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Fundus image fusion in EYEPLAN software: An evaluation of a novel technique for ocular melanoma radiation treatment planning

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Purpose: The purpose of this study is to evaluate a novel approach for treatment planning using digital fundus image fusion in EYEPLAN for proton beam radiation therapy (PBRT) planning for ocular melanoma. The authors used a prototype version of EYEPLAN software, which allows for digital registration of high-resolution fundus photographs. The authors examined the improvement in tumor localization by replanning with the addition of fundus photo superimposition in patients with macular area tumors.
Methods: The new version of EYEPLAN (v3.05) software allows for the registration of fundus photographs as a background image. This is then used in conjunction with clinical examination, tantalum marker clips, surgeon's mapping, and ultrasound to draw the tumor contour accurately. In order to determine if the fundus image superimposition helps in tumor delineation and treatment planning, the authors identified 79 patients with choroidal melanoma in the macular location that were treated with PBRT. All patients were treated to a dose of 56 GyE in four fractions. The authors reviewed and replanned all 79 macular melanoma cases with superimposition of pretreatment and post-treatment fundus imaging in the new EYEPLAN software. For patients with no local failure, the authors analyzed whether fundus photograph fusion accurately depicted and confirmed tumor volumes as outlined in the original treatment plan. For patients with local failure, the authors determined whether the addition of the fundus photograph might have benefited in terms of more accurate tumor volume delineation.
Results: The mean follow-up of patients was 33.6 ± 23 months. Tumor growth was seen in six eyes of the 79 macular lesions. All six patients were marginal failures or tumor miss in the region of dose fall-off, including one patient with both in-field recurrence as well as marginal. Among the six recurrences, three were managed by enucleation and one underwent retreatment with proton therapy. Three patients developed distant metastasis and all three patients have since died. The replanning of six patients with their original fundus photograph superimposed showed that in four cases, the treatment field adequately covered the tumor volume. In the other two patients, the overlaid fundus photographs indicated the area of marginal miss. The replanning with the fundus photograph showed improved tumor coverage in these two macular lesions. For the remaining patients without local failure, replanning with fundus photograph superimposition confirmed the tumor volume as drawn in the original treatment plan.
Conclusions: Local control was excellent in patients receiving 56 GyE of PBRT for uveal melanomas in the macular region, which traditionally can be more difficult to control. Posterior lesions are better defined with the additional use of fundus image since they can be difficult to mark surgically. In one-third of treatment failing patients, the superposition of the fundus photograph would have clearly allowed improved localization of tumor. The current practice standard is to use the superimposition of the fundus photograph in addition to the surgeon's clinical and clip mapping

of the tumor and ultrasound measurement to draw the tumor volume. [DOI: 10.1118/1.3488891]

Key words: proton beam radiotherapy, treatment planning, fusion of images, uveal melanoma

I. INTRODUCTION

The use of external beam with charged particles (protons, helium ions, and carbon ion) in the treatment of choroidal melanoma has grown considerably during the past three decades.[1–4] Charged particle beams travel through tissue in nearly straight lines with minimum multiple scattering. The deposition of energy increases along the path of the charged particle ending with a sharp maximum, known as the Bragg peak, at the end of the particle range. This Bragg peak can be "spread out" across the tumor range resulting in the delivery of a uniform radiation dose to the entire tumor and minimal dose to the surrounding tissue.

Long term local control rates of 95% and greater have been reported by Castro *et al.*[1] and Gragoudas *et al.*[2] As of December 2002, over 3000 uveal melanoma patients have been treated at MGH with proton beam radiotherapy (PBRT).[5,6] The 5 and 15 yr local control rates of 97% and 95%, respectively,[6–9] and overall survival rate of 80% were reported, which is comparable to the survival rates reported for enucleation.[10] The probability of eye retention at 5 yr was estimated to be 90% for the entire group. Egger *et al.*[11] recently reported long-term results of eye retention for 2645 uveal melanoma patients treated with PBRT at Paul Scherrer Institute (PSI) in Switzerland between 1984 and 1999. The overall eye retention rate at 5, 10, and 15 yr after treatment were 89%, 86%, and 83%, respectively. These groups have established strong evidence of the advantages of PBRT for patients with uveal melanoma, particularly with tumors of large size and posterior locations. For these types of tumors, other types of radiotherapy may not be suitable or may produce more complications. New photon techniques are being tried for the treatment of choroidal melanoma,[12] but none of these new techniques has shown similar local tumor control rates at 5 yr.

