Imaging Errors in Localization of COMS-Type Plaques in Choroidal Melanoma Brachytherapy

Mahdi Bayat,1 Azra Alizad,2 Rachel Tamminga,3 Jose S. Pulido,4 and Mostafa Fatemi2

1Department of Electrical and Computer Engineering, University of Minnesota, Minneapolis, Minnesota
2Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, Minnesota
3Department of Mechanical Engineering, University of Minnesota, Minneapolis, Minnesota
4Department of Ophthalmology, Mayo Clinic College of Medicine, Rochester, Minnesota

Correspondence: Mostafa Fatemi, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905; fatemi.mostafa@mayo.edu.
Submitted: December 14, 2012
Accepted: September 8, 2013

Purpose. To investigate mathematically and experimentally the sources of errors in localization of COMS-type plaques in melanoma brachytherapy when using ultrasound and transillumination and to give recommendations to avoid such errors.

Methods. A computer-aided simulation tool was developed to model the errors seen in the patient images when using ultrasound imaging and transillumination during localization of the COMS-type plaque in melanoma brachytherapy. Several laboratory experiments were performed on sheep eyes to confirm the validity of the error sources and the simulator outputs. Results were compared to the intraoperative ultrasonographic patient images for validation.

Results. Based on mathematical modeling and computer simulation results, transillumination provides acceptable accuracy for small to medium tumors with less than 7-mm height but shows poor accuracy as the tumor height increases. In ultrasound imaging, two sources of error are predicted in longitudinal scan using our computer simulation modeling, and the results are supported by the experiments on sheep eyes and patient images taken during the operation. Both errors are related to the lens. The first error is due to attenuation and refraction of the lens causing opaque areas and a change of curvature in the image of the plaque edge that is nearest to the lens. The second type of error is related to the total internal reflection from the lens.

Conclusions. The simulation method presented in this article allows quantitative assessment of the sources, mechanisms, and measures of errors in localization of the COMS type plaques by ultrasound and transillumination techniques. Errors predicted by the simulation method are validated by experiments. Error assessment by this method provides guidelines for avoiding such errors.

Keywords: ultrasound, transillumination, brachytherapy

Plaque brachytherapy has been proven to be an effective treatment for choroidal melanoma.1 In this method, a plaque made of gold alloy (or other radioactive shielding substances), which in most cases contains radioactive seeds, is sutured onto the sclera and left in place for a few days until the appropriate dose of radiation is delivered to the tumor.2-5 It is important for the plaque to be properly aligned with the tumor so that the correct radiation dose is delivered to the tumor. Before placing the actual plaque, a dummy plaque is used to mark the appropriate place of suturing the actual plaque. During the operation, based on the predetermined position of tumor, a muscle may be placed on a hangback suture to give more flexibility to the surgeon for placing and suturing the plaque. Then, using transillumination, the margins of tumor are marked on the sclera and a dummy plaque is temporarily sutured to the sclera. In this procedure, a fiber-optic light is placed against the sclera on the side of the eye opposite the tumor so that the tumor's shadow can be seen and its position marked. However, in some cases it may not be possible to place the light source on the other side of the eye from the tumor. Using ultrasonography, the accuracy of the position of the dummy plaque is examined and required adjustments are performed before suturing the actual plaque with radioactive seeds. For mostly anterior tumors, transillumination is easier, as the physician has accessibility to the sclera adjacent to the tumor. On the other hand, posterior tumors are harder to mark using transillumination due to physical accessibility. In these cases, indirect ophthalmoscopy6 can be used to delineate the anterior edge.

Ultrasound is useful in imaging of mostly posterior tumors where transillumination is difficult.7 In some cases, however, we have observed that one edge of the plaque is not well defined, which makes the accurate placement of the plaque more difficult. This tends to happen in longitudinal scans of tumors that are anterior to the equator. In these situations, it can appear as if the plaque does not adequately cover the tumor, even though other localization methods, such as transillumination and indirect ophthalmoscopy, suggest the plaque is correctly placed.

