Noninvasive referencing of intraocular tumors for external beam radiation therapy using optical coherence tomography: A proof of concept

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Purpose: External beam radiation therapy is currently considered the most common treatment modality for intraocular tumors. Localization of the tumor and efficient compensation of tumor misalignment with respect to the radiation beam are crucial. According to the state of the art procedure, localization of the target volume is indirectly performed by the invasive surgical implantation of radiopaque clips or is limited to positioning the head using stereoscopic radiographies. This work represents a proof-of-concept for direct and noninvasive tumor referencing based on anterior eye topography acquired using optical coherence tomography (OCT).

Methods: A prototype of a head-mounted device has been developed for automatic monitoring of tumor position and orientation in the isocentric reference frame for LINAC based treatment of intraocular tumors. Noninvasive tumor referencing is performed with six degrees of freedom based on anterior eye topography acquired using OCT and registration of a statistical eye model. The proposed prototype was tested based on enucleated pig eyes and registration accuracy was measured by comparison of the resulting transformation with tilt and torsion angles manually induced using a custom-made test bench.

Results: Validation based on 12 enucleated pig eyes revealed an overall average registration error of $0.26 \pm 0.08^\circ$ in $87 \pm 0.7$ ms for tilting and $0.52 \pm 0.03^\circ$ in $94 \pm 1.4$ ms for torsion. Furthermore, dependency of sampling density on mean registration error was quantitatively assessed.

Conclusions: The tumor referencing method presented in combination with the statistical eye model introduced in the past has the potential to enable noninvasive treatment and may improve quality, efficacy, and flexibility of external beam radiotherapy of intraocular tumors. © 2014 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4885975]

Key words: eye, intraocular tumors, external beam radiotherapy, tumor control, motion management

1. INTRODUCTION

External beam radiation therapy (EBRT) is currently considered the most common treatment modality for intraocular tumors, providing lower late recurrence rates with respect to radioactive plaque brachytherapy.¹ Tumor control is the primary goal but side effects such as cataract, neovascular glaucoma, radiation retinopathy, and optic neuropathy are potential local complications of ocular radiation therapy. Uveal melanoma (UM) is the most common primary eye cancer in adults and is associated with significant morbidity and mortality.² Consequently, UM requires sharply delimited irradiation treatment to achieve the necessary high tumor dose while sparing structures at risk (optic nerve, macula, ciliary body, and lens) involved in the preservation of visual function.³ To fulfill these requirements, proton beam and stereotactic radiation therapy have been applied with a control rate of more than 96% at 5 years.⁴⁻⁶

However, regardless of which form of EBRT is applied, quality and efficacy of ocular treatments strongly depend on the accuracy of the patient’s setup and on the delivery of the treatment. Localization of the tumor and the efficient compensation of tumor misalignment with respect to the radiation beam are crucial. Even small involuntary ocular movements may cause dose delivery errors and the steep dose gradients by proton and stereotactic radiation therapy may result in unacceptable underdosage to the tumor volume and excessive irradiation of structures at risk and surrounding healthy tissue.³⁻⁷⁻⁸
While the head of the patient can be well positioned and immobilized for treatment using a thermoplastic mask system, positioning of the eye as a fast moving, ball-shaped organ is challenging. In the past, different approaches have been applied including suction devices,\textsuperscript{9} retro- or parabulbar anaesthesia,\textsuperscript{10} or active fixation of light points.\textsuperscript{11-14} Suction devices are very uncomfortable and may cause damage to the anterior eye segment. Local anaesthesia is associated with discomfort for the patient and induces displacement of the eyeball in the orbit. According to the state of the art procedure for ocular proton therapy, localization of the target volume during treatment planning and dose delivery is indirectly performed by the invasive surgical implantation of radiopaque clips.\textsuperscript{3,7} Initial alignment between tumor and treatment beam is verified before each fraction by manually comparing the clip positions derived from multiple radiographies with respect to the planned reference coordinates. This procedure is repeated until deviation of the clip positions from the planned reference coordinates drops below a certain threshold causing repeated patient exposure to ionizing radiation.\textsuperscript{7} Gating of the beam is done manually if deviations in eye position are observed with respect to the reference pupil contour outlined on the control monitor, involving significant delays between ocular movement detection and treatment interruption. For state of the art stereotactic radiotherapy, referencing of intraocular tumors is limited to positioning the head using stereoscopic radiographies of the skull. However, eye movements with respect to the skull are not sufficient to properly align the eye in reference to the treatment delivery system, the eye model can be transformed into the isocentric reference frame. However, the proposed tumor referencing method based on a stereoscopic camera system is limited to generic eye models (e.g., spherical or elliptical eye models) and its integration into a stereotactic treatment setup is difficult because of the large space requirements. The missing compensation for cyclotorsion (rotation of the eye about its optical axis), which has been shown to be significant,\textsuperscript{16} represents another limitation.