The treatment of uveal melanoma with charged particles especially with PBRT is being used at many centers both in Europe and the United States.[11,13–16] A number of commercially made proton cyclotron facilities have either started treating patients or are in the commissioning phase. Currently there are seven proton beam facilities running in the USA and at least there are four more under construction.[17] With the emergence of new facilities, along with new surgeons, radiation oncologists, and physicists treating this rare disease, it has become imperative that accurate and reproducible tools be used in the planning process to ensure continued high success rates. Errors are possible during the surgical, planning, and/or treatment process, and hence methods to continually develop our standards of practice are essential.

Accurate delineation of tumors and surrounding organs at risk is a critical step for charged particle therapy. Tumors of the uveal tract are classically diagnosed accurately by ophthalmoscopy, fluorescein angiography, and A and B ultrasound. The standard technique for the surgeon to localize the tumor for PBRT is to suture tantalum clips around the tumor using transillumination combined with indirect ophthalmoscopy to identify the tumor margins relative to the edge of the tantalum clips. At the time of operation, the surgeon maps the clips in relation to the tumor and measures the distances between the clips and limbus, the clips and tumor, as well as interclip distances. Tumors located posteriorly can be more difficult to localize accurately and are associated with a higher rate of failure.[18] In these lesions, additional information from 3D T2 FSE MRI images is helpful in delineating the tumor.[19]

At the time of treatment planning two orthogonal x rays are taken either digitally or as a hard copy to delineate the exact location of the radio-opaque clips. EYEPLAN software relies on eye length, measured by ultrasonography. A user incorporates the clip coordinates into the model obtained from the orthogonal x rays. The localization accuracy of the clips is estimated by comparing with χ^2 values and comparing the measured data, such as interclip distances and clip-limbus distances, to the distances measured by the surgeon. The planner using a graphics interface then traces the tumor contour. The tumor height is finally introduced in the software to estimate the tumor volume.

Although, the tumor delineation is done as precisely as possible, there are potentials for error which can lead to poor modeling and thus to problems for tumor control and/or late side effects. These potential reasons for poor modeling include discrepancies in (1) the eye length as seen on ultrasound; (2) surgical measurements of the clips; (3) shape of the eye, which can be irregular and may need important approximations in the eye model; (4) the uncertainty in the range because of the estimate of the eye density; and (5) improper initial fixation at time of simulation. For example, the EYEPLAN software uses a spherical model of the eye and in some patients, the eye may not be spherical (due to myopia or hyperopia) as argued by Chauvel *et al.*,[20] where the uncertainties may be compensated by larger safety margins. Dobler *et al.*[21] have developed a new 3D treatment planning system OCTOPUS for proton therapy of ocular tumors, which takes account of precise modeling of the patient's anatomy, thus reducing the planning uncertainties. However, this planning software is not readily available.

Such discrepancies can result in improper modeling and estimations of the relationships between clips and structures. These modeling problems are often discovered by a high value of χ^2 and a disagreement between the surgeon's and the computer model's clip-to-limbus distances. In these cases, fundus images and 3D T2 FSE MRI images help to accurately delineate the tumor.

Ocular fundus imaging provides clear information of nu-

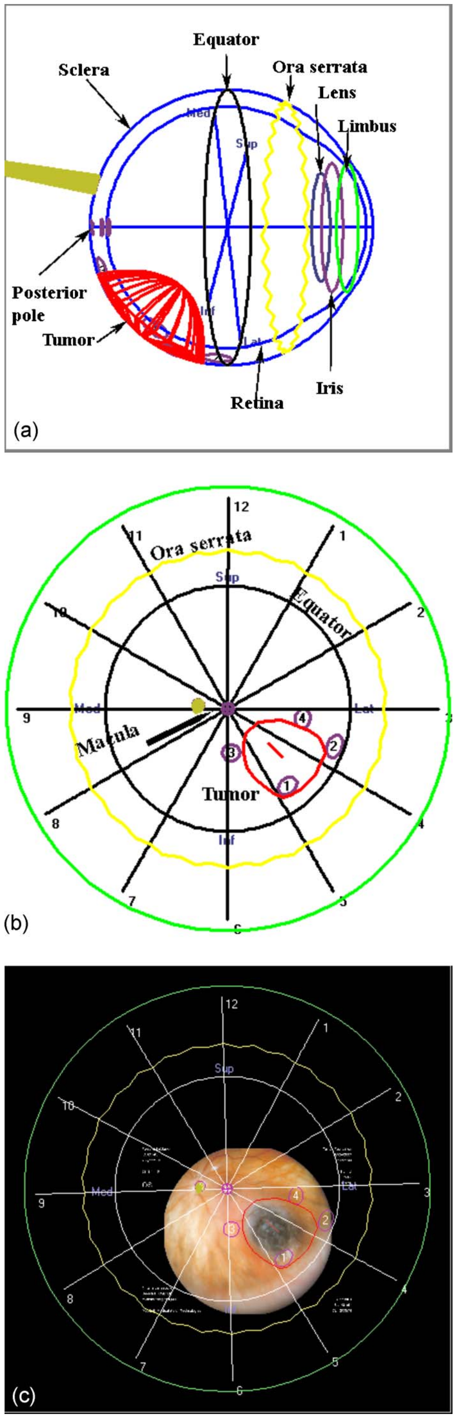

FIG. 1. (a) The anatomy of the left eye in a transverse plane relative to (b) fundus view. The different structures are labeled in both views. The tumor and other structures are labeled in the diagram. (c) shows the superimposition of fundus image.

