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Experimentally Observed Cherenkov Light Generation in the Eye During Radiotherapy

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Abstract

Purpose: Humans have reported sensations of seeing light flashes during radiotherapy, even with their eyes closed. These observations have been attributed to either direct excitation of retinal pigments or generation of Cherenkov light inside the eye. Both *in vivo* human and *ex vivo* animal eye imaging was utilized to confirm light intensity and spectra to determine its origin and overall observability.

Methods & Materials: A time-gated and intensified camera was used to capture light exiting the eye of a stereotactic radiosurgery patient in real-time, thereby verifying the detectability of light through the pupil. These data were compared with follow-up mechanistic imaging of *ex vivo* animal eyes with thin radiation beams to evaluate emission spectra and signal intensity variation with anatomical depth. Angular dependency of light emission from the eye was also measured.

Results: Patient imaging showed that light generation in the eye during radiotherapy can be captured with a signal-to-noise ratio of 68. Irradiation of *ex vivo* eye samples confirmed that the spectrum matched that of Cherenkov emission and signal intensity was largely homogeneous throughout the entire eye, from the cornea to the retina, with a slight maximum near 10 mm depth. Observation of the signal external to the eye was possible through the pupil from 0° – 90°, with a detected emission near 2,500 photons per millisecond (during peak emission of the ON cycle of

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COI Statement:

M. Jermyn is an employee and B. Pogue is a president of DoseOptics LLC. B. Pogue also personal fees from DoseOptics, LLC, outside the submitted work. P. Bruza has a patent PCT/US19/19135 pending and is the principal investigator in SBIR subaward B02463 (prime award NCI R44CA199681, DoseOptics LLC). D. Gladstone has patent US10201718B2 issued.

the pulsed delivery), which is over two order of magnitude higher than the visible detection threshold.

Conclusions: By quantifying the spectra and magnitude of the signal, we now have direct experimental observations that Cherenkov light is generated in the eye during radiotherapy and can contribute to perceived light flashes. Furthermore, this technique can be used to further study and measure phosphenes in the radiotherapy clinic.

Introduction

Phosphenes are visual light phenomena experienced when there is no apparent light stimulating the eye, and they can be induced by mechanical (direct pressure to the eye), electronic (electrode stimulation of the brain) and magnetic (transcranial) stimulation.¹⁻⁴ X-rays can also induce phosphenes, which became historically notable when Apollo astronauts reported “light flashes” during translunar flight.⁵ Theoretical modeling and testing on human volunteers in the 1970s suggested these light sensations were likely a result of direct activation of retinal photoreceptors or visual pathway neurons by ionizing radiation.⁶ Some reports also suggested that radiation-induced free radicals near retinal photoreceptors can cause lipid peroxidation and chemiluminescence leading to the creation of bioluminescent photons.⁷ However, an alternative hypothesis that the phosphenes resulted from direct Cherenkov light production in the vitreous humor or retina of the eye has also been suggested.⁸ Detailed reviews of the mechanisms underlying radiotherapy-induced phosphenes have been reported.⁹⁻¹¹ Specifically, it has been stated that Cherenkov light generation in the eye is the dominant mechanism responsible for perceived phosphenes during electron and photon radiotherapy.^{9,12,13} Despite this diversity of possible causes, there has been little direct mechanistic measurement of this phenomenon.

Cherenkov light is generated when a charged particle travels through a dielectric (charged) medium and its phase velocity exceeds that of light – a “photonic boom” of light is created. Examples of this phenomenon can be observed when fission products decay in water pools of nuclear reactors or when high-energy cosmic rays interact with Earth’s atmosphere.^{14,15} Quantitative models have shown that Cherenkov light can also be generated within the human eye when ionizing radiation transects the vitreous humor; the retina acts a light sensor, and the brain is able to, in turn, perceive Cherenkov emission created inside the eye.¹³ Astronauts in space, as well as cancer patients undergoing radiotherapy, have reported seeing blue flashes of light when encountering high-energy radiation.¹⁶

The study completed here provides the first direct evidence that perceived X-ray induced phosphenes result, at least in part, from production of Cherenkov light emission. Using a time-gated and intensified video camera, we detected Cherenkov light emissions coinciding with the delivery of external beam photon therapy through the eye, while the patient simultaneously noted seeing visual light phenomena. Furthermore, the magnitude and spectral profile of light emission observed from *ex vivo* animal eyes were measured, when the beam was localized to specific anatomical depths. The data and methodology described in this study provide a direct means of exploring the phenomenon of radiation-induced

phosphene production and is especially useful for observing this phenomenon within the setting of stereotactic radiosurgery and, more generally, brain radiotherapy.

