The Development, Characterization, and Clinical Investigation of a Novel Reusable Radiochromic Sheet for 2D Dose Measurement

by

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Graduate Program in Medical Physics
Duke University

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Graduate Program in Medical Physics
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ABSTRACT

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Abstract

Purpose: Radiochromic film remains a useful and versatile clinical dosimetry tool. While simple to use, current film options are single use, with no forms of reusable film available commercially. Here we introduce a novel 2D radiochromic sheet, derived from Presage material, which optically clears after irradiation and can be reused. We evaluate the sheets for potential as an economic alternative to radiochromic film and also as a radiochromic bolus with capability for dose measurement.

Methods: A novel derivative of reusable Presage® was manufactured into thin sheets of 5mm thickness. The sheets contained 2% cumin-leucomalachitegreen-diethylamine (LMG-DEA) and plasticizer (up to 25% by weight). A series of radiation experiments were performed to characterize the radiation response of the sheets irradiated with megavoltage radiation from a Varian medical accelerator over time and in different settings. The local change in optical-density (OD), before and after radiation, was obtained by scanning the sheets with a flat-bed film scanner and extracting the red channel of the RGB image. Repeat sheet scanning enabled investigation of the temporal decay of OD. Additional studies investigated dose sensitivity, consistency of response through repeat irradiations, intra and inter-sheet reproducibility, multi-modality response (electrons and photons), and temperature sensitivity (temperature range 22°C to 36°C) of the Presage® sheets. Clinical utility of the

sheets was investigated through application to IMRT treatment plans (prostate and a TG119 commissioning plan), and a chest wall electron boost treatment. In the latter test, the sheet performed as a radiochromic bolus.

Results: The radiation induced OD change in the sheets was found to be proportional to dose and to decay to baseline after ~24 hours with a decay constant of 6.0 $hours^{-1}$ (standard deviation 0.33). After this time the sheet could be reused and had similar sensitivity (within 1% after the first irradiation) for at least 8 irradiations. Importantly, the sheets were not observed to carry any memory of previous irradiations within measurement uncertainty. The consistency of dose response from photons (6MV and 15MV) and electrons (6-20MeV) was found to be within 1%. The dose sensitivity of the sheets was observed to have a temperature dependence of 0.0012 ΔOD/°C. For the IMRT QA verification test, good agreement was observed between the Presage sheet and EBT film (gamma pass rate of 97% at 3% 3mm and 99% at 5% 3mm dose-difference and distance-to-agreement tolerance, with a 10% threshold). For the TG-119 tests the gamma agreement was 93% pass rate at 5% 3mm, 10% threshold, when compared with Eclipse. For the electron cutout treatment, both Presage and EBT agreed well (within 2% RMS difference) but differed from the Eclipse treatment plan (~7% RMS difference) indicating some limitations to the Eclipse modeling in this case.

Conclusion: The reusable Presage sheets show promise as an economic alternative for film applications and as a radiochromic bolus for in-vivo dose measurement. The preliminary work presented in this thesis indicates that these sheets have the capability to improve care in the most well-equipped clinics in the world, as well as provide a fast, inexpensive, and easy to use dosimeter to clinics in low-income countries in desperate need of versatile resources. This work is still a preliminary study of feasibility, where the central current limitations include the narrow nature of application testing and lack of inter-batch comparison. Further work is recommended to establish use in a wide variety of clinical applications, establish a material more closely reflecting flexible bolus, and push the extent of the potential for reusability in the sheets.

Dedication

To my family: Mom, Dad, Phoebe, Kelsey, and the Fagans. Thank you for the unwavering support, thanksgivings in Virginia, and visits to Durham. I would not be here today without your love and guidance.

To my classmates, friends, mentors, committee members, lab-mates, Dr. Oldham, and DMBB: Thank you for your support, your encouragement, and your many hours helping me to conquer graduate school and enjoy my time at Duke. Go Blue Devils!

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I have so many wonderful, dedicated mentors to thank. Thank you for your support, for opening the door for me to share my work at various conferences, for giving me exciting research ideas, developing my academic skillset, and for all of the many opportunities that you provided me. Thank you to everyone for your contributions to my project and for helping me to put together a body of work that I am passionate about and very proud of.

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1. Introduction

Radiation sensitive films (both radiographic and radiochromic) are well established multi-purpose dosimetry and quality assurance tools in radiation therapy [1-3]. Although some traditional applications of film have been replaced by electronic-portal-dosimetry (EPID) technology [4], film maintains important clinical utility in applications such as composite dosimetry in the commissioning of new treatment techniques and end-to-end treatment verification [5,6]. In modern clinics, most film applications utilize Gafchromic (radiochromic) film because of the reduced energy sensitivity, and the lack of need for expensive processing equipment with associated uncertainties. Radiochromic films can be conveniently read-out by flat-bed optical scanners [7].

Recent work by Dumas and Rakowski introduced a sheet form of single-use in-house manufactured Presage and evaluated it in the context of applications for radiosurgery QA [8]. The sheets were 1mm thick and compatible with readout by a flat-bed-scanner. Dumas and Rakowski conclude that the single use sheets can be an effective quality assurance tool for SRS and SBRT. In the present work, we introduce and evaluate a novel commercial sheet form of Presage (Heuris Inc.) with the important distinction of being amenable to repeat use (reusable sheets). The reusable Presage sheets were based on a customized commercial formulation of Presage, a radiochromic sensitive polyurethane material that has found wide-spread utility in 3D dosimetry applications [9-16]. The reusability arises from the reversibility of the active radiochromic dye molecule leucomalachyte-green (LMG). Reusability opens up the potential for significant cost savings and applicability to different economic conditions [17]. The potential for reusable Presage has been explored before, as recently as work by Park et al., who developed and studied a reusable 3D dosimeter with limited success. They were able to reuse the dosimeter twice, with signal consistency only within 5% [18]. Previously, Pierquet et al. also studied a potentially reusable 3D dosimeter and developed a model that could be reused up to four times, with signal that returns to baseline in 2-3 weeks, and a significant increase in change in OD signal from one irradiation to the next [19].