merous retinal and choroidal conditions. It also aids in the diagnosis and localization of ocular tumors. Previously, fundus imaging used film based images for analysis of fundus disorders. However, for the current generation of retinal specialists, these standards have changed in response to evolving technology to digital imaging. Figure 1(a) shows an example of the transverse view of the left eye. The different structures of the eye are labeled. The posterior pole is at the center of the diagram. With respect to the center, the radial distance is directly proportional to the arc length along the retinal meridian. The distance measured circumferentially is also proportional to the arc length and the scaling factor is a function of radial distance. A schematic representation of this surface is shown in Fig. 1(b) as a series of three concentric circles in the coronal plane corresponding to anatomic regions of the eye. The innermost circle represents equatorial circumference and the next large circle represents the *ora serrata* in the coronal plane. This is the point at which the retina terminates at the *pars plana*. The outermost circle in this diagram is the circumference in the coronal plane at the limbus. This is the point at which the sclera terminates at the cornea. The center of Fig. 1(b) represents the posterior pole of the eye. The clock position of the tumor also gives geographic information with respect to the coronal plane of the patient. Figure 1(a) shows the tumor in the posterior part of the eye. Its corresponding position in the coronal view is shown in Fig. 1(b). Figure 1(c) shows the superimposition of fundus image.

The purpose of this study was to use a prototype version of EYEPLAN, which allows for the fusion of high-resolution fundus images in treatment planning. We aimed to study the utility of this novel technology compared to the standard manual viewing of the fundus image. The technique of image fusion potentially works (1) to continue improving an established and highly successful treatment technique, (2) as an aid for new particle centers still having to climb the learning curve in terms of treatment planning, and (3) as a tool to evaluate local recurrences. We retrospectively analyzed all patients treated by the coauthor surgeons with uveal melanoma involving the macula. All patients were treated by UCSF with proton beam therapy delivered at Crocker Nuclear Laboratory on the University of California Davis (UC Davis) campus.[22] For patients treated before 2006, digital images of the fundus were not available. Hence, we digitized the fundus slides and used them with the treatment plan. We replanned all macular melanoma patients with superimposition of the digital fundus photograph and evaluated the benefits in terms of more accurate tumor volume contouring and evaluation of tumor recurrence.

Macular lesions traditionally have a higher failure rate. These were chosen specifically for our study because posterior tumors can be particularly difficult to localize accurately during surgical clip placement. Suturing clips accurately around posterior tumors requires visualization and dexterity deep in the orbit, making them the most surgically challenging cases, especially for an inexperienced surgeon. In addition, fundus photographs project a flat image of a spherical globe, which are most accurate directly posterior.

II. METHODS AND MATERIALS

II.A. Patient population and study design

We identified 79 patients with macular melanoma who were treated with PBRT between 1995 and 2008 at UCSF, referred by three cooperating ophthalmologists (J.O.B, S.P, and T.T). Diagnosis was based on standard imaging and clinical parameters. All patients had primary uveal melanoma, with no signs of metastatic disease at presentation. No patients had prior resection or radiation therapy for ocular melanoma. All patients were treated to a dose of 56 GyE in four fractions of 14 GyE each at Crocker Nuclear Laboratory, located in the main campus of UC Davis. The proton facility[22] is a 76 in. cyclotron producing 67.5 MeV protons with a maximum range of 3.1 cm in tissue (proton RBE=1.1). Treatment time is approximately 2 min per fraction.

For this study, the 79 patients with macular tumors were evaluated. The original treatment plans for these patients with macular melanomas were reviewed. These original plans had been developed using the older EYEPLAN version (official v3), which did not allow for direct digital superimposition of fundus imaging. These macular melanoma cases were then replanned with pretreatment and post-treatment fundus images in the new EYEPLAN software (official version 3.05), which allows for digital superimposition of the fundus image so that the tumor volume can be visualized and adjusted directly over the fundus image. The pretreatment fundus images for the 79 patients were digitally fused to the original treatment plan in the new EYEPLAN software to check if the pretreatment fundus photograph tumor volume had been fully covered in the original treatment plan. For patients with local failures, the post-treatment time of failure fundus images were used to determine the exact location of the tumor growth with respect to the original target volume and the dose received in the region of tumor progression. The details of the planning software are described below.