Materials and Methods

A Varian TrueBeam (Varian Medical Systems, Palo Alto, CA) linear accelerator was used for irradiation of animal samples and patients. A C-Dose intensified complementary metal-oxide semiconductor (CMOS) camera was used (DoseOptics, Lebanon, NH) to obtain images of light emission. In order to enhance detection of Cherenkov signal while simultaneously suppressing ambient light, image acquisition was time-gated to linear accelerator pulses. The camera was triggered wirelessly using a remote triggering unit.¹⁷ All images were online background subtracted, spatial (5 x 5-pixel window size) and temporal median (5-image window size) filtered, as well as darkfield and flatfield corrected; all imaging sessions were conducted with room lights turned on. Specifications of the image processing workflow and triggering mechanism have been previously described.^{18–22} Image data was transmitted via fiber optic cable from the camera to a computer outside of the linear accelerator vault for image processing.²⁰ Output of the camera (1600 x 1200 pixel intensity maps, .raw format) was processed for real-time display using CDose software (DoseOptics, Lebanon, NH); additionally, MATLAB (MathWorks, Natick, MA) was used for image analysis and processing. Animal tissues used during *ex vivo* experiments were procured through a commercial vendor and human imaging studies were approved by the Dartmouth-Hitchcock Medical Center Internal Review Board – patient informed consent was obtained.

1. Animal Eye Experiments

Whole porcine eyes were harvested the same day of imaging; samples were kept fresh (not frozen) on ice during transport (Sierra Medical Inc., Whittier, CA). Samples were surgically cleaned to remove attached fat, connective tissue, and muscle remaining post-enucleation. Eyes were placed at isocenter of the linear accelerator treatment couch and irradiated with the gantry at 180° (top-down direction).

1.1) Light Emission Spectra & Signal Strength—The eye was positioned on a custom (poly-lactic acid, coated with black matte paint), 3D-printed stand (Entropic Industries, Endwell, NY). The sample was irradiated at repeated intervals using a 1 mm x 50 mm (width x length) 6-MV planar radiation “sheet”, generated using multi-leaf collimators with jaws completely open, from the top-down. Initially, the isocenter of this planar radiation field was placed at the center of the eye, and then the plane of irradiation was shifted incrementally anteriorly and posteriorly along the axis of the porcine eye sample with a step size of 0.3 mm (total of 100 steps resulting in a 30 mm scan length).

A PiMax3 (Princeton Instruments, Acton, MA) was coupled to a SpectraPro 2300i spectrograph (Acton Research Corporation, Princeton Instruments, Acton, MA) to obtain spectral profiles of light emission from eye samples. The spectrometer was calibrated to account for intensity and spectral detection sensitivity following previously described methods.²³ An exposure time of 10 ms was utilized to obtain 20 frames with a gain of 100x. A 1,300 mm fiber composed of 19 x 299 µm diameter fibers (CeramOptek, Bonn, Germany) was placed 10 mm from the front face of the eye. Figure 1A provides an illustration of the

experimental setup. A grating density and blaze of 150 g/mm and 500 nm were used, respectively. Background and native signals were collected by recording data with the radiation beam turned off and irradiating only the fiber, respectively. These spectra were subtracted from the data and a Savitzky-Golay filter was then employed to produce the final data set.

An identical radiation technique was used during spectral profile investigations to determine magnitude of light emission as a function of depth of irradiation inside the eye. The camera was placed 1.5 m away on a wheeled tripod, its height was adjusted so that the eye was centered in the field of view. As the eye was irradiated, 1000 image frames were captured using 10 frames per second (fps) with a Rokinon 135-mm f/2.0 ED UMC (Elite Brands Inc., New York, NY) lens. In the resulting images, a circular 10 mm diameter ROI in the area of the lens was selected for analysis, and the mean pixel intensity was computed per frame. The resulting curve was smoothed using a moving average filter.