The Presage sheets in the current study may also have utility as a radiochromic bolus, with potential to provide useful dosimetric information in a number of in-vivo clinical settings including electron treatments (e.g. chest-wall irradiation, where the SSD varies substantially across the field) and photon treatments (e.g. head and neck) [20-23]. With the advent of new sophisticated electron treatment techniques, such as dynamic electron arc radiotherapy (DEAR), it is now possible to resolve the discrepancies between treatment plans and delivered distributions that can arise when treating a curved surface such as the chest wall [24]. With this new technology comes the need for appropriate verification methods, of which the reusable bolus sheet introduced in this work is a strong fit.

In the present work we characterize the Presage sheets for radiation response in different conditions and study the temporal decay of the radiation induced change in optical-density (OD). The clinical feasibility of the Presage sheets is investigated through application to IMRT treatment measurements and recording the dose delivered by an electron chest-wall irradiation. These applications represent a typical film application and the potential utility of a radiochromic bolus.

1.1 Impact

The impact of this body of work is two-fold. The results that will be presented suggest the potential to advance the quality of cancer care in the most advanced clinics around the world. At the same time, however, these sheets are uniquely suited to make an impact in the cancer clinics of low-income countries. Innovation takes the form of both advancements in performance and economic advantage.

In the advanced cancer clinics of the world, new modalities are necessitating new dosimetry tools. The flexibility of these sheets and their ability to conform to the patient surface better than a sheet of EBT film, paired with their high resolution, allows them to improve upon existing in-vivo measurement options. With the potential for thickness customization, they can function as a bolus of desired thickness, or simply a thin surface measurement sheet with limited attenuation. Like with EBT film, the resolution of these sheets is limited by the resolution capabilities of the scanner. Perhaps an improvement upon EBT film, the signal of this sheet is linearly proportional to dose (R^2 = 0.9988), so a non-linear calibration curve does not need to be applied in order to analyze dose distributions. While these are all promising capabilities, this is a new tool that will require further study and verification.

With the advent of novel electron therapy treatment modalities, appropriate verification methods through the traditionally unpredictable delivery of electrons is becoming increasingly critical to proper care. One example of this is the DEAR electron arc therapy treatment method, where it is now possible to navigate curved surfaces and areas of steep change in source-to-surface distance in an effort to reduce the discrepancies between treatment plans and delivered dose across the patient surface [24]. This new mode of treatment would work effectively with the innovation provided by the reusable Presage bolus, which could serve as a strong verification for an expanding technique. With this application of the sheets as a radiochromic bolus, and the strong potential for applicability as a high-resolution reusable radiochromic film, there is potential for advancements in care in cancer clinics with a diverse collection of advanced modalities and treatments performed.

In the greater world perspective, 60% of the global cancer population lives in low- and middle-income countries [17]. Cancer is an important and growing health concern in the lower-income regions of the world, as it kills more people in Africa than AIDS, Tuberculosis, and Malaria combined [25]. Five year survival statistics are a result of many factors, most notably early detection in advanced countries, but quality of care and available tools for dosimetry and quality assurance are contributors to the deficit between low-income country care and high-income country care. The 5-year survival rate for prostate cancer in Australia is 89%, compared with 46% in Uganda. For breast cancer, it is 89% in the USA, compared with 43% in Jordan. The rate for childhood leukemia is an astounding 92% in Germany, compared with 34% in Mongolia [17]. While there are cancer clinics in these low-income countries, they are incredibly resource-limited and do not have enough skilled professionals to use the complex tools that are the standard of care in the United States and other advanced countries. As a result, much of the disparity in care and treatment outcomes can be attributed to a lack of customized research being dedicated to developing the specific tools necessary to enable clinics in low-income countries to function at maximum capability. These clinics are desperate for dosimeters and tools with three distinct qualities: they must be inexpensive, fast, and easy to use [17].

With the low-cost and reusability of the presage sheets, they present an inexpensive alternative to a variety of different pieces of equipment. As a patient-specific quality assurance (QA) measurement device, they offer an alternative to technology like EPID Portal Dosimeters and MapCheck diode arrays, which are quite costly. As a film alternative, they represent a multi-use replacement for expensive, single-use EBT Gafchromic films. SuperFlab bolus itself is rather costly, for a simple tool, and it provides no form of dose tracking. One possible tool for sheet readout analysis is the implementation of the program ImageJ, which is free to use. However, ImageJ is not an FDA approved software, which invokes questions of legal responsibility for accuracy. In terms of speed, the reusable Presage sheets are ready for readout immediately after irradiation. No post-processing is required other than simple alignment in the scanner and readout. Finally, to consider the third pillar of low-income country needs, “easy to use”: because the sheets can be read-out with a flatbed scanner, training on new or complicated equipment in order to be able to use the sheets is unnecessary. Analysis with ImageJ is quite self-explanatory, and requires very limited training. As a result, the sheets are also easy to use, read-out, and analyze. For these reasons, the reusable Presage sheets are great candidates for use as a versatile do-it-all dosimeter in resource-limited low- and middle-income countries.