II.B. EYEPLAN software

A dedicated treatment planning software (EYEPLAN) was used for all ocular melanoma patients. This planning software was developed by Goitein and Miller[23] at MGH and latter modified at PSI-Villigen (Switzerland)[24] and Clatterbridge, U.K.[25] The early version of the software was run on MicroVAX and was later written for Microsoft Windows by Martin Sheen of Clatterbridge U.K. The new version of EYEPLAN (v3.05) allows for the registration of fundus photographs so that it can be displayed as a background image for currently displayed graphics. The ophthalmologic input data to the software include

(a) The axial length of the eye (the distance between anterior surface of the cornea to the inner surface of the posterior retina) and the tumor height obtained from A and B scan ultrasound measurements.
(b) The spatial coordinates of the clips relative to the axis of the eye obtained from orthogonal x-ray films obtained during patient simulation. These clip coordinates can be obtained either automatically on digital images or can be measured manually on orthogonal x-ray films.
(c) The tumor base which is drawn manually in a wide-angle fundus view on the computer screen. Wide-angle fundus view is intended to mimic the options of wide-angle fundus camera, which also depends on the optical characteristics of the camera. This view has a choice of selecting either outer sclera or inner retinal view. The relation of the clips to the tumor edge is obtained from the surgeon's mapping of the fundus drawn at the time of tantalum ring placement and fundus photography as shown in Fig. 1.
(d) An image may be registered with EYEPLAN v3.05 so that it can be displayed as a background for the currently displayed graphics, i.e., a beam's-eye view may be displayed over a beam's-eye photograph of the eye. It displays an image directly if only one suitable image has been registered or offers a choice if there is more than one. The wide-angle fundus image is scaled and oriented according to the macula-papilla distance. The image is registered by clicking on

(1) The center of the macula then the center of the optic disk (for a fundus view),
(2) The beam isocenter then the point where the horizontal axis crosses the beam aperture (for a beam's-eye view),
(3) The center of the pupil then the edge of the iris (for a plane view on the eye's axis),
(4) The center of the eye then either side of the eye (for an axial camera view), or
(5) The center of the eye then the anterior cornea (for a lateral camera view or a view of the side of the eye).

The EYEPLAN software schematically displays a line drawing of the patient's eye including such anatomical structures as the globe, lens, optic nerve, and macula on a computer screen. The goal of the 3D planning system is to do the following: (1) Select the optimal fixation direction that minimizes the dose to critical structure including optic nerve, macula, lens, ciliary body, and cornea. (2) Translate the eye to center the tumor on the beam. (3) Calculate the beam aperture by adding a selectable safety margin of generally 2.5 mm around the tumor profile. (4) Calculate the necessary beam range and modulation depth. (5) Calculate the dose-volume histograms for each structure and determine the dose distribution in polar view and different planes as desired by the physician and planner.

The fundus view of the eye is generally used to draw the target contour, which shows the size as well as the geographical location of the tumor on the surface of the retina as shown in Fig. 1(b). In this view, the geometric distortion of the projection of contour on the 2D plane is minimum near the posterior pole of the eye and increases as one approaches the anterior pole. To get an idea of the magnitude of this error, we calculated the distance of a point 5 and 12 mm lateral to macula using both Cartesian coordinates and spherical coordinates, assuming an average diameter of the eye is 24 mm. This resulted in a distance error of 0.2 and 2.5 mm, respectively. Hence the more anterior tumor locations have a greater risk of distortion with fundus imaging. The fundus view of the diagram is a projection of a spherical surface extending from the posterior pole to the limbus shown in Fig. 1.

TABLE I. Characteristics of patients with macular melanomas.

Number of patients with macular melanomas	79
Age (yr)–mean (range)	60.5 ± 15 (19–92)
Sex: Male:female	46:33
Eye: Right:left	35:44
Largest tumor diameter (mm)–mean (range)	11.5 ± 4.1 (4.2–24)
Tumor height (mm)–mean (range)	4.4 ± 2 (1.7–10.7)
Follow-up (months)	
Mean (range)	33.6 ± 23 (8.3–112.1)
Median	27.6

III. RESULTS

Table I summarizes the characteristics of the macular melanoma patients treated with proton beam therapy. A total of 79 patients with macular melanomas were reviewed. The median age was 62 yr, mean tumor height was 4.4 ± 2 mm, and mean larger tumor diameter was 11.5 ± 4.1 mm. Ratio of right:left eye was 35:44 and ratio of male:female was 46:33. There were no patients with extraocular extension or ciliary body invasion. The mean follow-up of these patients was 33.6 ± 23 months (range 8.3–112.1 months). The patients treated before 2006 had fundus images taken with a film camera and were provided as slides. These slides were digitized and then the images were transferred to the planning computer. The high-resolution digital fundus images were available from 2007 onward.