A promising approach for referencing the moving eye during refractive surgery has been introduced by Schruender et al.\textsuperscript{17} They proposed intraoperative corneal topography for treatment plan registration using fluorescence based structured light. Features on the cornea surface such as natural with-the-rule astigmatism allow for reliable registration of the treatment plan in six degrees of freedom (DOF) and with a registration error of only a few μm. Although the results look promising, structured light as a technology for corneal topography can hardly be applied to ocular proton- and stereotactic radiotherapy. Projection of the fringe pattern and imaging (camera) of the fluorescence in front of the eye under a certain angle would take too much space and would unnecessarily prevent radio-oncologists from applying certain beam directions.

Optical coherence tomography (OCT)\textsuperscript{18} has become a widespread image modality in various fields of medicine particularly in ophthalmology, where its high resolution and noninvasiveness has allowed multiple applications for cross-sectional and volumetric investigations of the retina and anterior segment.\textsuperscript{19-22} Over the last years, OCT imaging speed has been increased drastically enabling 4D \textit{in vivo} imaging with high sampling density, field of view, and large axial ranges.\textsuperscript{23,24} The combination of high speed, high resolution, and minimum space requirements makes OCT systems well suited to overcome the limitations of existing tumor referencing systems.

In 2012 Fassi et al.\textsuperscript{14} proposed a direct 3D (three-dimensional) approach providing quantitative information on the 3D position and orientation of the monitored eye using a stereoscopic camera system and two corneal reflections. After applying this eye tracking technique during CT and MRI scanning and after calibration of the eye tracker with respect to the treatment delivery system, the eye model can be transformed into the isocentric reference frame. However, the proposed tumor referencing method based on a stereoscopic camera system is limited to generic eye models (e.g., spherical or elliptical eye models) and its integration into a stereotactic treatment setup is difficult because of the large space requirements. The missing compensation for cyclotorsion (rotation of the eye about its optical axis), which has been shown to be significant,\textsuperscript{16} represents another limitation.

In the past we introduced a 3D statistical shape model for precise eye modeling used in EBRT of intraocular tumors.\textsuperscript{25} In the meantime we extended the model to be also applied to ocular MRI imaging in order to include 3D tumor shape in the treatment plan. This work introduces the first steps towards a CT compatible, head-mounted device for noninvasive referencing of intraocular tumors to enhance quality and efficacy of EBRT. Although this referencing technique may be applied to different forms of EBRT, this prototype is particularly designed for stereotactic radiotherapy. We present a framework for direct tumor referencing in the isocentric reference frame based on anterior eye topography acquired using OCT and registration of the statistical eye model. Finally, registration accuracy is validated based on enucleated pig eyes mounted on a custom-made test bench.
FIG. 1. Principle of the proposed referencing method. Ocular tumors are localized during dose delivery by tracking the anterior eye segment and 3D registration of a statistical eye model.

2. MATERIALS AND METHODS

2.A. Basic principle

Under rigid body assumption local position of ocular structures can be considered invariant from planning to treatment phase. The tumor volume can, thus, be noninvasively localized during dose delivery by 3D tracking of the anterior eye segment and registration in 6 DOF (translation, rotation, cyclotorsion) of a statistical eye model. Calibration of the tracking device with respect to the treatment delivery system then allows expression of tumor volume and structures at risk in the isocentric reference frame to compensate for misalignment between tumor and radiation beam (Fig. 1).

2.B. Hardware implementation

The implemented tumor referencing system is based on a Fourier-Domain OCT system consisting of a SLED light source (λc = 840 nm, Δλ = 80 nm, EXALOS AG), a spectrometer (Wasatch Photonics Cobra SRC, pixel resolution 0.04 nm/pixel, 45 kHz A-scan rate), a 50:50 beam splitter interferometer, and a reference arm with a glass flat for dispersion correction [Fig. 2(a)]. The employed OCT system showed a limited SNR of 93 dB at a pixel integration time of 45 μs and a fall-off of approximately 20 dB over the measurement range. The OCT system features an axial resolution of 4 μm and a measurement range of 4.5 mm. As the delivery optics, a 2D galvo scanning unit, a focus lens (f = 140 mm), and a mirror are integrated into a head mounted tracking device [Fig. 2(b)]. This device can be easily attached (quick release system) to the brainlab mask system during CT scanning and dose delivery using a support frame with adjustment options in all directions [Fig. 2(c)]. Geometrical and optical design enables a scanning volume for anterior eye segment tracking of 20 × 20 × 4.5 mm at a working distance of 75 mm [Fig. 2(d)] and flexible beam delivery [Fig. 2(e)]. Tracking device and support frame are built out of aluminum and polyoxymethylene (POM) in order to guarantee for CT compatibility [Figs. 2(f) and 2(g)].

