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Espensen, CA, Jensen, PK, Fog, LS et al. (5 more authors) (2017) Ultrasonic mirror image from ruthenium plaque facilitates calculation of uveal melanoma treatment dose. British Journal of Ophthalmology, 101 (9). pp. 1206-1210. ISSN 0007-1161

https://doi.org/10.1136/bjophthalmol-2016-309626

Ultrasonic mirror-image from Ruthenium plaque facilitates calculation of uveal melanoma treatment dose

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Word count: 2530 words

SYNOPSIS:

In uveal melanoma patients, intra- and inter-observer variances were reduced by using ultrasonic mirror-images from Ruthenium plaques to determine dose depth. This indicates that the method facilitates a more reliable calculation of treatment dose.

BACKGROUND/AIMS:
To present a new method to determine dose depth and the distance from the concave side of the plaque to the tumour base in uveal melanoma patients treated with Ruthenium-106 based on ultrasonic mirror-image.

METHODS:
We used the mirror-image associated with ultrasound during plaque brachytherapy to determine intra-observer reproducibility and inter-observer agreement between two surgeons. 230 eyes with primary uveal melanoma were included in a retrospective analysis to determine the distance from the plaque to the tumour base using ultrasound. A phantom study was used to illustrate the effects on radiation dose to apex of the tumour when the dose depth was incorrectly determined. Doses to apex of the tumour were determined using Plaque Simulator™.

RESTULTS:
The intra-observer variation in dose depth measurement *with* plaque was significantly lower than for measures *without* plaque ($p<0.001$). Agreement between the surgeons was better with a plaque in place. Distances from the plaque to the tumour base were distributed with mean=0.99 (median: 1, range: 0.1 mm – 2.9 mm). From the phantom study it was clear that the tumour did not receive the prescribed 100 Gy if the dose depth was incorrectly determined.

CONCLUSION:
The dose depth in uveal melanoma patients must be measured accurately for correct calculation of the radiation dose to the apex of the tumour. Repeated in-vivo and in-vitro ultrasound measurements of dose depth showed higher variance than measurements using the mirror-image produced from a Ruthenium-plaque. Using the mirror-image thus help to improve the dose calculation.

INTRODUCTION

Ruthenium-106 (Ru-106) brachytherapy is widely used for patients with uveal melanomas (UM) as eye salvaging treatment[1–4]. To ensure sufficient radiation to the tumour with minimal damage to adjacent tissue it is crucial that dose depth determination is accurate[2,3,5–7].

Internal reflectivity, tumour size (Figure 1A), and correct positioning of the plaque (Figure 1B) can be evaluated by ultrasonography B-scans[2,8–12]. Dose calculations are often based on these ultrasound measurements, and include tumour height, scleral thickness and potential contribution from extraocular tissue such as muscle insertions and blood vessels:

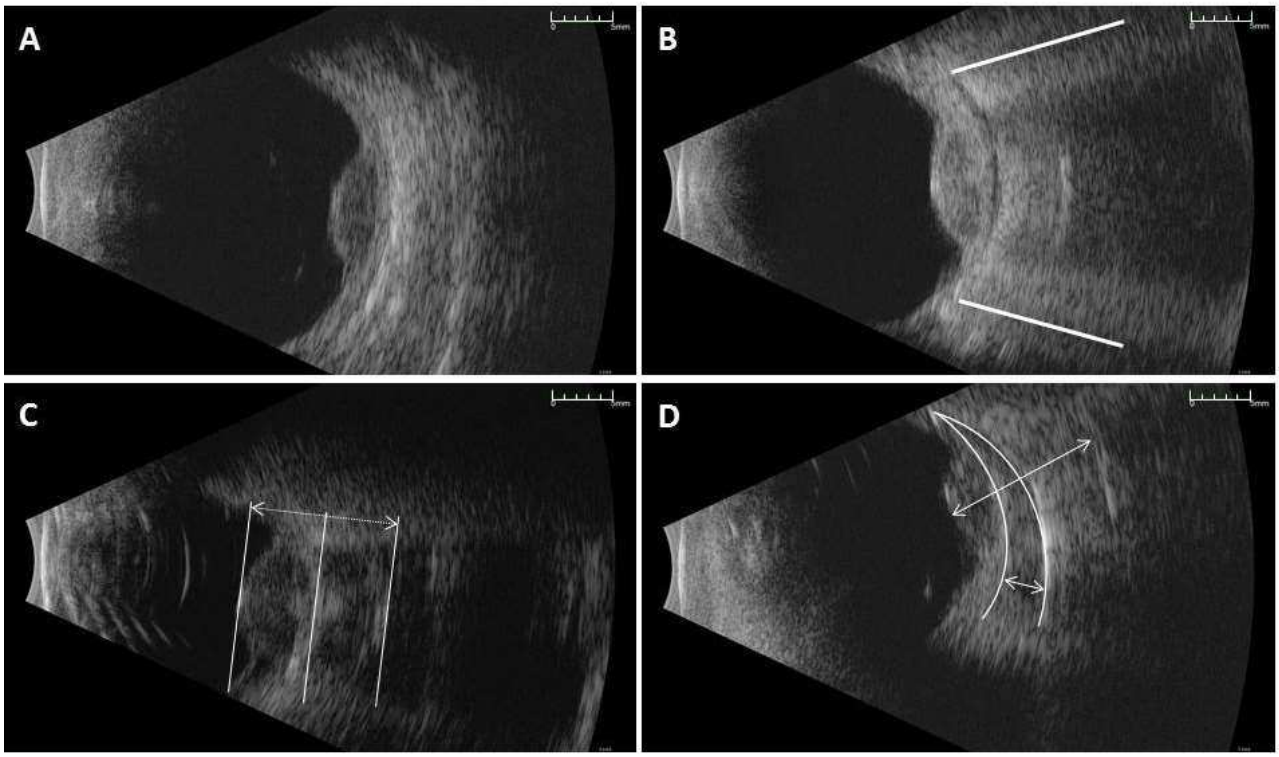
$$\text{Dose depth} = \text{tumour height} + \text{scleral thickness} + \text{extraocular tissue} \quad (1)$$

Due to the 3-dimensional shape of the tumour it is challenging to measure the correct dose depth with the 2-dimensional ultrasound method. Conventionally, dose depth is measured from apex of the tumour perpendicular onto the tumour base and 1 mm is added as this is assumed to be the scleral thickness[3,11,13]. However, in a normal eye, scleral thickness varies and is thickest at the posterior pole (1 mm) and thinnest behind the rectus muscle insertions (0.3 mm)[14,15]. Furthermore, scleral thicknesses vary between individuals, a statement possibly related to refractive variation (higher myopia, longer eyes and a thinner sclera; higher hyperopia, shorter eyes and a thicker sclera)[16]. This probably also underlies the gradually increase with age[15]. A standard scleral thickness may thus be incorrect for many eyes and may result in incorrect delivery of dose to the apex of the tumour. Furthermore, extraocular tissue and post-operative bleeding may contribute to an increased distance between the plaque and the tumour[11].

A new per-operative method for measuring the dose depth has been developed at the ophthalmic oncology service at Rigshospitalet: B-scan patterns perpendicular to the plaque often show a mirror-image (MI), represented as a brighter flare from the plaque surface behind the eye, with the profile of the intraocular tumour surface partly mimicked behind the retro-bulbar line. The MI is a result of transmitted and forward scattered sound encountering the plaque. When the focused soundwave encounters the tumour, some is backscattered to create its primary conventional image. The transmitted sound is reflected from the plaque, visualising the tumour again by sound scattered backward, and reflected a second time from the plaque to create the MI. The MI occurs equidistant behind the plaque and the signal from the MI is maximized where the sound beam is perpendicular to the plaque (Figure 1B-D). A minimal fraction of sound scattered in other directions contributes to the image[17,18].

We propose that this new ultrasonography method using MI can be used to reduce uncertainties and increase reproducibility and agreement between surgeons in the dose depth measurements. We retrospectively examined the distance from the concave side of the plaque to the tumour base in a cohort of patients treated at our institution. Finally, the effect of incorrect determination of dose depth on the minimum dose to apex of the tumour was explored.