Post-treatment tumor growth was seen in six patients. All these six patients had marginal failure in the region of lateral dose fall-off or tumor miss with one having in-field failure as well. Among the six recurrences, three were managed by enucleation and one underwent retreatment with proton therapy. Three patients developed distant metastasis and all three patients have since died.

All 79 patients were re-planned with EYEPLAN (v3.05) with registering and fusing their pretreatment and post-treatment fundus images in the EYEPLAN software. The re-planned image showed that in the 73 cases without local failure, the original treatment field adequately covered the tumor contour as seen in the fundus image. In these 73 cases, the fundus image was confirmed to be an appropriate and accurate depiction of the tumor contour and served as an objective data point to digitally confirm the tumor contour along with the traditional data inputs.

Six patients showed local tumor growth and their clinical details are listed in Table II. The mean time to failure for these six patients was 21.6 ± 8.6 months. In four cases, the direct superimposition of the pretreatment fundus image did not significantly change the contour of the original tumor volume and the post-treatment fundus image confirmed marginal failure. However, replanning of the remaining two cases with marginal failures showed that fusion of the pretreatment fundus image did alter the original tumor contour. The details on these two patients are given below.

Subject no. 1: A 62 yr old female presented with a moderately pigmented lesion extending along the superotemporal arcade, which nearly abutted the optic nerve. There was overlying orange pigmentation with interval development of subretinal fluid, which extended over the fovea. The size of this dome shaped peripapillary lesion was 4 × 6 × 3.0 mm. Clinical findings were consistent with choroidal melanoma. Three tantalum clips were placed around the periphery of the tumor in preparation for proton beam radiation as shown in Fig. 2(a). The figure shows the fundus view and the relation of the tantalum clips and the tumor edge as depicted at the time of surgery. The tumor was drawn per the surgical notes, clinical exam and measurements, and manual viewing of the fundus photo. The 95% isodose line covered the original tumor volume. The patient was treated to this tumor volume at our standard dosing of 56 GyE total and tolerated treatment well. Tumor regrowth was observed after 27.2 months in the superior and inferior aspect of the lesion and the eye was finally enucleated.

Our replanning of this subject's case with pretreatment and post-treatment fundus image superimposition provided important considerations. As seen in Fig. 2(a), only three clips were placed due to difficulty with the surgical technique in the posterior pole and hence the borders of the tumor were not well delineated by the clips placement. The positioning was less accurate particularly in the superior direction. Upon superimposition, it appears that potentially a portion of the tumor was not covered well. The replanning process showed there was a mismatch between the fundus imaging and surgical rings, such that the tumor contour did

TABLE II. Characteristics of patients with tumor recurrence after proton treatment. Pt = patient; Rx = treatment; TH = tumor height; OD = right eye; OS = left eye; DOD = dead of disease; and NED = no evidence of disease.

Pt no.	Age	Sex	Rx eye	Initial visual acuity	TH (mm)	Basal dimension (mm)	Time to local failure (months)	Outcome/comments
1	62	F	OS	20/80	3.0	4 × 6	27.2	Eye enucleated due to tumor growth, patient alive, NED
2	79	F	OD	20/70	3.0	12.5 × 10.5	10.8	Tumor growth and complications of intraretinal hemorrhage, patient died of distant metastases, DOD
3	61	M	OS	20/100	6.1	13.5 × 13	12.3	Liver metastases, DOD
4	62	M	OD	20/200	7.0	14 × 14	27.8	Radiation papillopathy and retinopathy, eye enucleated, developed CNS and lymph node metastases, DOD
5	64	M	OD	20/200	5.6	12.5 × 10	32.2	Vitreous and retinal hemorrhage, tumor growth, retreated to 56 GyE/4 fx after 3 yr, pt alive NED
6	48	M	OD	20/30	3.0	15 × 9	25.9	Tumor growth, eye enucleated, pt alive NED