2. Methods

2.1 Presage Sheet Manufacturing and Handling

The reusable Presage sheets were manufactured by Heuris, Inc. (Skillman, NJ 08558). The formulation consisted of the active ingredient cumin-LMG-DEA (2% by weight) (figure 1), 1% halocarbon initiator, 3% dissolution solvent with dibutyl phthalate (25% by weight) and polyurethane (70% by weight). The leuco dye was synthesized using Baeyer condensation where one equivalence of cumin aldehyde is reacted with 2 equivalence N,N-dimethylaniline [26].

The sheets consist of a uniform active layer of Presage with no coatings or substrates. Vigorous mixing ensured the active leuco dye molecules were uniformly distributed throughout the sheet for uniformity of response. The bulk of the sheets investigated in this work were 5mm thick, with dimensions of 20x20 cm. The consistency of thickness of sheets was confirmed using an electronic caliper.

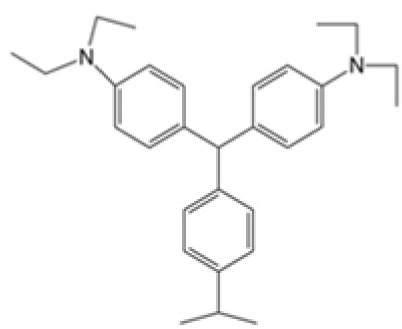


Figure 1: Structural formula of leuco dye cumin-LMG-DEA.

2.2 Presage Sheet Readout

Presage sheets were scanned on an Epson Expression 10000 XL flatbed scanner typically within 24 hours of a pre-irradiation (baseline scan) and within 10 minutes post-irradiation. Improved sheet readout was achieved by administering a small drop of clear mineral oil to the bed of the flat-bed scanner. Each sheet was gently pressed into this fluid to eliminate the potential for artifact-inducing air bubbles under the sheet. The sheet was scanned again typically 10 minutes post-irradiation (Section 3.2 below outlines experiments to determine an optimal scan-time window of opportunity to preserve accuracy). For both pre and post scans the scanning software was configured such that no image enhancement or color processing was applied. Scan resolution was RGB 48-bit color, with a spatial resolution of 0.51x0.51 mm, and a 5 mm median filter was applied to reduce noise. The red channel of the RBG image from the scanner was selected for image analysis, corresponding to the peak absorption wavelength of the LMG dye molecules. This is a similar process to that recommended in EBT film analysis [27]. After use, sheets were stored in a light-tight bag at room temperature.

2.3 Characterization of Presage Sheets

2.3.1 Linearity of Dose Response

To determine the way in which the sheets respond to increasing delivered dose in the clinical range of interest, one reusable Presage sheet was cut into six 6x6cm^2 sheets and pre-scanned for dose delivery. Using a 10x10cm^2 field, a different dose was delivered to each sheet, with doses including 1 Gy, 2 Gy, 4 Gy, 6 Gy, 10 Gy, and a 0 Gy control sheet scanned for readout with the others. The change in OD was calculated using the pre- and post-scans and an averaged ΔOD measurement from a $1cm^2$ region in the center of each sheet was collected and plotted against dose delivered. The linear relationship between points was computed along with the R^2 value.

2.3.2 Temporal Characteristics (Single Irradiation)

The temporal decay of the radiation induced optical-density change was evaluated by irradiating four sheets to different doses of 6, 4, 2, and 1 Gy with a Varian medical linear accelerator. Sheets were positioned in a solid water stack at a depth of maximum dose (e.g. 1.5cm depth for a 6 MV beam). The sheets were pre-scanned immediately before irradiation and then scanned every 10 minutes for the first hour post-irradiation and then every hour until 9 hours post irradiation. A final readout was taken at 26 hours post irradiation.

2.3.3 Reusability (Multiple Irradiations)

Two experiments were performed, the first referred to as the pyramid test and the second as the repeat irradiation test. In the pyramid test, a series of four concentric square fields of gradually increasing size were delivered, with a time interval of at least 24h between each of the fields. The starting field size was 4x4cm followed by field-sizes of 6x6, 8x8 and 10x10cm. Each field was delivered centered on the sheet with a dose of 4.5 Gy, such that the cumulative dose would be a pyramidal step function with 4 levels.

In the second repeat irradiation test, the same field was delivered to the same sheet each day. This time the field size was 30x30 cm to ensure the whole sheet was irradiated. One sheet was given a dose of 4 Gy each day, and a second sheet was given 2 Gy each day. The change in OD was quantified by averaging a 0.5 cm^2 region in the center of the uniform field.

2.3.4 Dose Sensitivity and Consistency

To investigate the consistency of dose response for different treatment modalities, separate sheets were irradiated to 4 Gy with 6 MV, 15 MV, 6 MeV, 9 MeV, 12 MeV, and 16 MeV beams from a Varian linac. Sheets were positioned for irradiation in a solid water stack at a depth of maximum dose as in prior irradiations. To examine the dose response consistency within the same batch of Presage sheets, five sheets were irradiated with a 6 MV beam to a dose of 4 Gy in the solid water stack.

2.3.5 Thermal Characteristics

The effect of temperature on the background OD of unirradiated sheets was investigated by submerging sheets in a water bath at 34°C (close to skin temperature) for 20 hours. OD readings were measured every hour for the first 4 hours of submersion and then once more after the full 20 hours. The water bath temperature was then raised to 40°C and an additional OD reading was taken 3 hours after submersion.

