Three-Dimensional Ultrasound for the Measurement of Choroidal Melanomas

Juan M. Romero, MD; Paul T. Finger, MD; Richard B. Rosen, MD; Raymond Iezzi, MD

Objective: To evaluate the reliability of 3-dimensional ultrasound (3D-US) for the measurement of choroidal melanomas.

Design: Retrospective case series.

Participants: Forty-two consecutive cases of choroidal melanoma imaged with 3D-US.

Methods: Tumor measurements obtained with ophthalmoscopy, transillumination, standard ultrasound techniques, 3D-US, and pathological studies. Tumor diameters, heights, and volumes were compared. Our 3D-US tumor measurement techniques were tested for intraobserver and interscan reproducibility.

Results: Fifty 3D-US images were studied. The 3D-US tumor measurements were found to be reproducible (height coefficient of variation [CV] ≤3%; diameter CV ≤9.7%; volume CV ≤13.2%). There was significant correlation with the usual methods of tumor measurement (diameter \( r = 0.76 \); height \( r = 0.98 \)). Significant differences were found between measurements at pathological examination, as compared with both 2-dimensional and 3D-US height measurements (range, 0.73-0.83 mm). This finding was thought to be due to specimen shrinkage. Three-dimensional ultrasound was found to be at least as reproducible as clinical examination and standard ultrasound techniques used for measurement of diameter and height of choroidal melanomas. It was our impression that the 3D-US volume measurements accounted for the geometry of the tumor better than volume estimates calculated from basal area and tumor height.

Conclusions: Three-dimensional ultrasound measurements of choroidal melanoma were reproducible, correlated well with other tumor measurement techniques, and can be used for measurement of choroidal melanomas.


CHOROIDAL melanoma size is the most important factor in determining both treatment options and prognosis (ocular and for metastasis). For example, apical tumor height and largest tumor dimension (typically the largest diameter in contact with sclera) have been reported to be risk factors for extrascleral extension, posttreatment recurrence, and metastasis. Accurate measurements of tumor height and basal diameter are also critical for monitoring tumor growth and are used to define treatment alternatives. For example, accurate measurements of tumor apical height and basal diameters are critical for choosing plaque size and radiation dose. In clinical practice, tumor height and basal diameters are typically measured using combinations of ultrasonography (2-dimensional [2D] B-scan and A-scan), ophthalmoscopy, fluorescein angiography, and transillumination. The accuracy and reproducibility of these methods have been described. Ultrasonography is currently one of the most reliable techniques for measurement of choroidal melanomas (except in cases of anteriorly located tumors). This is because tumor diameters obtained by ophthalmoscopy are based on relative proportional measurements compared with normal ocular structures and the ophthalmoscopic field of view (20 diopters [D]= 12 mm; 28 D=16 mm), and can be affected by the axial length of the eye. However, ophthalmoscopy can reveal flat regions of the tumor margin that can be missed with ultrasound. Measurements using photographs and measuring grids can be more accurate, but many tumors do not fit into the conventional fundus camera field or are located anterior to the equator, rendering them difficult to photograph.

From the New York Eye and Ear Infirmary (Drs Romero, Finger, Rosen, and Iezzi), and the New York Eye Cancer Center (Drs Romero and Finger), New York, NY. The authors have no proprietary or financial interest related to this article, including the equipment used in this project.
MATERIALS AND METHODS

STUDY DESIGN AND CLINICAL ASSESSMENTS

We present a clinical case series of 42 patients whose choroidal melanomas were measured with 3D-US. The tumor's minimum and maximum diameters were measured by ophthalmoscopic examination by a trained specialist in ophthalmic oncology (P.T.F.). Transillumination was used for measurement of anterior tumor diameters. B-scan and A-scan examinations were performed using the Ophthalmic Technologies Inc. Downview, Ontario). The ultrasound protocol used by the Collaborative Ocular Melanoma Study as well as interpolative A- and/or B-scan techniques were used as applicable. Ultrasound techniques were used to achieve a "best clinical assessment" of tumor size based on ultrasonography. Ultrasound measurements were documented with Polaroid pictures (Polaroid Corp, Cambridge, Mass).