METHODS



Figur 1: A: Pre-operative ultrasonic posterior B-scan. The tumour is seen as an elevated mass with middle-to-low internal reflectivity posteriorly in the eye. B: Per-operative ultrasonography B-scan of a Ru-106 plaque (CCB) fully adapted to the eye-wall. Acoustic shadowing behind the radiation plaque is seen as central attenuation of the signal flanked by enhancement of the signal. In the attenuated part of the signal a mirror effect is observed. The white lines illustrate the border of the acoustic shadowing. C: Per-operative ultrasonography B-scan showing the MIA. The white lines mark the apex and the base of the tumour and the mirror image of the tumour. The arrows indicate the double dose depth. D: Post-operative ultrasonography B-scan. The plaque is not fully adapted to the eye due to bleeding and the double dose depth is increased. The contribution of additional tissue must thus be included in the distance from the plaque to tumour base used for dose calculation. Measuring bar=5mm.

Scanning technique

The transducer was placed with the scan plane vertical and pivoted around the centre of the eye in the horizontal plane to locate the maximum tumour height perpendicular to the ultrasound beam. Subsequently, the transducer was translated to maximize the underlying echo from the plaque and the image was frozen and stored. The manoeuvre was repeated with the transducer scan plane horizontal. Only cases where the maximal heights were identical in both vertical and horizontal scans through the tumour apex were considered for dose depth measurements.

Reproducibility of dose-depth determination

Intra-observer reproducibility was determined from three repeated measures of dose depth made by a single experienced ophthalmologist on ten human eyes with and without a plaque in place, and from three repeated in-vitro ultrasound measurements on two porcine eyes with an artificial tumour (see below) with and without a plaque in place made by two experienced ophthalmologists.

Inter-observer agreement between two surgeons was determined from the same two porcine eyes with and without a plaque in place on both porcine eyes. One eye was scanned twice by one

surgeon making a total of 5 ultrasonographs *with* and 5 ultrasonographs *without* plaque available for measurements. Threefold repeated measures were made by each surgeon on each of the ultrasonographs leading to a total of 60 measurements. The height without plaque was determined from the apex perpendicular onto the base of the tumour. After placement of the plaque, the dose depth was estimated from the MI (Eq. 2 below).

The enucleated porcine eyes were kept in saline water for approximately 24 hours before use. Approximately 0.5 cc Healon GV® from Abbott Medical Optics was injected in the supra-choroidal space to produce a tumour. An incision was made 2 mm behind limbus, and blunt dissection in the supra-choroidal space was performed using a sub-Tenon cannula (KD Medical GmbH, Berlin, Germany). Ultrasound system Ellex Eye Cubed™ with a posterior segment 10 MHz probe (Adelaide, Australia) was used for measurements.

Acoustic shadowing and MI appeared only simultaneously with perpendicular propagation of the ultrasound onto the plaque. This ensured that the obtained image represented the structures in the central axis of the plaque. The double dose depth could be identified as the distance from tumour apex of the actual tumour to apex of the mimicked tumour (Figure 1C). The actual dose depth was calculated as half of the double dose depth.

$$\text{Dose depth} = \text{double dose depth}/2 \quad (2)$$

Intra-observer reproducibility was evaluated by comparing measurement variances with and without the plaque in place: For each image separately, the mean of the three measures was calculated, and this mean value was subtracted from the three individual measures. The total variance for all adjusted measures for a single setting (e.g. porcine eyes with plaque in place) was then estimated. Fligner-Killeen test for homogeneity between variances was used to compare measurement variation with and without the plaque in place. Agreement between the two surgeons was evaluated by a two-way model of intraclass correlation coefficient (ICC) for single measures.

Retrospective analyses of uveal melanomas

230 eyes with primary UM (in the choroid or the ciliary body) were included in a retrospective analysis of dose depth determination using ultrasound. Patient and tumour characteristics are listed in Table 1.

Patients characteristics	
Gender (no. male/female)	116/114
Mean age at treatment (years)	61
(median, range)	(62, 23-94)
Tumour characteristics	
Mean tumour height (mm)	4.4
(median, range)	(3.8, 1.3-11.7)
Mean largest basal diameter (mm)	11.4
(median, range)	(11.1, 4.4-23.0)
Diagnosis	

Choroidal melanoma (no.)	224
Ciliary body melanoma (no.)	6

Table 1: Patient characteristics, tumour characteristics and diagnosis of included patients.

All eyes received Ru-106 brachytherapy as primary treatment between 2005 and 2014 at the Department of Ophthalmology at Rigshospitalet, Denmark. Plaque insertions were performed in the operating theatre under sterile conditions and general anaesthesia. We used Ru-106 plaques in different sizes and shapes (CCA, CCB, CCC, and COB), all supplied by Eckert & Ziegler BEBIG (GmbH, Berlin, Germany). The surgeries were done by three experienced ophthalmologists during the entire period.