1.2) Angular Dependency—The angular dependency of Cherenkov emission from the eye was explored. Porcine eye samples were placed in the center of a square (50 mm x 50 mm) 6 MV beam and irradiated at isocenter. The eye and camera were setup in the same geometry as the light emission signal strength experiment described above in *1.1) Light Emission Spectra & Signal Strength*. The angle between the sample and the camera was changed from 0° – 90° by shifting the camera incrementally, with images (200 frames at 10 fps per angle) captured every 10°. Throughout the experiment, the eye remained stationary and was irradiated with 100 MU at each angle.

2. Patient Imaging

A patient undergoing stereotactic radiosurgery for a recurrent meningioma adjacent to the orbit underwent imaging during treatment. Following simulation and treatment planning, the patient was positioned on the linear accelerator couch, the head was immobilized using a stereotactic surgical head frame (Varian Medical Systems, Palo Alto, CA), and the target volume was treated to a total dose of 18.0 Gy utilizing flattening-filter-free 10 MV photons delivered with intensity-modulated, image-guided stereotactic radiosurgery.²⁴ A pair of ceiling-mounted C-Dose cameras (DoseOptics LLC, Lebanon NH) identical to those utilized during animal experiments imaged the patient during actual treatment. The cameras were located 2,500 mm from the linear accelerator isocenter, and light emission was captured in real-time simultaneously at 14 fps using both cameras coupled to a Nikon 50-mm f/2.8 AF lens (Nikon Inc., Tokyo, Japan). Figure 1B provides an illustration of the patient imaging setup. Only Cherenkov intensity maps from the camera located on the left side of the patient were used for data analysis, because the gantry obstructed the right-sided view of the patient during a large portion of the radiation treatment. Immediately following the treatment, the patient was interviewed regarding perceptual epiphenomena. Plans for Cherenkov imaging had no impact on the radiation treatment planning and, specifically, irradiation of the eye was not the primary objective of the treatment – this occurred independently in the course of plan optimization to irradiate the targeted tumor and maximally spare neighboring normal tissues.

Results

1. Animal Eye Experiments

1.1) Light Emission Spectra & Signal Strength—Figure 2 (upper panel) shows that strength of emission was 5x greater with irradiation of the entire eye compared to treatment with a radiation sheet placed at depth 5 – 10 mm. Upon normalizing the results from Figure 2A, the spectral profiles become clearer. The spectra of light emission from the eye remained mostly unchanged as the sheet was scanned across the entire depth of the eye. However, the pattern of Cherenkov emission was no longer present upon irradiation, posterior the eye, in the region of the optic nerve. In the range of 550 – 700 nm, the spectra resembled that of Cherenkov emission previously observed in 1% v/v Intralipid (measured and Monte Carlo simulated), a tissue-mimicking head phantom, and 1% v/v solution of Intralipid + 1% v/v whole porcine blood, Figure 2B.^{25–27} All spectra presented in Figure 2B were found to be on average $25 \pm 20\%$ similar – similarity was computed by calculating approximate integral using via the trapezoidal method.

Considering a 3D coordinate axis where the X-Y plane corresponds to the front face of the eye and Z relates to depth into the eye, one can see how light emission varies as the radiation sheet is scanned across the X-Y plane along the Z-axis. Video 1 shows light emission from the eye as it is irradiated with radiation sheets from various directions and gantry angles. A plot of mean pixel intensity within an ROI in the lens versus depth of the radiation sheet scan is shown in Figure 3. Maximum signal intensity was detected when the radiation sheet was placed 9.8 – 10.1 mm deep into the eye (from the front of the eye). Irradiation outside the eye, from both in front of the lens and behind the eye in the region of the optic nerve, yielded a signal strength of < 10% of the maximum intensity.

1.2) Angular Dependency—As the observation angle of the camera was changed, and the position of the eye and incoming square radiation beam were kept constant, it was found that the average pixel intensity inside the ROI of the lens decreased by 40%. Maximum signal intensity in the ROI decreased by 10% over the range of angles tested. Furthermore, these images show a depth-dose effect within the volume of the eye, explaining the distribution of pixel intensity seen in Figure 4. Raw pixel intensity values were calibrated to average photon radiance (32 counts = 1 photon) using a 635 nm laser source and S120C Standard Photodiode Power Sensor (Thorlabs, Newton, NJ) following previously described methodology.²⁸ For the ROI utilized in the 0° image within Figure 4, 1.62×10^8 summed counts were detected translating to 8.13×10^6 summed counts per frame. At 10 fps, the total number of photons leaving the eye was thereby measured to be 8.13×10^3 photons per 0.001 seconds during peak emission of the ON cycle of the pulsed delivery.