The effect of temperature on dose sensitivity at time of irradiation was investigated with 9 sheets that were heated to various temperatures in a water bath. A thermometer was placed in the water bath as it cooled so that an alarm would go off when the water reached a desired temperature. When the alarm signaled the desired temperature had been reached, the irradiation began. The temperature immediately after irradiation was also recorded, and the average was recorded as the irradiation temperature. Typically the temperature change was less than 0.5 degrees. Irradiation temperatures ranged from 22.1°C-35.7°C in one to two degree increments. This range outlined the clinically relevant temperature range from a cool room temperature to a few degrees above skin temperature. Ten minute post-irradiation readout scans were collected for each sheet. These images were converted to change in OD and analyzed to determine whether the optical density change with dose depends on sheet temperature at the time of irradiation.

2.4 Clinical Application

Two clinical applications of the sheets were evaluated: a radiochromic film and bolus.

2.4.1 Radiochromic Film Applications

The sheets were first tested as an alternative for film-based IMRT QA by delivering two different single IMRT treatment fields and then tested by delivering a complete 9 field IMRT treatment to a separate sheet. The first single field was a prostate plan delivered normally to both a Presage sheet and an EBT film placed on a 10 cm solid water stack, with 1.5 cm standard bolus on top of the sheet. The second single field had the same set-up but delivered a large-field pelvic plan to the Presage and EBT plan. This trial used a slightly modified formulation of reusable Presage with a different softener employed than in previous experiments. The dose distributions measured by the EBT film, the Presage sheet, and the treatment plan expected dose distribution were compared using gamma map comparisons at 3% 3mm dose-difference and distance-to-agreement tolerance and a 10% threshold.

The 9 field treatment was delivered to a Presage sheet standing vertically on the couch sandwiched between two 5 cm slabs of solid water, such that the sheet measured the axial plane of the delivered distribution. This treatment plan was created with an energy of 6 MV and 9 fields at 40° intervals from the vertical in a commissioned Eclipse treatment planning system for a representative "C Shape" IMRT commissioning test taken from TG-119[6] (figure 2). The test contained a contoured C-shaped PTV region 2.25 cm thick with a circular region (2 cm diameter) in the middle of the C-shape, representing a critical structure. The PTV and critical structure contours did not change in the z-direction longitudinally along the couch. A dose of 6 Gy was prescribed, reflecting an ultra-hypofractionated prostate treatment [28]. The dose distributions measured by the EBT film and the Presage sheet were compared using gamma map comparisons at 5% 3mm and 3% 3mm dose-difference and distance-to-agreement tolerance and a 10% threshold.

C-Shape Test Prompt (TG-119)

Structures

The target is a C-shape that surrounds a central avoidance structure. The center core is a cylinder 1 cm in radius. The gap between the core and the PTV is 0.5 cm, so the inner arc of the PTV is 1.5 cm in radius. The outer arc of the PTV is 3.7 cm in radius. The PTV is 8 cm long and the core is 10c m long.

Dose goals (easier version)

Structure		
CShape PTV	95% of volume to receive at least 5000 cGy	10% of volume to receive no more than 5500cGy
Core	5% of volume to receive no more than 2500 cGy	

Beam arrangement

6 MV, 9 fields at 40° intervals from the vertical

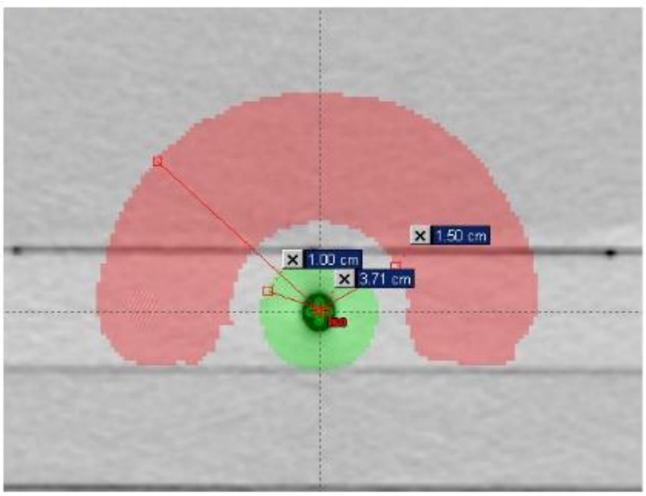


Figure 2: Prompt and illustration of TG-119's C-Shape test for IMRT commissioning using radiochromic film and a solid water phantom to test the capabilities of the IMRT delivery system.

2.4.2 Radiochromic Bolus Applications

The utility of Presage sheets as a radiochromic bolus was investigated for a 9 MeV electron chest wall scar irradiation on a torso phantom (figure 3A), utilizing a cone of 25x25cm with a long thin cut-out insert of ~20x4cm (figure 3B). The plan incorporated a 5 mm bolus, where the reusable Presage sheet acted as the bolus (figure 3C,D). The plan was administered twice, first in an idealized geometry (en-face to a flat sheet placed on top of a solid water phantom stack), and secondly to a more clinically realistic geometry where the sheet was taped to the surface of an anthropomorphic thorax phantom (figure 3E). The dose prescription was 10.79 Gy at a depth of 2.0 cm central to the field. The treatments were also delivered to EBT films and optically stimulated luminescence dosimeters (OSLs) for independent dose measurement and comparison. Area distributions and line profiles were taken for each of the four irradiations for comparison with Eclipse and independent dosimeter measurements.