We used posterior segment 10 MHz probes for all the examinations. In the first 112 patients an I3-ABD System (Innovative Imaging Inc., Sacramento, CA, USA) was used. In the latter 118 patients the same probe but a new machine (Ellex Eye Cubed™, Adelaide, Australia) was used as the I3 Company was bought up by Ellex. Ultrasonic posterior B-scans were recorded in all eyes before and immediately after plaque insertion. All patients had additional scans performed one day after surgery to ensure plaque position. The MI was assessed in all of the 230 included eyes.

Combining Equations 1 and 2 yields:

$$\text{double dose depth}/2 = \text{tumour height} + \text{scleral thickness} + \text{extraocular tissue} \quad (3)$$

Tumour heights were identified and measured from the apex to the base of the tumour in the recorded ultrasound images (Figure 1B), while the double dose depths were determined from the MI (Figure 1C). The distances between the concave side of the plaque and the tumour base which consist of the sclera and extraocular tissue are thus calculated as:

$$\text{scleral thickness} + \text{extraocular tissue} = (\text{double dose depth}/2) - \text{tumour height} \quad (4)$$

Equation 4 allows the distance from plaque to tumour base to be calculated and evaluated for all eyes included in the cohort study.

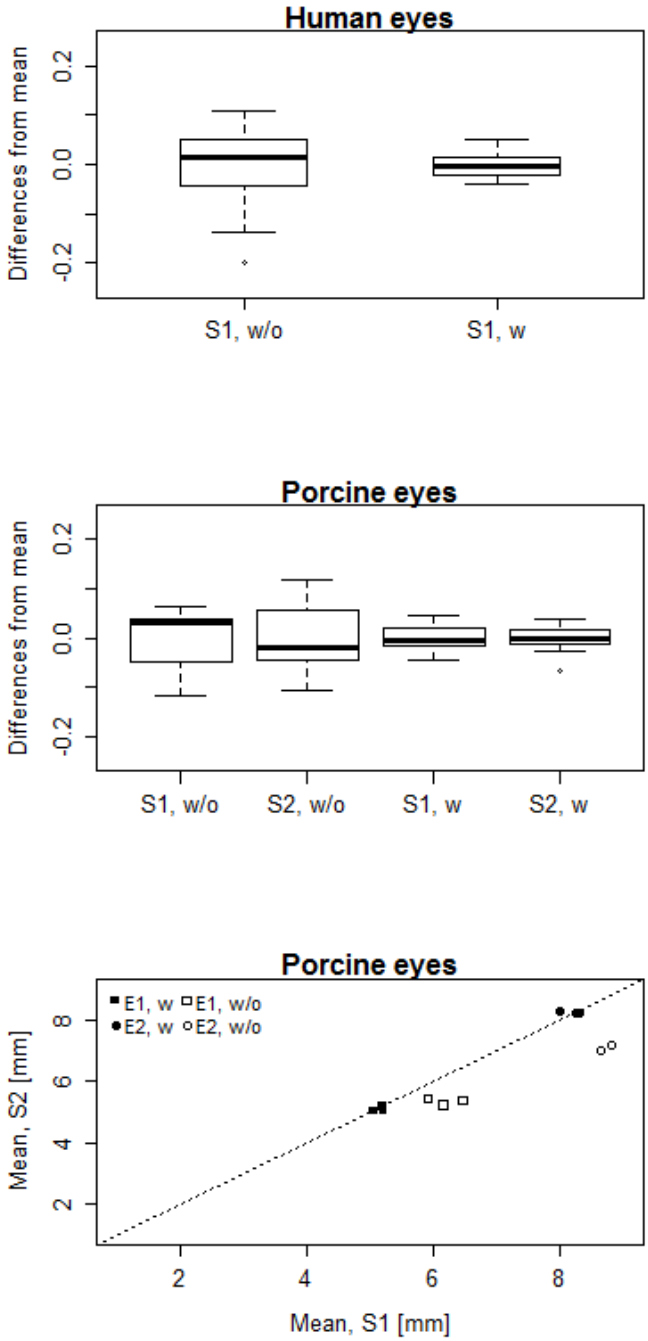
Relation between gender and distance from plaque to tumour base was examined using a Mann-Whitney U-test, Spearman's correlation coefficient was used for correlation with age.