3D-US STUDIES

Three-dimensional ultrasound was requested after the clinical assessment. Three-dimensional ultrasound studies were performed using the 3D i-scan (Ophthalmic Technologies Inc., Downview, Ontario). Three-dimensional ultrasound uses a conventional brightness mode (B-mode) transducer, combined with a motorized, rotating holder and computerized image processing. During data acquisition, the transducer is rotated while multiple 2D images are collected and processed by the computer to form a 3D block. After acquisition, it is possible to view and manipulate the 3D block interactively. Since the 3D block can be rotated and sliced, it allows for viewing 2D images derived from unique perspectives.

The 3D B-scan probe operates at a frequency of 10 MHz, with an axial resolution of 0.15 mm and a lateral resolution of 0.27 mm. The focal point is 25 mm, with a total image depth of 50 mm. For image processing, the proprietary software 3D i-scan was run on a Macintosh computer (Apple Computer Corp, Cupertino, Calif). The acquisition and reconstruction times were 7.5 and 6 seconds, respectively. All 3D-US measurements were made at an equivalent sound velocity of 1532 m/s (speed of sound in vitreous), as compared with 1530 m/s used for standardized A-scan. This difference would make 3D-US height measurements 1.16% smaller than those derived by A-scan. This difference was not considered to be a significant factor in our measurements of heights or volumes.

Three-dimensional ultrasound was done within 1 week after the clinical assessment. These evaluations were performed by one of us (J.M.R.), who spent 2 years in training as a retinal imaging fellow with clinical experience in ultrasonography, and under the supervision of the other authors. He had no prior knowledge of the clinical measurements (performed by P.T.F.). During the examination, the patient lay in the supine position, and the ultrasound probe (with coupling media) was in contact with the eyelid. The patient was asked to look at a fixation target while the ultrasound probe was oriented in the direction of the tumor. The area of interest was centered in the ultrasound screen. The ultrasound gain was adjusted to optimize the image (typically 70 dB). During acquisition time, the patient was asked to be still. Ordinarily, a sequence of images was saved for later measurement.

This study was complied in accordance with the Declaration of Helsinki recommendations on biomedical research involving human subjects. Before scanning, all patients were informed that 3D-US would be performed, that the 3D-US transducer emissions were essentially equivalent to a 2D unit, and that there was no additional risk.

TUMOR CHARACTERISTICS

Fifty 3D-US images of 42 eyes were analyzed in this study (Table 1). The cases were collected from October 1996 to May 1998. The status of the cases when imaged was as follows: 6 cases were under observation (1 dormant, 3 small, and 2 treatment refused), 19 were prebrachytherapy (17 palladium 103, and 2 iodine 125), 12 were postbrachytherapy, and 13 were pre-enucleation (1 tumor regrowth, 2 neovascular glaucoma, 10 as primary treatment). Three cases had imaging studies performed on more than one date. The tumor apex locations were as follows: 3 posterior, 16 posterior-eqator, 18 equator-posterior, 8 equatorial, 5 equator-anterior. Thirty-nine of the imaged tumors were dome-shaped, and 11 were mushroom-shaped. Five of the mushroom-shaped tumors were treated by enucleation.
Clinical diameters were not documented in 18 cases. In 8 of these cases, the tumor was too large for the base to be completely visualized by ultrasound. The other 10 were treated with plaque radiation therapy, with a good clinical response, and no posttreatment measurements of tumor base diameters were recorded. A-scan ultrasound height measurements were not obtained in 3 cases. In these 3 cases, 2 large and 1 medium-sized melanomas were evaluated with 3D-US only. Tumor heights obtained at pathological evaluation were not included in 2 cases because the eye section did not include the maximum tumor elevation.