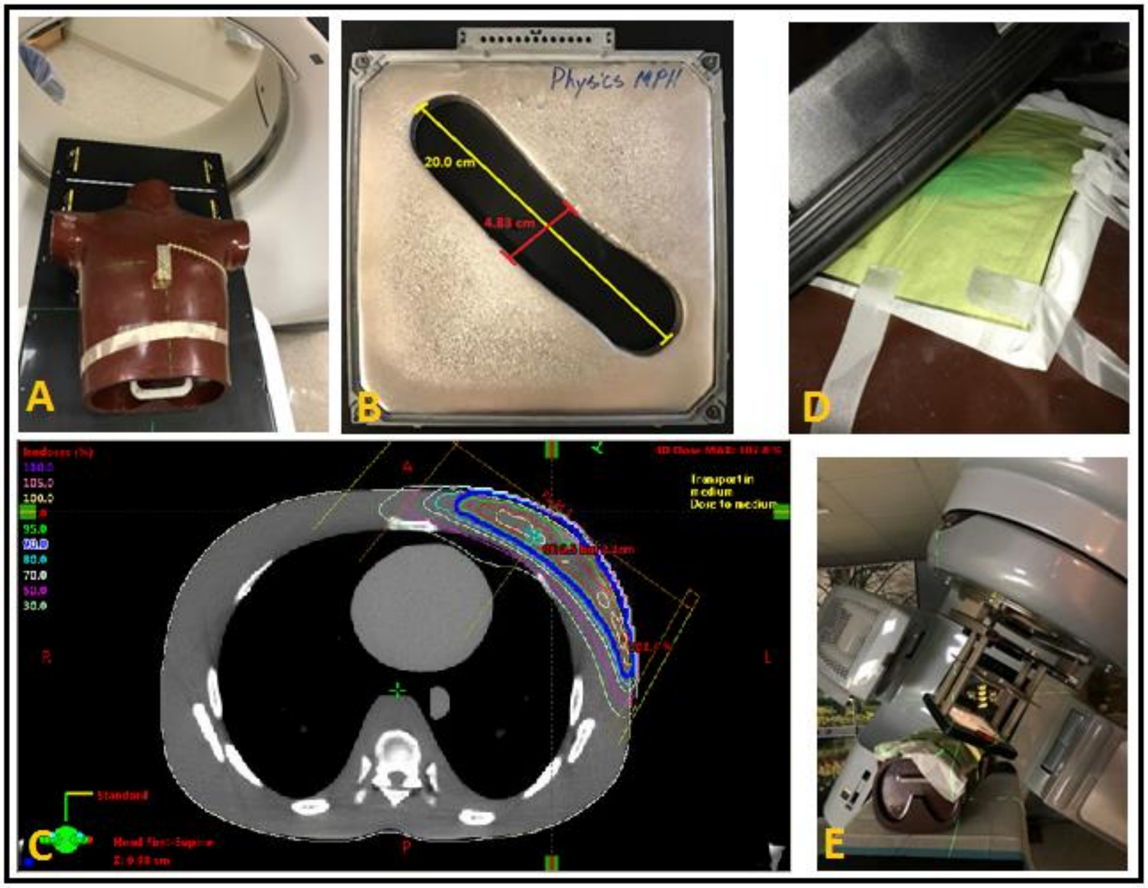


Figure 3: Set-up of reusable Presage bolus application experiment. (A) Torso phantom with applied chest wall scar was used as the test patient. (B) Electron cutout tracing the length of the scar was created for electron treatment. (C) Treatment plan, employing a 0.5 cm bolus and using the torso phantom CT scan was created. (D) The reusable presage sheet was used as the bolus prescribed in the treatment plan. (E) The phantom was set up and shifted just as a typical patient would be for treatment delivery.

3. Results and Discussion

3.1 Linearity of Dose Response

As part of the foundational study and characterization of these sheets, the sheets were found to have a linear response to dose. This is illustrated in figure 4, where the Presage calibration curve up to 10 Gy is compared with the EBT calibration curve up to 6 Gy and the non-linearity at higher doses in EBT is illustrated. The relationship between change in OD and dose in the Presage sheet was found to have an R^2 value of 0.9988. This was completed by delivering dose with a $10x10cm^2$ field.