Simulation of effects of incorrect determination of dose depth on tumour dose distributions

A phantom study was used to illustrate the effects on radiation dose to apex of the UM when the dose depth was incorrectly determined. We prescribed 100 Gy to the apex of the phantom tumour with an assumed scleral thickness of 1 mm. At a range of scleral thicknesses (0.3, 0.4 … 1.7 mm) the actual minimum apex dose was determined. The study was simulated with a standard sized spherically dome-shaped tumour with base dimension of 10x10 mm and varying heights (1, 2, 3, 4, and 5 mm respectively) using Plaque Simulator™ (Version 6.1.3, EyePhysics LLC, Eckert & Ziegler BEBIG GmbH, Berlin, Germany). A CCB-plaque was used in this phantom study. Finally, four different plaque types (CCA, CCB, CCC and COB) were used to irradiate a standard sized (10x10x5 mm) tumour in order to examine differences between plaques.

RESULTS

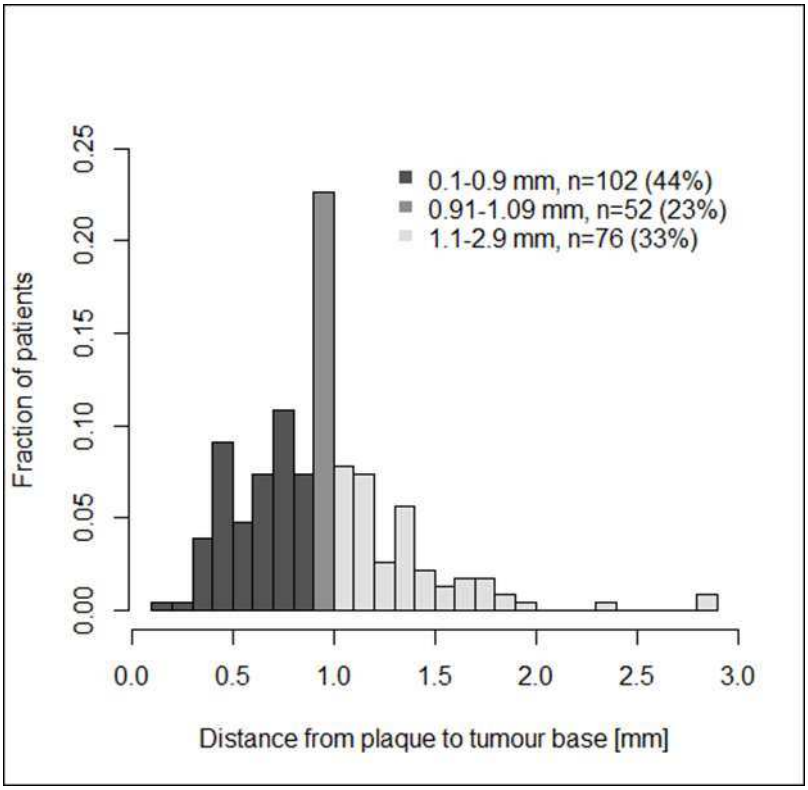
The intra-observer variation in dose depth measurement *with* Ru-106 plaque was significantly lower than for measures *without* plaque ($p<0.001$), in both human and porcine eyes, indicating a better reproducibility of measurements when done with the plaque in place. The top boxplot in Figure 2 illustrates the differences from the mean distance for each of the three repeated measurements on 10 human eyes (n=30) before and after placement of the Ru-106 plaque. The middle boxplot shows variation from repeated measurements with and without plaque on two different porcine eyes performed by two experienced surgeons.



Figur 2: S1=Surgeon 1, S2=Surgeon 2, w/o=without plaque, w=with plaque, E1=Eye 1, E2=Eye 2. Top: Boxplot from repeated measurements on 10 human eyes with and without plaque. Middle: Boxplot from repeated measurements from two individual surgeons made on two porcine eyes with and without plaque. Bottom: Agreement between surgeons with and without plaque based on the mean from three repeated measures.

ICC from the measurements without Ru-106 plaque sutured to the porcine eye was 0.63 (95% CI: -0.07 – 0.95), while ICC with plaque was 0.99 (95% CI: 0.93 – 1). Agreement between the surgeons is better with a plaque in place, illustrated in Figure 2 bottom.