3D-US MEASUREMENTS

Based on 3D-US measurements, the tumor dimensions were as follows: mean diameters ranged from 5.7 to 18.5 mm (mean, 10.3 mm; SD, 3.1 mm), heights ranged from 1.3 to 13.9 mm (mean, 4.5 mm; SD, 3.2 mm), and volumes from 17.8 to 1569.1 mm³ (mean, 277.5 mm³; SD, 375.5 mm³) (Table 1).

The intraobserver and interscan reproducibility for 3D-US measurements of the choroidal melanomas were also tested (Table 2). When the observer performed repeated measurements of an image, smaller coefficients of variation were noted with increasing tumor size. From the measured dimensions, height was less variable (CV, 0.7%-3.0%), diameter was intermediate (CV, 0.0%-9.2%), and volume was more variable (3.6%-13.2%). The volume CV was inversely proportional to the size of the tumor. Diameters were more variable than heights. The explanation for that could be that the system has less lateral resolution (0.27 mm) than axial resolution (0.15 mm), and that, as any experienced ocular ultrasonographer knows, tumor margins are less distinct with ultrasonography.

3D-US VS STANDARD CLINICAL EVALUATIONS

Results of Pearson correlation and paired t tests comparing clinical examination, 3D-US, and pathological examination measurements are presented in Table 3. Three-dimensional ultrasound was found to be equivalent to 2D-US for measurement of tumor height. In fact, statistically significant correlations were shown between all methods of diameter and height measurement. Measurements of diameter on clinical examination were slightly larger than those done with 3D-US by...
a mean difference of 0.4 mm. These differences were not statistically significant. Similarly, measurements with 3D-US were slightly larger than those made with pathological examination. The standardized ultrasound and 3D-US height measurements were 0.8 mm larger, on average, than heights obtained at pathological evaluation, which could be due to cut of perfusion, fixation, and pathology processing. Clearly, there was no significant difference between 3D-US and 2D-US height measurements.

TUMOR VOLUME

Linear regression analysis was used to predict choroidal melanoma volume (V) (measured by 3D-US) from basal area and apical height (A × H) (Table 4). Tumors were divided into groups by volume and shape. All groups, except those with an A × H greater than 1600 mm³, resulted in significant correlations. For all 50 images, volume could be estimated using the prediction formula:

\[ V = -10.17 + 0.53 (A \times H) \]

plus or minus 38.7 mm³ (95% confidence interval). Prediction equations with smaller confidence intervals were obtained in small low-volume and dome-shaped tumors, which had more predictable geometry. Equations with larger confidence intervals were obtained in large collar-button–shaped tumors. It was difficult to predict the volume of large tumors and collar-button–shaped tumors. Volumes determined by 3D-US were less variable (lower SD in repeated measurements) than volumes calculated using area and height (large confidence interval).

3D-US REPRODUCIBILITY

Investigators have studied the reproducibility of indirect ophthalmoscopy, standardized A-scan ultrasound, and 3D-US for measurement of choroidal melanomas. We compared the reported reproducibility of those methods with the reproducibility of 3D-US (Table 5). Three-dimensional ultrasound was found to offer better intraobserver and interscan reproducibility than those conventional methods. Three-dimensional ultrasound in vivo interobserver reproducibility is not available.

Fisher et al²⁵ studied the accuracy and reproducibility of measurements in vitro using the 3D i-scan system, and we studied the reproducibility of measurement in vivo using the same system (Table 6). Fisher et al found that the in vitro measurements were accurate, with an error of 0.2% for linear measurements and 2.9% for volume measurements. Based on the data of Fisher et al and our own data, we have found that 3D-US
Table 1. Fifty 3-Dimensional Ultrasound Images of 42 Consecutive Cases of Choroidal Melanoma

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</table>

*3D-US indicates 3-dimensional ultrasound; postbrachy, after brachytherapy; E, equator; P, posterior; A, anterior; D, dome; CB, collar button; and ellipses, not applicable.

is accurate and reproducible for measuring choroidal melanomas.