2.C. Calibration procedure

OCT systems are designed to detect backscattered and backreflected light in order to measure pathway differences between sample and reference arm. The spatial separation of the two scanning mirrors [Fig. 2(a)] causes a so-called fan beam distortion, which makes perfectly flat surfaces appear curved in OCT volumes. In order to compensate for fan beam distortion and to transform the OCT volume into the device specific reference frame defined by marker spheres [Fig. 3(a)-top], a device specific calibration is performed as proposed by Ortiz et al. The procedure consists of collecting series of 3D volumes of a dot grid calibration target [Fig. 3(a)-right] at different axial positions within the measurement range. The target is placed into a custom-made calibration unit (production tolerance < 10 μm), which is mounted on top of the tracking device and aligned with the device specific reference frame using dowel pins and fixation screws
FIG. 2. Design of the prototype. (a) Optical principle consisting of OCT system and head mounted device. (b) Assembly drawing of tracking device and (c) support frame. (d) Free working distance. (e) Possible application of treatment beams. (f) CT slice through optical tube and (g) support frame.

[Fig. 3(a)-left]. A 3D volume is acquired every 0.5 mm along the z-axis using a built-in linear stage (10 \( \mu \)m per division) and a mechanical stop, enabling the absolute positioning of the target in the device specific reference frame. For each volume, 3D coordinates of the dot centers are automatically detected using the Hough transform [Fig. 3(b)]. Dot centers are then related to the corresponding coordinates in the device specific reference frame to build a 3D deformation field. Later the deformation field can be interpolated and applied to OCT volumes in order to get the exact position for every voxel in the device specific reference frame. Figure 3(c) illustrates the amount of fan distortion before (top, max. deviation >6 um) and after calibration (bottom, max. deviation <1 um) by 3D OCT imaging and segmentation of a flat optical surface (20 \( \times \) 20 mm).

2.D. Treatment planning

In the CT scanner the tracking device is applied [Figs. 4(a) and 4(b)], and ocular CT acquisition (<12 s) and OCT scanning is performed simultaneously. Most of the light detected by the OCT system is reflected from the surface of the cornea and sclera due to the mismatch of optical indices between tissue and air causing a high intensity peak along each A-scan. From the calibrated OCT volume, anterior eye topography can be automatically extracted by finding and thresholding
the maximal intensity along each A-scan, resulting in a dense point cloud. Since CT and OCT has been acquired at the same time, topography and ocular CT can be registered using fiducial markers. Finally, treatment planning can be performed based on an extended version of the statistical eye model,\textsuperscript{25} which is adapted to the patient’s anatomy based on the automatic segmentation and registration of structures of interest in ocular CT and MRT data. Application of the tracking device during MRT scanning is not required.

2.E. Stereotactic radiotherapy

During stereotactic radiotherapy the tracking device is applied as well [Figs. 4(c) and 4(d)] in order to acquire topography of the eye to be treated. Referencing of the treatment plan is finally performed by 3D registration (translation, rotation, cyclotorsion) of the reference point cloud extracted in the CT scanner with the point cloud acquired during dose delivery. In a preprocessing step, outliers are removed using statistical outlier removal.\textsuperscript{29} The floating point cloud is then registered with the reference point cloud in a two-stage procedure. During prealignment the limbus border is automatically extracted by finding the nearest neighbor to the center within sectors of 1° resulting in two closed lines with 360 points each. Based on the limbus border, prealignment is performed using nonlinear iterative closest point (ICP) based on Levenberg-Marquardt optimization.\textsuperscript{30} The final transformation is then found using all points where convergence is ensured if the difference between previous and current transformation drops below a defined threshold. ICP minimizes the euclidean distance between two point clouds and enables registration of the treatment plan in 6 DOF within the reference frame of the tracking device. Stereoscopic X-ray sources integrated in the treatment device setup or an optical tracking system then allows for tracking of the device (fiducial markers) and therewith referencing of the treatment plan in 6 DOF. Each point cloud was then registered with the respective reference point cloud using the algorithm described above [Figs. 5(g)–5(l)]. After convergence, the measured angle was compared with the angle manually induced using the test bench in order to compute the mean registration error.