Previous research has described a variety of techniques for verification of plaque placement. One technique involves transillumination of the plaque's edges8-10; a similar technique uses light-emitting diodes mounted on the plaque instead of a...
fiber-optic light pipe.\textsuperscript{10,11} In addition, there have been several reports that have been written about the use of ultrasound to verify plaque placement\textsuperscript{12–14}; however, no mention has been made of possible limitations involved or errors that may arise.

In this article, we developed a computer-aided simulation based on the mathematical modeling of the ultrasound wave propagation within the layers of the eye. This simulation tool is used to explore possible causes of the problems encountered with ultrasound imaging. The errors that are predicted by the simulation are verified by ex vivo experiments. For this purpose, excised sheep eye samples are used in an attempt to reproduce the situation in which it is difficult to accurately image the plaque. The results of our computer simulations, laboratory experiments, and actual intraoperative ultrasonographic patient images are then compared. We also mathematically evaluated the errors that might occur with transillumination in brachytherapy. The advantages of each imaging method in relation to the tumor size and anatomic location are highlighted.

\section*{Methods}

\subsection*{Transillumination Errors}

To quantify the amount of error due to distortion of the tumor shadow during transillumination, a computer simulation was developed using MATLAB programming language (MathWorks, Inc., Natick, MA). In this simulation, the transilluminator was modeled as an omni-directional point source attached to sclera. The simulator determined the location of the tumor’s shadow on the sclera and evaluated three kinds of error. The first error, which we call \textit{diameter error}, is defined as the difference between the actual tumor basal diameter and the basal diameter of its shadow on sclera. In Figure 1a this error is quantified as the difference between $D_1$ and $D_2$. The second error, called \textit{displacement error}, is defined as the difference between the center of the actual tumor and the center of its shadow. In Figure 1b these two centers are marked as points a and b, respectively, where $E_1$ indicates the displacement error. Finally, we define the \textit{corner error} as the difference between the corner of the tumor and the corner of its shadow at the side the surgeon uses for plaque adjustment. This error is shown as $E_2$.

\subsection*{Ultrasound Errors}

During intraocular melanoma surgery, a 10- to 20-MHz B-scan ultrasound probe suitable for examining the eye is used. Due to
Imaging Errors in Localization of COMS Plaques

the limited field of view, it is essential to place the probe on the opposite side of the area to be examined to have a complete image, as shown in Figure 2a. This is not always possible because of the physical limitations imposed by the orbit and nose, which prevents the probe from becoming properly positioned, especially for mostly anterior tumors. Another limitation of its use is due to the lens. Because of high attenuation of ultrasound waves by the lens, the probe is always placed on the sclera such that the lens is bypassed. As described in later sections of this article, there are situations in which the ultrasound beam might pass through the lens or bounce off the lens due to total internal reflection. These two major sources of error during intraoperative imaging of brachytherapy are illustrated in Figures 2b and 2c, respectively.

A two-dimensional ultrasound beam-tracing simulator was developed to model the refraction and attenuation within the different ocular layers. For simplification, the different layers of the eye are modeled as circles and the physical parameters are chosen based on the average size of a human eye.15

The lens is modeled as the intersection of two circles with different diameters and centers. This model does not include all anatomical parts and it comprises only those parts affecting the ultrasound signal significantly. Each beam is assumed to be emitted from an ultrasound point source positioned closely on the sclera. Due to varying speeds of the ultrasound waves in different layers, refraction takes place in each interface. The incident and outgoing angles are related according to Snell’s refraction law:

\[
\sin(\theta_i) = \frac{v_2}{v_1} \sin(\theta_o),
\]

where \(\theta_i\) and \(\theta_o\) are the incident and outgoing angles respectively measured with respect to the perpendicular line on the interface at point of incident, and \(v_1\) and \(v_2\) are the velocities of ultrasound wave in layers 1 and 2, respectively. An example of this phenomenon is given in Figure 3, where the velocity of an ultrasound wave in medium 2 is less than the velocity of the wave in medium 1.