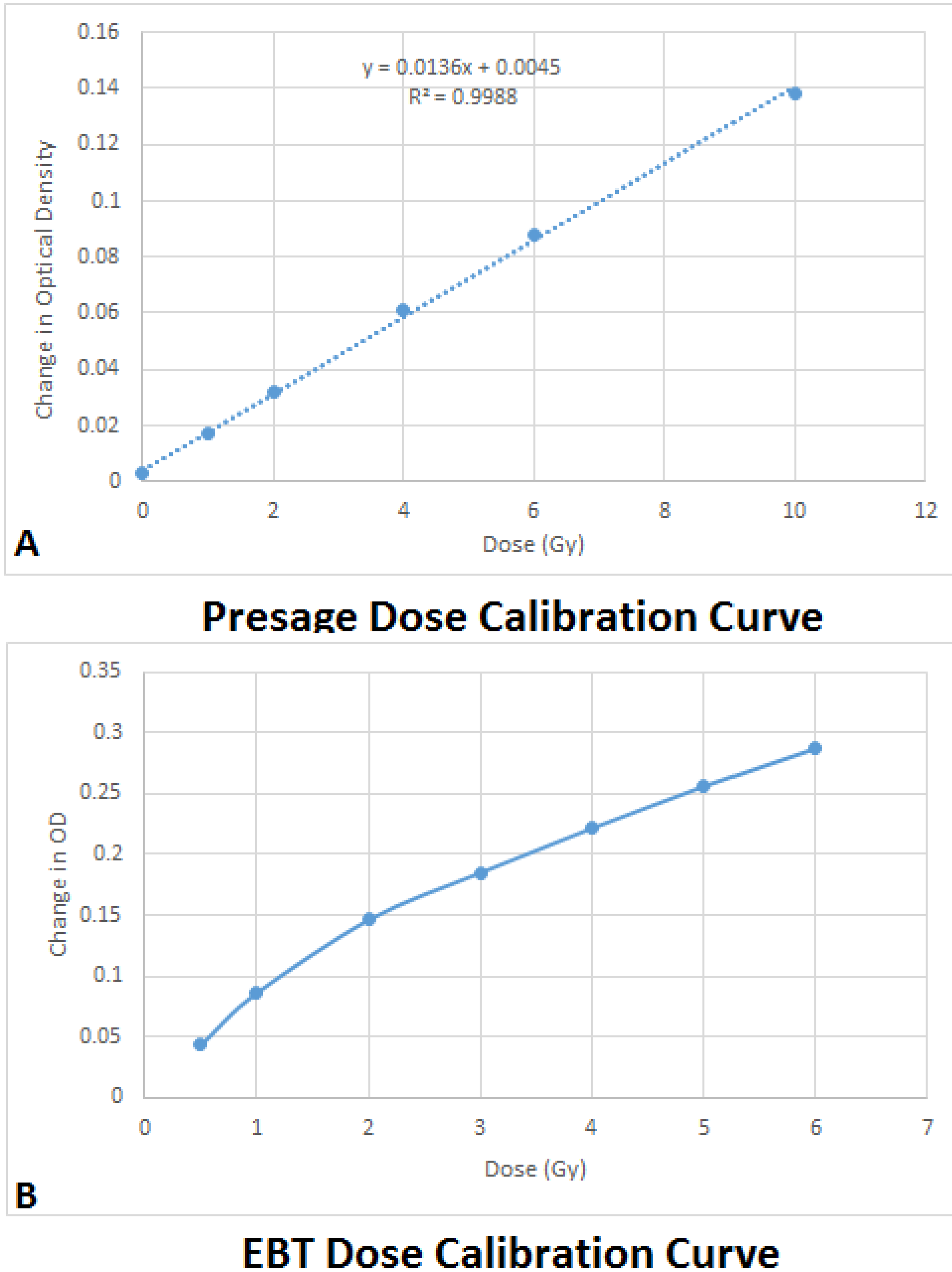
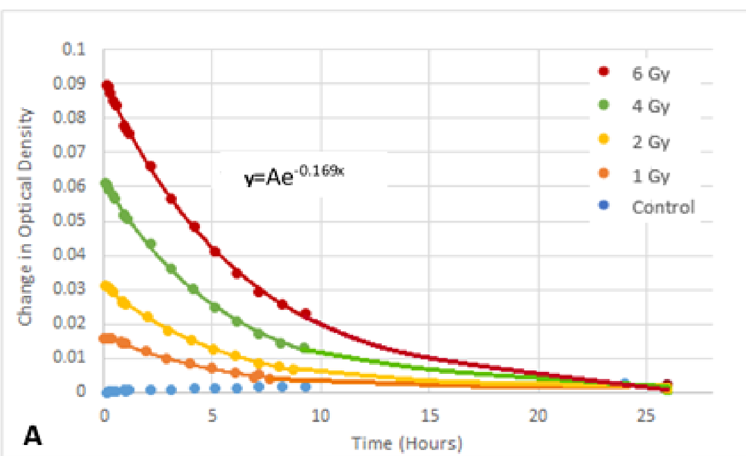


Figure 4: Comparison of relationship between dose and change in OD in both reusable Presage sheets (A) and Gafchromic EBT film (B). The linear relationship between dose and change in OD in the Presage sheet had an R^2 value of 0.9988.

3.2 Temporal Characteristics (Single Irradiation)

The temporal decay signal of irradiated Presage is shown in figure 5 for sheet irradiations to 6, 4, 2, and 1 Gy. The 26 hour readout scan demonstrates effectively cleared signal for all doses (less than 2% of signal remaining), showing that the signal has returned to the pre-irradiation starting point. The decay is well modeled by exponential decay (R^2=0.9986) and the mean temporal decay constant for the data is 6.0 hours^{-1}. The unirradiated control sheet showed a slight increase in change in OD after every few hours of scans, from a ΔOD of 0 to 0.002. This is due to the sheets' light sensitivity. For this experiment only, the films were scanned a total of 18 times in one day. It is suspected the scanner light causes a gradual color change in the sheets, highlighting the importance of storing the sheets in a light-tight bag.



B

Scan Time:	Signal Decay:
Within 5 mins:	1.4%
Within 10 mins:	2.8%
Within 15 mins:	4.0%
Within 20 mins:	5.5%

Figure 5: Temporal decay of single irradiated Presage signal in a 26 hour period. Five different sheets were irradiated to four doses. Decay is well modeled by exponential decay, R^2 = 0.9986. The formula for the decay is displayed in the image with A representing the amplitude of decay, which is dependent on the irradiation

dose. (B) is a table of maximum percent signal drop (loss of OD change due to clearing, proportional to dose) when sheets are scanned within a certain time window.