2.F. Validation

In order to measure the performance of the proposed referencing technique, accuracy and speed were evaluated in the device specific reference frame based on 12 freshly enucleated pig eyes mounted on a custom-made test bench [Figs. 5(a)–5(c)]. A cylindrical eye chamber has been manufactured using rapid prototyping, which was mounted on a goniometer (±5° tilt range, resolution <10 arcmin, Thorlabs) and a manual rotation stage (360° rotation range, resolution <5 arcmin, Thorlabs) in order to apply different tilt and torsion angles. According to the literature the average human eye rotates inside its socket around a center point, which lies 13.5 mm behind the corneal apex on the optical axis.\textsuperscript{31} To simulate human eye movements, each pig eye was manually positioned within the eye chamber using a removable cap as a mechanical stop and a bottom panel, which was screwed into the eye chamber. The chamber itself was screwed onto a screw base mounted on the goniometer [Fig. 5(a)]. To each pig eye tilt and torsion between 1° and 5° have been applied and OCT volumes with 500 × 500 uniformly distributed A-scans were acquired within a fixed scanning volume of 20 × 20 × 4.5 mm using a integration time of 40 μs per A-scan. Since limbal epithelium is more scattering than the rather transparent cornea [Fig. 5(d)] only limbal topography was computed by global thresholding of A-scans and applying of the deformation field for undistortion of the resulting point cloud [Fig. 5(e)]. Only minor changes in OCT signal amplitude have been observed within the applied tilting range of ±5°. Figure 5(f) illustrates the spherical surface of the limbus and the prominent surface features, which enable registration of limbal topography in 6 DOF. Each point cloud was then registered with the respective reference point cloud using the algorithm described above [Figs. 5(g)–5(l)]. After convergence, the measured angle was compared with the angle manually induced using the test bench in order to compute the mean registration error.

3. RESULTS

Validation based on 12 enucleated pig eyes revealed an overall average registration error of 0.26 ± 0.08° in 87
FIG. 5. Validation of the proposed method. (a) Custom-made test bench. (b) Photograph of test setup. (c) Photograph of pig eye mounted on eye chamber. (d) En-face view on the OCT volume (top) and B-scan extracted along the red line (bottom). (e) Limbal topography. (f) Deviation of limbal topography from best fitting sphere. (g) Overlay of point clouds acquired with 0° tilt (red) and 5° tilt (green). (h) Extraction of limbus border (pink line). (i) Registered point clouds. (j) Deviation between point clouds (5° tilt), (k) after prealignment and (l) after registration.

± 0.7 ms for tilting and 0.52 ± 0.03° in 94 ± 1.4 ms for torsion when using a dense sampling of 500 × 500 A-scans (Table I). To quantitatively assess dependency of sample density on mean registration error, registration was furthermore performed for subsampled volumes. For a coarse sampling density of 125 × 125 A-scans an overall average registration error of 0.35 ± 0.07° in 19 ± 1 ms for tilting and 0.79 ± 0.06° in 25 ± 2.9 ms for torsion was found. OCT acquisition time was 10 s for 500 × 500, 2.5 s for 250 × 250, and 0.6 s for 125 × 125 A-scans and computation time for the segmentation of the limbus border as part of the total registration time was within 15 ms for all acquired volumes. Registration error for torsion was found to be slightly increased compared to tilting due to less prominent surface features defining torsion state. The results also illustrate increasing registration errors due to sparser sampling and nearly linear dependency between sampling density and mean registration time (Fig. 6). Fassi et al. reported an average angular accuracy of 0.5° evaluated based on five human subjects. With an average registration error below 0.36° for tilting even with
TABLE I. Registration error for different tilting and torsion angles applied to enucleated pig eyes using a custom-made test bench (N = 12).