As the ultrasound beam passes through the different layers, its power drops according to the following equation

\[
P_i = P_{i-1} - r_i \alpha_i, \quad i = 0, 1, 2, \ldots,
\]

where \(P_i\) is the signal power at the end of \(i^{th}\) layer relative to the source power \(P_0\) and measured in dB scale, \(\alpha_i\) is the attenuation coefficient in dB/mm, \(r_i\) is the beam path length in the \(i^{th}\) layer in mm, and \(P_{i-1}\) is the power at the end of \((i-1)^{th}\) layer relative to the source power and is measured in dB scale. The values for the attenuation coefficients of different parts of the eye can be found in Reference 16.

From the ultrasound viewpoint, the metal plaque should act as a strong specular reflector. However, due to the presence of the filling and the seeds, it also acts as a defused scatterer that bounces the ultrasound in many directions. For this reason, we have modeled the plaque as a combination of specular reflector and defused scatterer with random distribution. Each point of the plaque is designated as either a reflector or a scatterer with equal probability. A specular reflector reflects the ultrasound beam at an angle that mirrors the incident angle. Hence, when the incident angle is wide enough, the reflected beam misses the transducer, which results in loss of the signal. On the other hand, the signal from a defused scatterer can be detected almost regardless of the beam orientation.

To simulate different errors, the plaque is placed in its optimal position behind the tumor and the simulator forms the synthetic ultrasound image based on the emission angle, the round trip traveled distance, and the attenuation along the path. For visualization purposes, unlike the usual ultrasound B-mode images, the brightness of each point in the image is inversely gray scaled according to the received signal power. The following example illustrates the performance of the software.

![Figure 3](http://tvst.arvojournals.org/)

**Figure 3.** Refraction of ultrasound beam due to different velocities in two media \((v_1 > v_2)\).

![Figure 4](http://tvst.arvojournals.org/)

**Figure 4.** Example of performance of beam-tracing simulator. (a) Ultrasound beam model. (b) Gray-scale image; the brightness of each point is inversely proportional to the received signal power (not to scale). Few artifactual spots are visible behind the plaque, which are due to indirect reception of the ultrasound beams. In such cases, the effective path length is longer than the direct reflection path; hence, the result is seen as a deeper shadow behind the plaque.
Figure 4 shows how the ultrasound image is simulated. To model the limited area of the probe, beams received more than 5 mm away from the center of the probe are discarded. Figure 4a shows the mechanism in which the simulator generates the ultrasound beams using a three-layer model for the eye. We have included the retina, choroid, and sclera with thicknesses of 0.2 mm, 0.4 mm, and 0.4 mm, respectively. A 0.02-degree difference between two consecutive beams is used. The simulation predicts some artifactual spots behind the plaque. These spots are due to alternative beam paths, such as a beam reflected by the plaque then re-reflected by the lens before reaching the probe (see Fig. 4a). The situation shown in Figure 4 can be used to model either longitudinal or transverse scan modes, as the physical properties are the same.

**Human Images and Experiments on Sheep Eye**

The results of the developed simulation were compared against the patient images taken during an operation. We also developed a phantom using a sheep eye, because its size and properties are close to those of a human eye. A dummy plaque was placed on top of the sheep eye close to equator and the combination was cast in gel inside of a plastic container such that the anterior part was accessible for placing the probe. The
rest of the container was filled with water and the probe was immersed in water and placed on the sclera.

**RESULTS**

**Transillumination**

To quantify the transillumination errors, we applied our simulation to different tumor heights. The light angle is measured relative to the point 180 degrees opposite of the center of the tumor. The diameter error, the displacement error, and the corner error for a tumor with a diameter of 10 mm and different heights are shown in Figure 5. Figure 5a depicts the location/size of the simulated tumors. From Figures 5b and 5c, it can be seen that as the tumor height increases, both the diameter error and the center error increase. Figure 5d, which can be regarded as the actual localization error, shows that the deviation of the light source from its optimal position/direction can largely increase the error. It can also be concluded that the transillumination error can be minimized by adjusting the position and direction of the light source but it increases remarkably as the tumor height increases if the light source is not positioned optimally. This figure also shows that the corner error is negligible (less than 1 mm) as long as the tumor height is less than 7 mm and the light source is positioned not more than 25 degrees away from its optimal location.