The data and mean temporal decay constant presented in figure 5 were used to characterize the sheet clearance rate (proportional to dose and relative to time t=0). So that the sheets can be used once each day, the sheet clearance rate is relatively high, meaning the knowledge of the time in which the sheets were scanned for readout is important for many applications. Given the decay constant of 6.0 hour-1, the signal decay within 5 minutes is 1.4%. This means a 5-minute variation in scanning time post-irradiation would result in 1.4% signal drop. In practice there are several methods for accounting for the fading sheet signal. First the drop may be corrected for by calibration, irradiating sheets to known doses and scanning at different and corresponding time intervals, interpolating if needed. Alternatively, if the sheets are used for relative dose measurement, because the dose decays at the same rate at all dose levels, the relative dose distribution is unaffected (except for increasing the noisy component with increasing time). The third, and perhaps most convenient approach for many situations, would be to include an independent measurement (e.g. TLD or OSL) to obtain a known dose at a point against which the relative distribution can then be scaled.

Additionally, if a measurement is taken, the absolute dose at the time of irradiation can be traced back using the exponential curve equation.

3.2 Reusability (Multiple Irradiations)

The pyramid style test was used to determine whether the Presage sheets were truly reusable and whether they carried any memory effects from prior irradiations. Figure 6 illustrates the irradiation pattern used to conduct the test and shows readout scan images recorded after each irradiation. At least 24 hours was allowed in between irradiations. Figure 7 shows the line profile results from this experiment. All profiles show a smooth straight line pattern across the irradiated section and each line reaches up to about the same change in OD value, with a coefficient of variation of 1.1%.

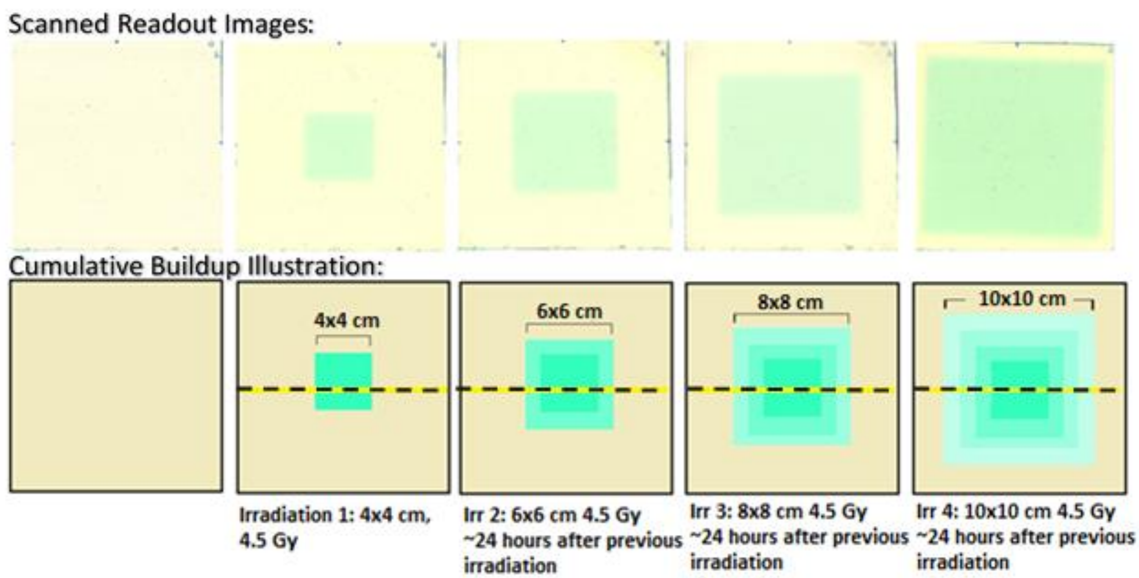


Figure 6: Pyramid reusability test setup illustrations and readout scan images from each subsequent irradiation. A minimum of 24 hours was allowed between each irradiation, and subsequent irradiations were conducted on the same sheet on top of previous irradiations. The top row of images are true post-irradiation readout scan images. The bottom row are illustrations diagramming the cumulative buildup of subsequent rounds of irradiations. A line profile, as depicted by the yellow and black lines above, was taken after each irradiation.