COMPARISONS WITH PATHOLOGICAL STUDIES

There have been studies correlating pre-enucleation tumor measurements with pathological studies.21,28 Those investigators reported correlation of height measurements (r=0.92) and ophthalmoscopic diameters (r=0.81). It is well known that there is tumor shrinkage after cutting the blood supply and formaldehyde fixation.21,27 In our study, we found that both A-scan and 3D-US height measurements had excellent correlation with measurements obtained at pathological examination (r=0.99 and r=0.98, respectively). Also, in our pathological studies, tumor height measurements were significantly smaller than
preoperative measurements. Nicholson et al27 also noted shrinkage of the tumor dimensions after enucleation.

LINEAR REGRESSION ANALYSIS OF TUMOR VOLUME

Favilla et al28 used linear regression analysis to find the functional relationship between B-scan volume and the volume calculated from A × H. The B-scan volume was measured using ultrasonographic tomography and computer-assisted calculation of area of each tomographic slice, the sum of which constituted the volume. They analyzed 51 follow-up measurements of 15 cases with tumor volumes on B-scan that were less than 500 mm³. For the total of tumor measurements, the obtained prediction equation to estimate tumor volume was:

\[
(2) \quad V = 13.15 + 0.38 (A^3H)
\]

This formula was slightly greater than the volume formula of a cone (0.33 A × H). In our series, the obtained prediction equation for tumors with an A × H less than 600 mm² (V < 300 mm³) was:

\[
(3) \quad V = -4.05 + 0.51 (A^3H)
\]

This formula was in between the volume formula of a cone (0.33 A × H) and a hemisphere (0.67 A × H).

*All data are presented as mean (SD) [CV%]. CV indicates coefficient of variation.

*3D-US indicates 3-dimensional ultrasound.

*3D-US indicates 3-dimensional ultrasound; a, intercept; b, slope; A × H, area × height; and CI, confidence interval.
Intraobserver & Interscan & Interobserver & 

producer rotation.29,30 Software uses this information to re-

2D B-scan images, which are stored with each trans-

lost for comparison to future examinations.

Clearly, most of the tumor’s surface characteristics are

not possible. Static 2D images may demonstrate the larg-

2D images. Future review of the entire tumor volume is

presentation. The observer records a limited number of

ods for measuring choroidal melanomas. Because the im-

age of the whole tumor is stored and analyzed, it has the

potential of providing more reproducible measure-

ments. In addition, 3D-US provides the advantage of the

ility to measure tumor volume, no matter the shape

of the tumor. As with conventional ultrasound, it is im-

portant to combine ultrasound evaluation with clinical

amination and indirect ophthalmoscopy to identify all

tumor margins, including flat areas that can be missed by

ultrasonography.

### Table 5. Comparison of Average Reproducibility of Indirect Ophthalmoscopy, A-scan Ultrasound, and 3-Dimensional Ultrasound Choroidal Melanoma Measurements*

<table>
<thead>
<tr>
<th>Method</th>
<th>Diameter</th>
<th>Height</th>
<th>Diameter</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraobserver</td>
<td>7.9</td>
<td>21.3f</td>
<td>2.7</td>
<td>2.8</td>
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<tr>
<td>Interobserver</td>
<td>19.4</td>
<td>28.6†</td>
<td>11.5‡</td>
<td>2.2§</td>
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<tr>
<td>Interscan</td>
<td>...</td>
<td>4</td>
<td>4.6</td>
<td>1.8</td>
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</table>

*Values represent the coefficient of variation. Values are expressed as percentage. 3D-US indicates 3-dimensional ultrasound; ellipses, not available.
†Data from Char et al.*
‡Data from Fisher et al.25
§Data from present study.