| Angle | 500 × 500 A-scans | 250 × 250 A-scans | 125 × 125 A-scans |
|-------|--------------------|--------------------|--------------------|
|       | Error (RMS) mean ± std (°) | Time mean ± std (ms) | Error (RMS) mean ± std (°) | Time mean ± std (ms) | Error (RMS) mean ± std (°) | Time mean ± std (ms) |
|       |                  |                    |                  |                    |                  |                    |
| Tilt  |                                                                 |                    |                  |                    |                  |                    |
| 1°    | 0.17 ± 0.10       | 85 ± 22            | 0.20 ± 0.13       | 46 ± 15            | 0.18 ± 0.11       | 16 ± 4             |
| 2°    | 0.23 ± 0.15       | 86 ± 24            | 0.29 ± 0.25       | 48 ± 15            | 0.22 ± 0.17       | 18 ± 4             |
| 3°    | 0.26 ± 0.19       | 86 ± 26            | 0.34 ± 0.23       | 49 ± 17            | 0.35 ± 0.28       | 19 ± 10            |
| 4°    | 0.28 ± 0.19       | 89 ± 28            | 0.35 ± 0.31       | 50 ± 18            | 0.42 ± 0.24       | 20 ± 8             |
| 5°    | 0.37 ± 0.24       | 88 ± 27            | 0.45 ± 0.34       | 51 ± 21            | 0.57 ± 0.31       | 22 ± 18            |
| Mean  | 0.26 ± 0.08       | 87 ± 0.7           | 0.33 ± 0.04       | 49 ± 0.7           | 0.35 ± 0.07       | 19 ± 1.0           |
| Torsion |                                                                 |                    |                  |                    |                  |                    |
| 1°    | 0.43 ± 0.10       | 90 ± 23            | 0.58 ± 0.27       | 52 ± 19            | 0.64 ± 0.34       | 23 ± 10            |
| 2°    | 0.48 ± 0.14       | 91 ± 22            | 0.74 ± 0.33       | 54 ± 20            | 0.69 ± 0.37       | 25 ± 10            |
| 3°    | 0.54 ± 0.21       | 94 ± 23            | 0.76 ± 0.36       | 55 ± 20            | 0.83 ± 0.48       | 25 ± 12            |
| 4°    | 0.57 ± 0.15       | 95 ± 25            | 0.79 ± 0.39       | 55 ± 22            | 0.88 ± 0.51       | 37 ± 12            |
| 5°    | 0.60 ± 0.26       | 98 ± 27            | 0.82 ± 0.48       | 57 ± 23            | 0.93 ± 0.56       | 29 ± 13            |
| Mean  | 0.52 ± 0.03       | 94 ± 1.4           | 0.74 ± 0.04       | 55 ± 0.8           | 0.79 ± 0.06       | 25 ± 2.9           |

4. DISCUSSION

We present a method for noninvasive referencing of intraocular tumors used in EBRT. A first prototype for LINAC based treatment, requiring a minimal amount of space, has been implemented and tested based on enucleated pig eyes. To the best of our knowledge, this work is the first that uses topography of the anterior eye acquired intraoperatively using OCT for tumor referencing. The proposed method overcomes limitations of 2D and 3D eye tracking systems currently employed in ocular radiotherapy and enables direct registration of a nonspherical and nonelliptical eye model (Fig. 7) with 6 DOF.

With an overall average registration error for pig eyes below 0.4° for tilting and below 0.8° for torsion, our method has proven to be significantly lower than the maximum eye rotation allowed during stereotactic radiotherapy of intraocular tumors, involving acceptable angular deviations of 5°.
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FIG. 8. Example for integration of the proposed tumor referencing system into a proton beam treatment setup.

Based on dosimetric issues, However, we did not validate the proposed system regarding translation since the mask system prevents from meaningful translation of the eye during treatment. Because even small translations cause an extensive change in the OCT signal, we expect tracking accuracy to lie in the micrometer range depending on axial and lateral resolution. To pursue proof-of-concept we used a commercially available OCT spectrometer system, which has shown to be suboptimal for anterior eye imaging due to an insufficient depth range and yielding unnecessary high acquisition time. Future work will, therefore, be focused on improving OCT hardware regarding wavelength, sensitivity, and A-scan rate in order to enable in vivo experiments. For example, a 1300 nm MHz-OCT system developed for anterior eye imaging as proposed by Wieser et al. with an A-scan rate of 1.6 MHz would allow for OCT image acquisition in 10 ms (125 × 125 A-scans). Furthermore, increased measurement (>6 mm) and scanning range (>23 mm) would enable for tumor referencing with optimized gazing angle in order to move the tumor to an optimal treatment position. Processing, segmentation, and registration times presented in this work are achieved with nonoptimized algorithms. In order to allow for in vivo experiments the proposed pipeline should be optimized regarding processing time and additional algorithms for the removal of motion artifacts should be implemented. Implementation of the pipeline on the graphics processing unit (GPU) as proposed by Kraus et al. should allow for tumor referencing at up to 20 Hz. Integration of the proposed referencing system into a proton beam treatment setup seems to be straightforward (Fig. 8). Since only frontals beams are applied, scanning unit and focus lens can be directly attached to the proton tube in order to reference the tumor with respect to the proton beam.

5. CONCLUSIONS

In conclusion, the tumor referencing method presented in combination with the statistical eye model introduced in the past has the potential to enable noninvasive treatment and may improve quality, efficacy, and flexibility of external beam radiotherapy of intraocular tumors. Optical design of the proposed prototype needs to be improved in order to allow for in vivo tests.
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