**Ultrasound**

**Refraction Errors.** Refraction in ultrasound beams can cause some errors, as the image formation method used in B-mode ultrasound does not account for any bending of the beams. Because this type of error depends on the angle of incident of ultrasound beam on sclera, a simulation was performed such that the position of the probe on sclera is fixed but the direction of the probe can be slightly changed so as to generate different incident angles. We call this slight probe direction change the *steering angle*, where steering angle of zero corresponds to the situation where probe is perfectly tangential to the sclera. In this simulation, the displacement error in the imaging of a point on the retina is simulated using our simulator. Figure 6 shows the displacement error in millimeters and, as can be inferred, the error is less than 0.2 millimeters.
mm in the range of ±20 degrees steering angle variations and thus this error can be ignored.

**Errors Due To Lens Attenuation and Refraction.**

*Simulator Results.* To illustrate the effect of the lens, we consider the following example.

Consider a longitudinal ultrasound image of a plaque behind an anteriorly located (anterior to the equator) medium-size tumor with a base diameter of 14 mm and apical height of 4 mm that is modeled using our simulator. The simulator uses 0.02 degrees of resolution for forming the ultrasound image. Figure 7 shows the situation in which the ultrasound probe is placed in the wrong position and the beams pass through the lens. Figure 7a shows the beam model that helps to understand the formation of different artifacts, whereas Figure 7b depicts the formed image. From Figure 7b it can be noticed that all the back-scattered signals from the parts behind the lens are highly attenuated and the corresponding image is not clear.

The other unwanted effect is related to the refraction properties of the lens. Due to the high curvature of the lens, the image of the parts behind the lens is distorted and shifted, which can be seen in Figure 7b. Although this effect is similar for both the tumor and the plaque, it causes an error in the estimation of tumor diameter: the main parameter that the surgeon relies on for adjustments when not seeing both sides of the plaque in the ultrasound image. We call this image distortion effect by lens the refraction artifact.

**Experiment on Sheep Eye.** A 10-MHz probe with an overlying sterile sleeve was used to image the plaque in the sheep eye phantom in the longitudinal mode. The result is shown in Figure 8. Multiple reflections between the plaque back wall and front edge caused fanning of the ultrasound image, which is known as comet tail artifact. Despite its name, this type of artifact helps the surgeon in identifying the edges of the plaque. From Figure 8, it can be seen that the lens severely attenuates the ultrasound signal, which causes a dark

---

**FIGURE 9.** Artifacts due to beam passing through the lens seen during operation (longitudinal).

**FIGURE 10.** Artifact due to total internal reflection from the lens into the vitreous: (a) ultrasound beam model, (b) image distortion due to total internal reflection artifact; region B is the ghost image of region A (not to scale). As one side of the plaque is deformed in this kind of artifact, estimation of the relative position of the plaque and tumor can be mistaken, leading to wrong placement of the plaque.
area behind it and completely eliminates the comet tail on the opposite end of the plaque. A change of curvature of internal layers of the eye behind the lens also can be seen, which we anticipate to be due to lens refraction artifact.

Human Studies. The artifacts due to beams passing through the lens seen in the simulations and animal experiments were also identified in some real images taken during surgery on a patient with a medium-sized choroidal melanoma. Figure 9 shows the longitudinal ultrasound image of an anteriorly positioned tumor with an overlying COMS-type plaque. The high attenuation due to the lens obscures the comet tail artifacts, which are an indicator of the plaque edge. There is also a change of curvature in the image of internal aspects of the eye due to the refraction effect of the lens.

Errors Due To Lens Total Internal Reflection.

Simulator Results. To show the possibility of total internal reflection and its potential errors, we consider the following example.

A tumor/plaque complex that extended from the equator anteriorly is simulated. The tumor has a base diameter of 14 mm and height of 4 mm. As seen in Figure 10a, the beams that reflect inside the vitreous alight on the posterior layers of the eye in angles different from the straight-line direction (region A) and cause an artifact (ghost image) in region B. Indeed, the total internal reflection artifact is a mirrored version of part of the plaque and the tumor.

Experiment on Sheep Eye. Using the sheep eye phantom with the dummy plaque placed anterior to the equator, we examined the possibility of total internal reflection. Figure 11 shows the resulting image in which an artifact similar to the computer simulation result seen in Figure 10b can be recognized. As the brightness of the artifact behind the plaque is high, we anticipate that due to total internal reflection, the ultrasound beams have reflected off the lens rather than passing through it, in which case they would have been highly attenuated.