2. Patient Imaging

A visualization of the planned cumulative dose volume (shown in color) was overlaid on the CT scans (shown in grayscale) of the patient. A sample slice of this rendering (depth of 112.5 mm from the top of the head) is shown in Figure 5D. One can clearly see that the beam path directly transects the left eye and vitreous humor.

Immediately post-treatment, the patient was interviewed and reported visual sensations similar to those described in the literature.⁹ She stated that bright blue flashes were noticeable in one eye (the left eye, corresponding to the treatment's lateralization) and were persistent regardless of whether her eyelids were opened or closed. The patient stated that these flashes, perceived as "blue, streaks, sparks, and pinpoints" were only noticeable during certain portions of the treatment. The time points corresponding to moments when the radiation beam transected the eye were isolated from the image stack. Video 2 shows real-time, cumulative and planned contours from this particular range of time points. Cumulative images obtained for this time segment of the treatment are shown in Figure 5A–C. Cherenkov emission from the eye is distinct, the signal-to-noise in the region of light emission from the left lens and temple were found to be 68 and 55, respectively – mean pixel intensities of the ROIs were compared to standard deviation of the background signal.²⁹ Following a calculation method similar to that described in *1.2) Angular Dependency*, it was found that the sum of photons exiting the ROI of the lens was 2.5×10^3 photons per 0.001 seconds during peak emission of the ON cycle of the pulsed delivery.

Discussion

By utilizing an intensified camera synchronized to pulses of a linear accelerator, we have been able to capture light emission from the eyes of a human and porcine animal samples. We have measured the emission spectra as a function of depth in the eye – the signal is only present when the vitreous fluid is irradiated and resembles that of Cherenkov light; the spectrum in Figure 2A matches the known λ^{-2} dependence for Cherenkov light and is present until the beam is behind the retina. The excessively noisy and unreliable signal in the range of 20 – 25 mm of scan depth, corresponding to irradiation outside of the volume of the eye, further confirms this observation. Differences in the spectra of light exiting the eye, compared to previously published Cherenkov emission from phantoms (Figure 2B), can be mostly attributed to variances in tissue optical properties i.e. light spectra are highly influenced by tissue-specific properties such as scattering and absorbance coefficients.³⁰ We have observed that Cherenkov light is produced nearly homogeneously throughout the vitreous humor (Figure 3) and is isotopically emitted from the pupil (Figure 4). This data is direct evidence that Cherenkov light emission is at least in part a contributing factor in the process of light generation in the eye during radiotherapy. However, while theories regarding direct nerve stimulation, scintillation of the lens, and ultra-weak bioluminescent photons cannot be ruled out, it seems clear that Cherenkov light production throughout the eye is quantifiable and significant. The alternate phenomenon can also contribute to the sensation of seeing light flashes, but are less quantifiable via external measurement.^{4,9,31}

Our ability to capture Cherenkov emission from the eye was enabled by the fact that, as light exits the eye, it is focused through the lens, lending itself well to imaging. Porcine eye samples were strategically chosen since the composition and mechanical properties of porcine vitreous humor resembles that of human eyes.^{32,33} In turn, data relating optical spectra and signal strength are translatable to human eyes. During sheet scans, we note that weak light signal was detected from the lens during periods of time when the radiation sheet was located outside of the eye. This can potentially be attributed to scattered radiation entering the eye and causing Cherenkov light production in the vitreous humor.

Potential applications of Cherenkov imaging in the radiotherapy clinic have been previously described.^{19,34,35} For example, this type of imaging allows verification of radiation field geometry, potential detection of motion-induced errors during treatment, and even measurement of surface dose.^{20,28,36,37} Since monitoring dose to the eye is important (the threshold for radiation-induced damage – which can be significant e.g. cataract formation – is quite low), this technology may potentially be of important clinical utility, enabling verification of treatment dose to or around the eye.³⁸ Thus, there exists the possibility for monitoring field geometry in real-time and potentially identifying cases when direct or excessive scatter radiation strikes the eye.