### Table 6. Average Accuracy and Reproducibility of 3-Dimensional Ultrasound Measurements*

<table>
<thead>
<tr>
<th>Method</th>
<th>Error Linear Volume</th>
<th>Error Linear Volume</th>
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<tbody>
<tr>
<td>In vitro‡</td>
<td>0.2</td>
<td>2.9</td>
</tr>
<tr>
<td>In vivo†</td>
<td>0.6</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Error is presented in percentage of true value; intraobserver, interscan, and interscan reproducibility are coefficients of variation. Ellipses indicate not available.
†Data from present study.
‡Data from present study.

### 3D-US MEASUREMENTS OF TUMOR VOLUME

In comparison with the linear regression analysis, in which a dome-shaped tumor with an A × H of 167.57 mm³ has an estimated volume of 81.41 ± 21.00 mm³ using equation 3 (the prediction equation with the smallest confi-
dence intervals), the same tumor repeatedly scanned with 3D-US had a volume measurement of 72.40 ± 5.18 mm³. Note the smaller confidence interval of the 3D-US-measured volume. This finding was the same for all the other tumors we measured. It was our impression that the 3D-US volume measurements were closer to the true tumor volume than volume estimates from A × H because 3D-US measurements account for the shape or ge-

ometry of the whole tumor. Our study showed that 3D-US volume measurements were more reproducible than vol-

ume estimates from A × H.

### 3D-US VS CONVENTIONAL ULTRASOUND

Conventional ultrasound and 3D-US share the same oph-
thalmic ultrasound principles and limitations. Both tech-
niques can have limitations in visualizing the tumor marg-
ins and anteriorly located tumors. While both 2D ultrasone and 3D-US studies are initially dynamic, they differ in that the collected images from conventional ul-

trasound studies are visualized in a 2D format. Typical-
y the user takes 5 to 10 minutes imaging the tumor with A- and B-scans, while performing a mental 3D rep-

resentation. The observer records a limited number of 2D images. Future review of the entire tumor volume is not possible. Static 2D images may demonstrate the largest tumor diameter or may not include the tumor’s apex. Clearly, most of the tumor’s surface characteristics are lost for comparison to future examinations.

In contrast, 3D-US involves acquisition of multiple 2D B-scan images, which are stored with each trans-
cducer rotation.29,30 Software uses this information to re-

construct a 3D block. Then, without further contact with the patient, the 3D image, which is a block of data, can be rotated, sliced, and viewed in planes oriented in any direction. After an image acquisition, there can be no miss-
ing points of the lesion. Any tumor dimension can be mea-

sured in consecutive planes until obtaining the most ap-

propriate measurement. A plane perpendicular to the
tumor diameters can be displayed to obtain a more re-

producible tumor height measurement. It is also pos-

sible to measure volume by outlining areas of tumor on consecutive planes.

In this study, we are reporting our experience with 3D-US, a newly available technology. This case series demons-

trates that it can be as reliable as conventional meth-

ods for measuring choroidal melanomas. Because the image of the whole tumor is stored and analyzed, it has the potential of providing more reproducible measure-

ments. In addition, 3D-US provides the advantage of the

ability to measure tumor volume, no matter the shape

of the tumor. As with conventional ultrasound, it is im-

portant to combine ultrasound evaluation with clinical

amination and indirect ophthalmoscopy to identify all
tumor margins, including flat areas that can be missed by

ultrasonography.

Accepted for publication March 30, 2001.

This study was supported in part by the EyeCare Foun-


Corresponding author and reprints: Paul T. Finger, the New York Eye Cancer Center, 115 E 61st St, New York, NY 10021 (e-mail: pfinger@eyecancer.com).

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A look at the past . . .

VALUDE bandages only one eye and this only for four days. The patient is kept in a light room which keeps the pupil moderately contracted and lessens the tendency to prolapse. In case of infection he washes out the eye with sublimate 1:1000 and applies a light bandage. Before operation the conjunctival sac must be carefully cleansed with formal 1:1000, but epilation of the lashes is superfluous.