Discussion

This article presents a novel quantitative approach in analyzing the sources and mechanisms of errors in localization of the plaques used in melanoma brachytherapy. Two main modalities, transillumination and ultrasound, are investigated in this study.

Using a mathematical model, we confirmed by simulations that transillumination error highly depends on the size and shape of the tumor and the position and direction of the light source, such that the deviation from the optimal position can cause considerable errors even for medium-size tumors. We showed by examples that transillumination provides acceptable accuracy for small to medium tumors with less than 7-mm height.

Using a simple ultrasound wave propagation model and computer simulation, we then investigated the possible sources of errors in ultrasound imaging. We showed that the error due to refraction of ultrasound waves is negligible and posteriorly located tumor/plaque can be accurately localized using B-mode scan. As the tumor location becomes more anterior, physical limitations prohibit optimal probe positioning. This, in turn, causes the lens to become the main barrier for accurate imaging. In the transverse mode, due to inherent symmetry of the lens, the operator can bypass it and avoid any possible artifacts. On the other hand, in longitudinal images, two major sources of error are possible: imaging through the lens and total internal reflection from the lens. Both can cause errors in interpretation of the correct location of the plaque relative to the tumor. Using software simulation and laboratory experiments, we showed the condition under which lens errors occur. Imaging through the edge of the lens was seen clinically. The total internal reflection error predicted by our simulator was seen only in laboratory experiments, but it is a potential source of error that can appear in imaging of the human eye from specific angles.

The Table summarizes all different types of errors when using transillumination or ultrasound, with hints and recommendations to identify and avoid such errors. The ultrasound errors are only for the longitudinal imaging, as in transverse mode errors can be identified by symmetry.

Using the information listed in the Table, we recommend using ultrasound imaging as a reliable modality for posterior tumors where the lens can be easily bypassed in both transverse and longitudinal scans and transillumination is hardly possible. On the other hand, as the tumor location becomes more anterior, the longitudinal images become less reliable due to artifacts caused by the lens. Because anterior tumors are easier to access by the surgeon, transillumination or other methods, such as indirect ophthalmoscopy, may be used to verify the accuracy of positioning and avoid potential errors from ultrasound localization. With transillumination, as the tumor height increases, the positioning error increases, such...
<table>
<thead>
<tr>
<th>Type of Error</th>
<th>Location of the Tumor-Plaque Combination</th>
<th>Cause(s)</th>
<th>Identification / Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transillumination refraction error</td>
<td>Mostly anterior tumors</td>
<td>Shadowing by the tumor, change in speed of sound in different layers of the eye (excluding lens)</td>
<td>Ultrasound aberration due to passing through the lens</td>
</tr>
<tr>
<td>Ultrasound refraction error</td>
<td>Mostly anterior tumors</td>
<td>Shadowing by the tumor, change in speed of sound in different layers of the eye (excluding lens)</td>
<td>Ultrasound aberration due to passing through the lens</td>
</tr>
<tr>
<td>Combining identification / recommendation</td>
<td>Mostly anterior tumors</td>
<td>Shadowing by the tumor, change in speed of sound in different layers of the eye (excluding lens)</td>
<td>Ultrasound aberration due to passing through the lens</td>
</tr>
</tbody>
</table>

that finding optimal position for the light source becomes more essential.

**Acknowledgments**

Throughout this effort, the authors received generous help from both clinical and laboratory staff at the Mayo Clinic, Rochester. We especially thank James F. Greenleaf for his insightful comments and Randall R. Kinnick at the Ultrasound Research Laboratory of the Mayo Clinic for his invaluable help during laboratory experiments and animal phantom preparation. We also thank LuAnne Sculley at the Department of Ophthalmology of the Mayo Clinic for her help in providing clinical ultrasound images of patients.

Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, and Terrance and Judith Paul.

Disclosure: M. Bayat, None; A. Alizad, None; R. Tamminga, None; J.S. Pulido, None; M. Fatemi, None

**References**