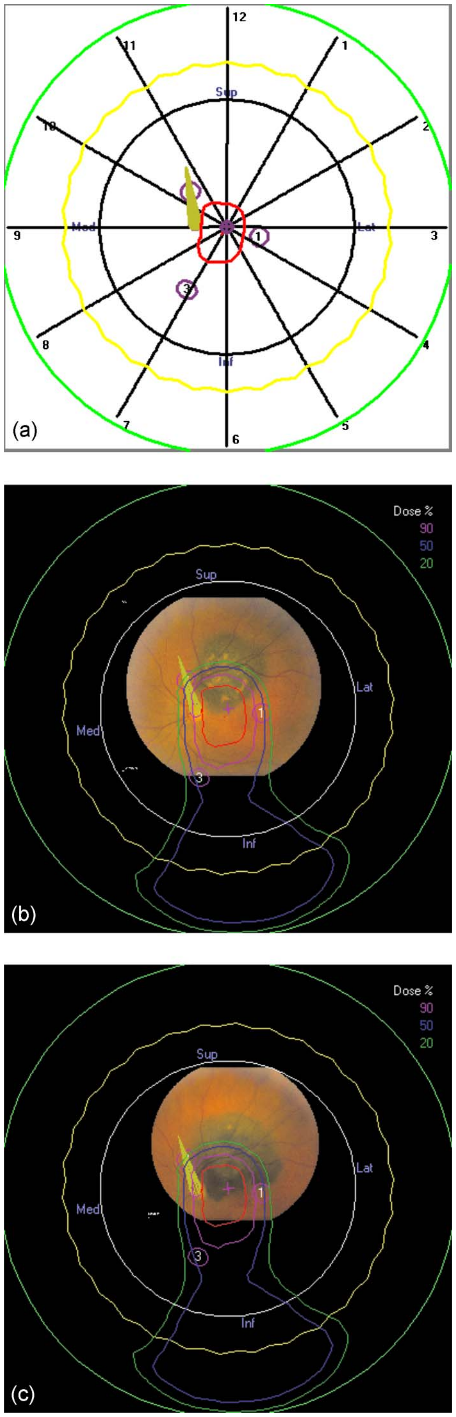

FIG. 2. (a) The original view of tumor in fundus view. Replanning with the fundus photograph with overlaid isodose lines of subject no. 1. (b) Baseline and (c) 27 months after PBRT.

not align well with the fundus image. Replanning with direct fusion of the pretreatment fundus image [Fig. 2(b)] showed that a more accurate delineation of the superior most portion of the tumor might have been possible with the use of direct superimposition of fundus imaging. Based on the post-treatment fundus image fusion to the original treatment plan [Fig. 2(c)], the area of local failure was at the superior margin as well as in-field. The superior part of the tumor as seen on fundus image superimposition received less than 20% of the prescribed dose of 56 GyE. The fundus image fusion may have helped in avoiding such surgical and/or planning errors.

Subject no. 2: A 79 yr old female presented with a moderately to darkly pigmented choroidal lesion in the right eye. The lesion extended from the optic nerve head into the macula and along the superotemporal quadrant. Clinical findings were consistent with a macular melanoma in her right eye. Tumor dimensions were 12.5 mm vertically $\times$10.5 mm horizontally$\times$3 mm thick. The posterior edge of the tumor was 1.5 mm from optic disk. Four tantalum clips were sutured around the tumor in preparation of PBRT. The clips were placed as seen from Fig. 3(a). It was difficult to mark the nasal aspect of the tumor given its peripapillary location. The tumor was drawn based on the clips as in Fig. 3(a) and the 95% isodose line covered this original tumor volume as seen from Fig. 3(b). A lateral margin of 2.5 mm was given on the aperture and the distal margin of 3 mm was given on range. The patient was treated to 56 GyE total and tolerated treatment well. As is observed from Fig. 3(c), the tumor had recurrent growth inferiorly and near the macula after 10.8 months.

Our replanning of subject no. 2's case with pretreatment and post-treatment fundus image superimposition showed that a more accurate delineation of the inferior portion of the tumor may have been possible with the use of direct superimposition of fundus imaging [Fig. 3(b)]. Based on the post-treatment fundus image fusion to the original treatment plan [Fig. 3(c)], the area of local failure was at the inferior margin. The inferior part of the tumor received only 90% of the prescribed dose of 56 GyE, which may have contributed to the failure.

IV. DISCUSSION

PBRT is a standard of care treatment for uveal melanoma with excellent local control rates reported at 95% or higher by numerous authors.[1,2,13,26] Accurate and reproducible tools for use in the planning process are of utmost importance in continuing this high success rate, particularly as new proton facilities, along with new surgeons, radiation oncologists, and physicists, may be seeing and treating this rare disease. In the present paper we have studied the potential benefit of using a new advancement in the latest version of EYEPLAN (v3.05), which now allows for digital fusion of the fundus image.

The application of digital imaging technology to ophthalmology has grown in the past decade. The current imaging techniques for fundus have contributed significantly to our understanding of the treatment of posterior segment disorders of the eye. Current technology has given us the capability to acquire, edit, archive, retrieve, compare, and transmit fundus images with several diagnostic and treatment planning systems for patient management, remote constellation, teaching, and collaborative research. Although in medical imaging the fusion of images is a standard topic, for ophthalmologic applications, it has not been studied extensively.