Previous review studies have indicated that patient perception of Cherenkov light can be enhanced when ambient lighting conditions are dim; furthermore, these visual phenomena can be substantially suppressed if the patient is staring directly into a bright light.^{13,39} The patient presented in this study was treated with only scone lights illuminated in the linear accelerator vault. Similar to our patient, other radiotherapy patients have often reported that light flashes are blue in color, spark-like in nature, and move across their range of vision.¹¹ This again supports the idea that Cherenkov light propagation in the wavelength range of blue-green colors is contributing to the visual perception of light flashes.^{9,12} Using a model of light production in the eye during radiotherapy, it has been shown that 2.08×10^4 Cherenkov photons are generated in 0.001 seconds during 6MV irradiation.¹³ Differences in experimental results (8.13×10^3 and 2.5×10^3 in 0.001 seconds for *ex vivo* animal and *in vivo* human data, respectively) versus these model calculations can be attributed to experimental setup-specific characteristics such as the light collection efficiency of the imaging system and solid angle diversion of light exiting the eye. Nonetheless, both theoretical and measured data show that the threshold for visual perception is exceeded by Cherenkov light generation in the eye during radiotherapy – the human eye requires 5 – 14 photons exciting the retina in 0.001 seconds in completed dark conditions to illicit a visual sensation.⁴⁰

Clinically, patient visual prognosis depends on the dose delivered to the key anatomic structures responsible for vision. At a minimum, the presence of phosphene perception by the patient, or measured Cherenkov light, may confirm that the ocular structures are receiving radiation. However, it is still unknown whether this correlates with, or provides any additional information about, visual loss independently from calculated dose. Further work to correlate recorded ocular Cherenkov light and delivered dose to long-term visual outcome may be relevant, as previous studies have shown that lack of phosphene perception predicts vision loss after therapeutic irradiation.⁹ Quantification of radiation dose may be a useful application of this technology as well. Another clinical point is that a valid explanation of the phosphene mechanism can be provided to the patient which may relieve anxiety during treatment.

Conclusions

We have shown that when ionizing radiation is incident upon the eye, the light produced appears dominated by Cherenkov emission, as identified by the spectrum, and an emission that is readily detectable through the pupil. When a thin beam was used to image emission

from an *ex vivo* eyes, the maximum light emission was detected at approximately 10 mm of depth, but there was similar Cherenkov-like spectrum and intensity observed from the cornea through to the retina. Observed light from the pupil decreases if no vitreous fluid is irradiated. Quantitative tracking of irradiation to the eye appears possible from a range of angles, using time-synchronized imaging of the emission. This technique for studying and tracking the phenomenon of light generation in the eye works during standard stereotactic radiotherapy, in real-time, and without disrupting clinical workflow

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1:

A) Experimental setup for light emission spectra measurement. An enucleated pig eye was placed on a custom 3D stand (grey step box) and a sheet of radiation (6 MV photons), 1 mm width x 50 mm length (light grey square), was scanned along the length of the sample. For spectral analysis, an optical probe was placed directly 10 mm from the front face of the eye. For emission imaging, a C-Dose camera was placed on a tripod 1500 mm away from the front of the eye. Ruler dimensions (cm) are drawn to scale. B) Illustration showing the imaging setup inside the linear accelerator treatment vault. The patient was secured to the couch using an SRS immobilizing frame. Two cameras were mounted on the ceiling along the side (near the foot) of the treatment couch on both the left and right side of the patient.

Figure 2:

A) Plots of emission spectra of light exiting porcine eye sample. Full eye corresponds to square radiation beam encompassing the entire eye. Depth values represent thickness of eye being irradiated; front of eye is equivalent to a depth of 0 mm. Bottom row is a normalization of the top row of data. Data is shown as counts and normalized counts vs. wavelength, respectively. B) Emission spectra from irradiation of the full eye, 1% v/v Intralipid (measured and Monte Carlo simulated), a tissue-mimicking head phantom, and 1% v/v Intralipid + 1% v/v whole porcine blood are shown.²⁵⁻²⁷ Spectra were normalized to emission at 550 nm and presented in the range of 550 – 700 nm.

Figure 3:
Plot of normalized mean intensity in ROI of the lens vs. depth of the radiation sheet scan (depth in z-axis).

Figure 4:
Angular dependency of Cherenkov light emission from a porcine eye. Number in the top-right corner of each panel represents camera-eye angle.

Figure 5:

A – C) Cumulative images of Cherenkov emission obtained over time during patient treatment. D) Sample slice (depth = 112.5 mm from top of head) of 3D planned cumulative dose volume displayed on CT scan. Dose is shown in color while CT image is in grayscale.