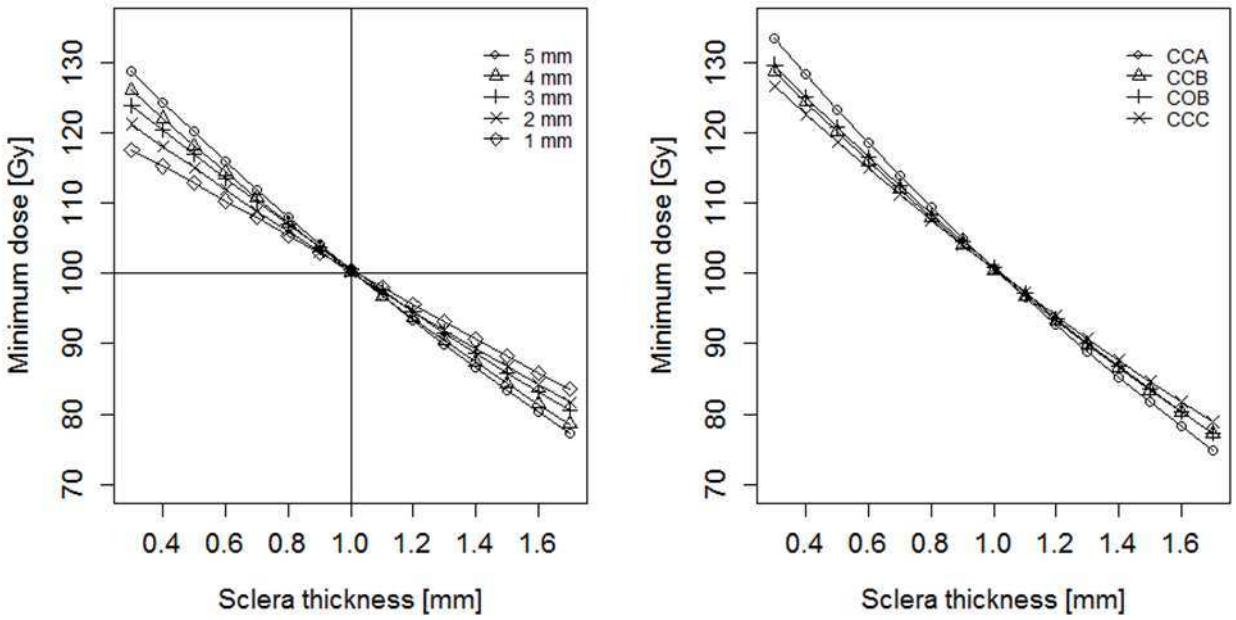
Distances from the plaque to tumour base were calculated in the retrospective human cohort from Equation 4. The mean distance was 0.99 mm (median: 1 mm, range: 0.1 mm – 2.9 mm), but the distances were not normally distributed (Figure 3).



Figur 3: Histogram of distances from plaque to tumour base.

There was no relation between distance from plaque to tumour base and gender (p=0.67), nor any correlation with age (p=0.99).

Minimum dose to apex of the tumour as a function of scleral thickness is shown left in Figure 4 for each of the tumour heights.



Figur 4: Left: Minimum dose to tumour apex as a function of sclera thickness from a CCB plaque for tumour heights 1-5 mm. Right: Minimum dose to tumour apex as a function of sclera thickness from 4 different plaque types for a 5 mm tumour.

As scleral thickness increases from 0.1 mm to 1.7 mm, the minimum dose delivered to the apex of the tumour tapered off from approximately 130 to 80 Gy. In the left plot in Figure 4 the standard sized tumour was irradiated with four different plaque types but delivered dose showed the same pattern for all plaques.

DISCUSSION

In the present study we used the ultrasonic mirror-image to measure the double dose depth in uveal melanoma patients as well as in porcine eyes. The reproducibility and agreement between two individual surgeons improved considerably as a result of the new method, which utilises well defined ultrasound echoes from the tumour surface and its reflected image in contrast to the conventional method with a poorly defined echo at the base. Furthermore, the new method alleviates the conventional arbitrary assumption of distance of 1 mm from the tumour base to the plaque. Hence, precision and accuracy of dosimetry is improved.