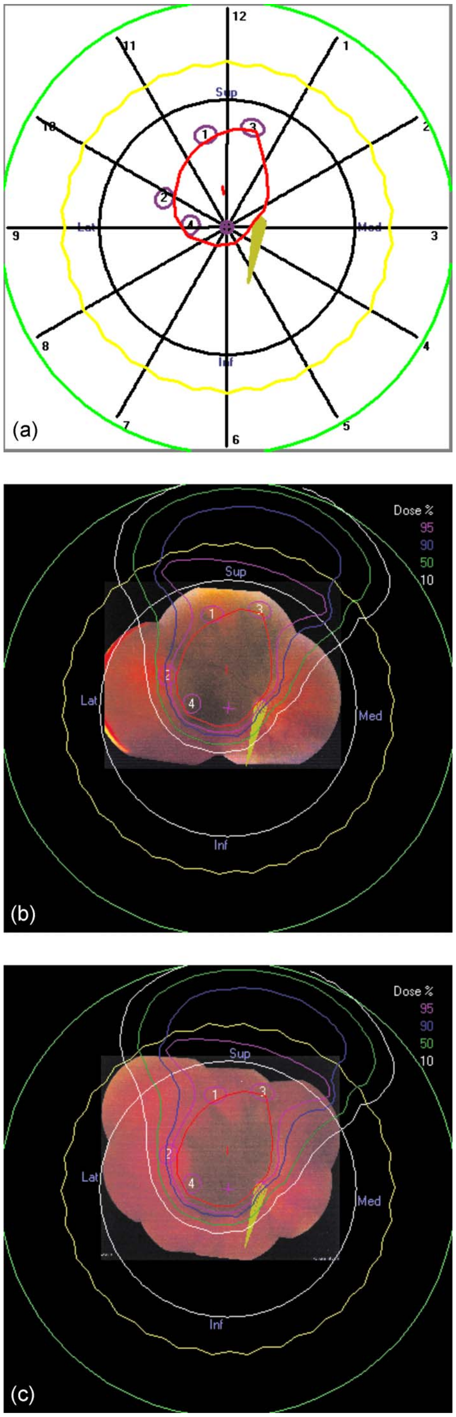

FIG. 3. (a) The tumor in fundus view. Replanning with the fundus photograph with overlaid isodose lines of subject no. 2. (b) Baseline and (c) 11 months after PBRT.

The present study evaluates the use of the fusion of high-resolution fundus images in treatment planning to better understand the utility of this novel technology in more accurately depicting and confirming tumor volume contours for radiation planning in uveal melanoma. We reviewed and replanned macular melanoma cases with superimposition of pretreatment and post-treatment fundus imaging in the new EYEPLAN software to determine patterns of local failure and potential benefit of fundus imaging in terms of accurate tumor volume delineation.

Choroidal melanomas located in the posterior uvea are technically difficult to localize and are associated with the highest rate of irradiation failure.[18] Various authors have reported a rate of local relapse of 4%–18% in posterior uveal melanoma treatment with brachytherapy.[26–28] One of the contributing factors for the local tumor relapse after plaque radiotherapy is difficulty with plaque localization in the posterior location. In proton beam therapy, the surgeon's placement of tantalum ring markers are similarly of utmost importance in terms of tumor delineation and can be subject to specific surgical challenges in the posterior region. The placement of the rings has a substantial impact on the planning tumor volume and if certain margins cannot be marked adequately, this can result in subtherapeutic radiation dose to the tumor. In such cases, the consideration of tumor margins used and fusion of fundus images with the treatment plan can be very beneficial.

In our study, all 79 cases of macular melanomas were replanned with the new version of EYEPLAN (v3.05), with digital fusion of the fundus image. Among the 79 patients, six patients had marginal failure in the region of dose fall-off or tumor miss, including one who also had an in-field recurrence. In the 73 cases without local failure, the original treatment field adequately covered the tumor volume as seen in the fundus image. Hence, in the majority of cases, the fundus image serves as a confirmatory data point to ensure appropriate and accurate depiction of the tumor volume by surgical rings. As an objective, digital, reproducible measure of tumor contour, it complements the traditional data inputs.

Replanning of the six cases with local failure confirmed that in four patients, the pretreatment fundus image tumor volume was adequately covered by the original tumor volume used. Hence, in these four patients, the fundus image would not have changed tumor contouring and presumably local failure outcomes. However, in two patients the pretreatment fundus image showed that the tumor volume as delineated by the tantalum clips were inadequate for at least one margin including the region of marginal miss. In these patients, the digital superimposition of the fundus photo may have benefited in terms of tumor delineation.

In one patient (subject no. 2), on review with fundus imaging, it was seen that the area of failure received only 90% of the tumor dose, which may have contributed to the failure at this margin. Although, in a randomized study of 50 vs 70 GyE in five fractions at Massachusetts General Hospital,[5] there was no difference in local control. Thus 90% of the prescribed dose covering the tumor may in fact have been sufficient for local tumor control. However, in the unpublished UCSF/Lawrence Berkeley National Laboratory patient population, there were clinically lower local control outcomes with 48 GyE which resulted in an increase in dose to the current standard practice of 56 GyE (private communication, Dr. J.R. Castro).

