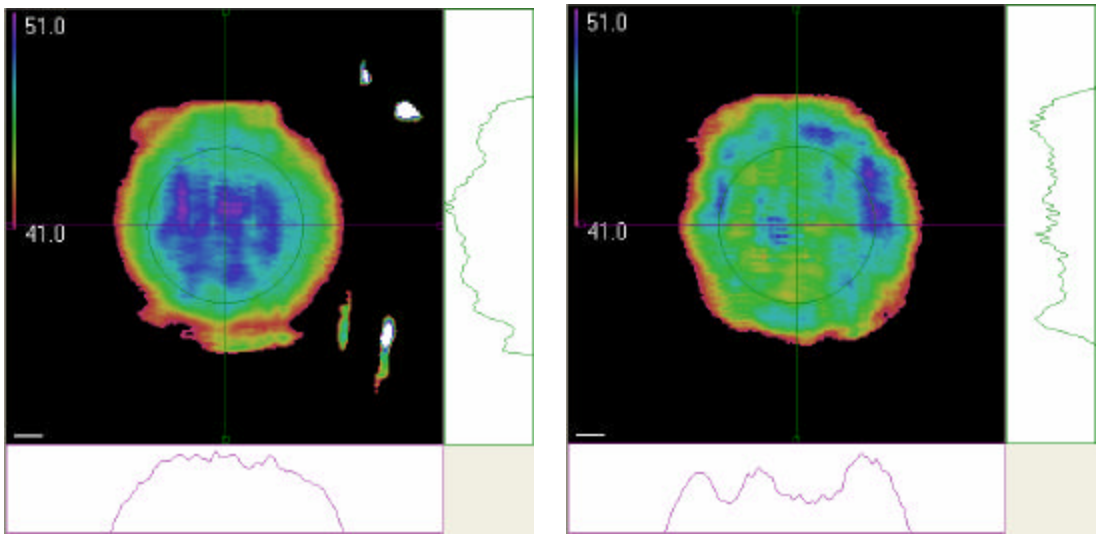


Smida OS: -4.5D -1D x 50°, TZ 6.2mm, BZ 1mm

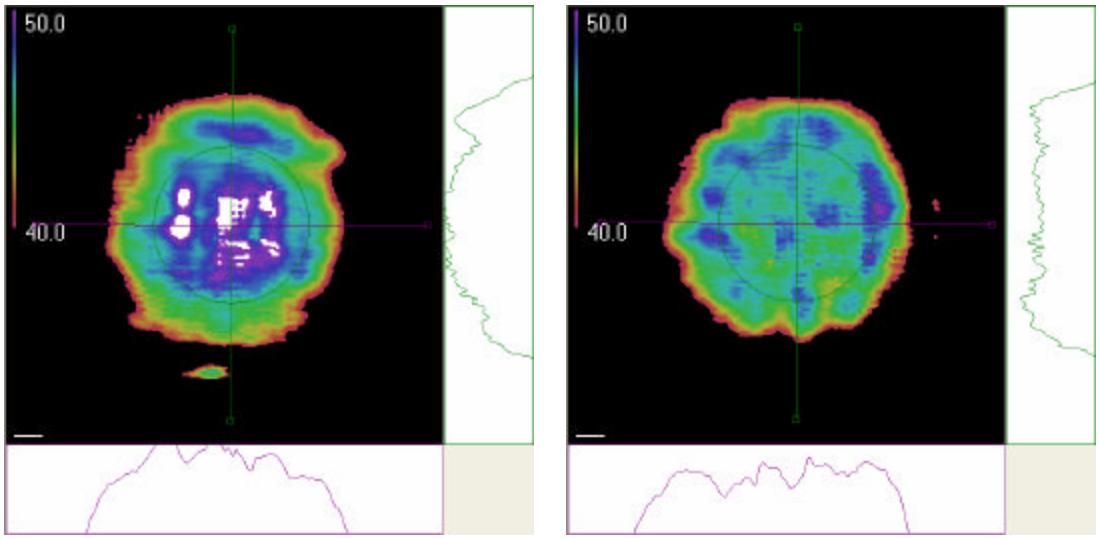




Zemankova OD: -2.6D, TZ 6.5mm



Zemankova OS: -2.75D, TZ 6.5mm



Kindlova OS: 2.6D, TZ 7mm