The proposed use of ultrasonic MI is an addition to already established surgical techniques, which need no alteration. Also, MI is a known phenomenon associated with ultrasound imaging. The ultrasonography method primarily provided information about plaque borders and location from the plaque shadow. Additionally, it refines the estimate of tumour height, as the MI only occurs when the soundwave is perpendicular to the plaque. In obstetric ultrasonography, Ahn et al[19] described MI to consist of two similar imaging configurations separated with equal distance from the reflective interface. Ahn et al[19] further described the duplicated image to be blurred compared to the actual image. This is in agreement with our ultrasonographs.

The B-scan probe was used to optimize the transducer position and insonification angle. The greater dynamic resolution of an unfocused A-scan transducer had no advantage for determining the transit times of the reflected sound pulses. Furthermore, it proved very difficult and time consuming to assure perpendicular angles to the tumour top and the plaque simultaneously.

The agreement analysis is carried out based on the assumption that the clinically used measure of dose depth is calculated from the mean of three measurements by the ophthalmologist at each treatment. This is the ideal setup in clinical practice to ensure the most correct measure for the dose depth. Since the true measure is unknown, we can only consider similarity between the two observers. The MI from the Ru-plaque on ultrasonography gives a more reproducible measure of the dose depth. The confidence intervals do not overlap, indicating significant differences between the measurements with and without plaques.

Distances from the plaque to the tumour base varied considerably among patients, showing a range from 0.1 mm to 2.9 mm. We found that in 52 of the patients (23 %) the distance was in the interval from 0.91 mm to 1.1 mm, in accord with the normally assumed 1 mm. Consequently, the distance differs from the otherwise generally accepted 1 mm in 77 % of the patients. A single cause for the larger distance was not obvious, but it could possibly be explained by additional scleral tissue including muscle insertions, blood vessels or connective tissue, primarily posterior Tenon's capsule, which all contribute to additional dose depth when the plaque appears displaced by such structures. Post-operative bleeding also may force the plaque away from the eye-wall and result in an increased dose depth (Figure 1D). This was only the case in two patients in the present patient cohort. Gender and age showed no relation to dose depth. These findings are in accordance with Vurgese et al[20], who reported same scleral thickness in men and women. One could speculate that atrophy of connective tissue would be more prominent with age, but this found no support in our study.

From the phantom study (Figure 4) it is clear that the tumour does not receive the prescribed 100 Gy if the scleral thickness exceeds 1 mm. Conversely, a too large dose is delivered to the tumour, and adjacent radiation-sensitive structures (like the macula), if the factual scleral thickness is less than 1 mm. This emphasizes that it is necessary to measure dose depth specifically for each patient, to ensure correct calculation of dosage. Figure 4 further demonstrates that type of plaque has minimal influence on the delivered dose when compared to the distance from the plaque to the tumour apex, and we thus identified no significant change between plaque sizes.

Knowledge of the correct dose depth is pertinent during Ru-106 treatments due to the steep radiation dose gradient. From the MI, the dose depth can be confirmed with higher precision than previously and help improving the dose calculation. The technique described in this paper has been developed based solely on patients treated with Ru-106 plaques, and this method may not be directly translated to the use of seeded plaques.

COMPETING INTERESTS

None of the authors have any conflicts of interest to disclose.

FUNDING

The work was supported by research grants Synoptik-Foundation, The Danish Eye Research Foundation (Øjenfonden), the Danish Cancer Research Foundation (Dansk Kræftforsknings Fond) and Arvid Nilssons Foundation.

CONTRIBUTORSHIP

CAE collected the data, cleaned the data, wrote the statistical analysis plan, did the data analysis and interpretation, drafted the manuscript, and did critical revision of the final paper. She is guarantor.
JFK helped collecting the data, helped in the data analysis and interpretation, contributed to drafting the manuscript, and did critical revision of the paper. Furthermore, he approved the final version to be submitted.
PKJ helped collecting the data, contributed to drafting the manuscript, and did critical revision of the paper. Furthermore, he approved the final version to be submitted.
LSF helped with data analysis and interpretation and did critical revision of the final paper. Furthermore, she approved the final version to be submitted.
ALA wrote the statistical analysis plan, did the data analysis and interpretation, and did critical revision of the final paper. Furthermore, she approved the final version to be submitted.
KK helped collecting the data and did critical revision of the final paper. Furthermore, he approved the final version to be submitted.
HCF helped collecting the data, contributed to drafting the manuscript, and did critical revision of the final paper. Furthermore, he approved the final version to be submitted.
LS did critical revision of the final paper. Furthermore, she approved the final version to be submitted.

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