Of note, one of these two patients had three rings in place. Generally, our surgeon's standard is to place four rings to depict the four edges of the tumor (nasal, superior, temporal, and inferior). However, there are difficult surgical cases in which three rings have been placed. This can result in difficult modeling and hence the fundus photo may provide additional objective data to determine the tumor contour and ensure that no significant mismatch is occurring with tumor volume depiction. Review of all 79 patients revealed that although most of the tumors were delineated by four rings, there were 12 patients whose tumors were delineated by placing three clips. A detailed review of all documents related to the treatment revealed that the clips were usually placed on one side of the tumor and the other side was delineated by the optic disk. In such cases, if initial fixation was not correct, it could affect the macula/optic nerve position without disturbing clip-to-limbus distances.

Our study analyzes a new software tool, which we believe to be an important step in the accurate and reproducible planning of a treatment course for a rare tumor. Only a small subset of patients was analyzed for this purpose. However, even in this subset, we were able to find that one-third of the marginal misses may have benefited from direct superimposition of fundus photographs to the treatment plan. In these cases, the fundus image better delineated certain margins that were otherwise difficult to mark at the time of clip surgery. Since the newest version of EYEPLAN (v3.05) has been made available to us, we have used fundus image fusion extensively at our institution as at least a confirmation of the ring placement and in certain cases, as those discussed above, to extend the tumor margin to include areas of potential tumor volume seen on the fundus image that the clips may not represent fully. Also, in those clinical situations where sensitive tissues are in close proximity with target volume, the fusion of fundus images allows for potential to improve tumor and normal structure delineation and dosing. The usefulness of digital fundus images may be less for tumors ≥ 10 mm thick, which can obscure the disk and fovea from view. Tumors in the anterior location such as ciliary body tumors may not be useful for image fusion because the complete tumor base and disk and macula is difficult to see on the same view of the fundus image.

Additionally, we believe orbital MRIs provide important information about tumor and eye dimensions, which could be beneficial in future versions of planning software. Daftari *et al.*[19] compared 3D MRI-based tumor delineation of ocular melanoma with EYEPLAN planning techniques for 60 consecutive patients with ocular melanoma. The tumor volumes obtained with 3D MRI were comparable to tumor volumes obtained from EYEPLAN software. Though small tumors were difficult to visualize, MRI imaging was particularly helpful in delineating tumor margins in patients where tumor was surrounded by hemorrhage or dark reactive pigmentation. Also, having postsurgery MRIs can clearly show the position of clips and optic nerve. Thus, one can check the clips to optic nerve distances. Hence, high-resolution 3D fast spin echo T2 weighted MRI images may provide helpful objective information on intraocular tumor volumes and potentially clip locations.

Overall, we have found the use of digital superimposition of the fundus image in treatment planning to be a beneficial new step to potentially help in tumor volume delineation. Our current practice standard is to use the direct superimposition of the high-resolution digital fundus photograph for all patients including anterior tumors and thick posterior tumors, in addition to the surgeon's clinical and clip mapping of the tumor and ultrasound to draw the tumor volume. The tumor volume is extended if the fundus photo shows potential disease beyond the volume that may otherwise be depicted by the rings. Clinical expertise and planning experience must be always used when adding any new technology to clinical practice. Hence, any cases with discrepancy between surgical rings and fundus imaging are reviewed very carefully. Generally, the planning process takes an additional 10 min for image fusion. The ultimate goal in using the superimposition of the fundus imaging in the new EYEPLAN software is to benefit in terms of confirming accurate tumor delineation and potentially reducing local failure.

V. CONCLUSIONS

Proton beam therapy of uveal melanoma with a dose of 56 GyE in four fractions results in excellent local control. Posterior lesions can be difficult to mark at the time of clip surgery and hence may be better defined with the additional use of fundus imaging. A novel version of the EYEPLAN treatment planning software now allows for digital superimposition of high-resolution fundus imaging assisting in tumor volume contouring. Replanning with the new software showed that the fundus image serves as an objective data point to accurately depict and confirm the tumor volume for planning purpose. In one-third of patients with local treatment failure, the superposition of the fundus photograph may have allowed improved localization of tumor. Fundus image fusion can serve to confirm the ring placement and, in certain cases, to extend the tumor margin to include areas of potential tumor volume seen on the fundus image that otherwise may not be fully represented. Our current practice standard is to use the direct superimposition of the high-resolution fundus photograph for all patients in addition to the surgeon's clinical and clip mapping of the tumor and ultrasound to draw the tumor volume.

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