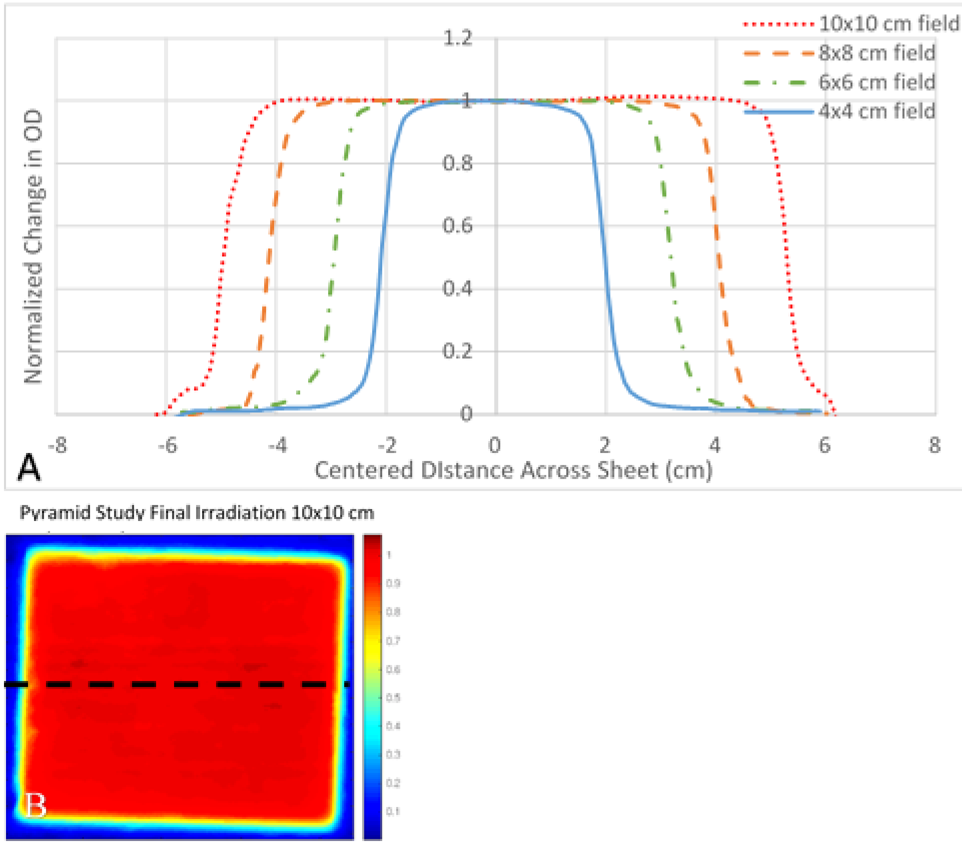


Figure 7: Pyramid reusability test. The plot presents line profiles through the center of the pyramid irradiation field shown in figure 6. Each irradiation delivered 4.5 Gy to the sheet. (B) is a color-map of the final pyramid irradiation dose distribution, line profile indicated in black dashed line.

In the pyramid test (figure 7), if there were to be a sheet memory, or residual effect, from previous irradiations, we would expect to see an inverted pyramid-type plot pattern where there is decreased OD sensitivity in the areas with a greater number of overlapping irradiations. Instead of exhibiting this trend, the plot shows consistent flat profiles no matter how many previous irradiations had taken place. In the line profiles where several previous irradiations occurred, such as the 10x10 line in red in figure 7, the line in the irradiated area is flat without variation in the regions where previous irradiations occurred. This indicates that the sheets exhibit reusability with negligible ghosting remnants from previous irradiations that could affect the composition of the new signal if present. Based on a comparison with ion chamber data, there was no ghosting observed to the level of 1%. The raised bump on the edge of the 10x10 cm field line profile is an edge distortion artifact as the profile moves through the roughly cut edge and off of the sheet. To further confirm the lack of memory between subsequent irradiations, a color-map was created for the final pyramid irradiation, the 10x10 cm field, to examine whether any sign of square-shaped previous dose could be identified in the readout scan. The color-map, normalized to maximum dose, is pictured in figure 7 where no sign of previous irradiations is visible.

To quantitatively study the reusability of the Presage, a separate sheet was irradiated to the same dose on 8 different days over a one month period. This procedure was completed for both a 4 Gy repeated irradiation on one sheet, and a 2 Gy repeated irradiation on another. In the 0.5 cm^2 region averaged to get a measured value for change in OD, all of the change in OD values on each sheet were consistent within 1%, after the first irradiation and readout. This suggests that a uniform sheet commissioning irradiation to warm-up the sheets and eliminate the first reading, which has been found to be consistently higher than the others, may be useful before the sheets are applied clinically. After the first irradiation, it is clear that the signal is the same from one irradiation to the next.

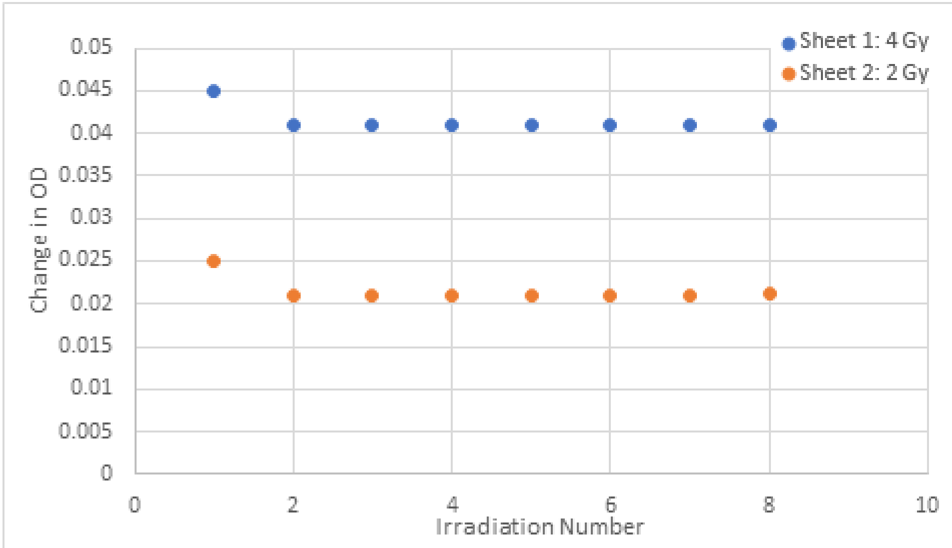


Figure 8: Consistency of signal upon repeated irradiation. The same reusable Presage sheets were irradiated with a 30x30cm field to 4 Gy on 8 different days (blue) and a different sheet to 2 Gy for the same duration (orange). Signal was read at 10 minutes post-irradiation.

3.4 Dose Sensitivity and Consistency

The dose sensitivity and consistency of signal in the reusable Presage was tested across various modalities and energies. The change in OD normalized to 1 Gy is quantified in table 1. Each change in OD per Gy value was consistent across different energies and modalities with a standard deviation of 8.09x10-5 and a coefficient of variation of 0.77%. This indicates that the sheets can be used across a variety of different energies, with both electrons and photons, and yield consistent results per applied dose.

Table 1: Multi-modality comparison. Sheets were irradiated to six different energies with both electrons and photons and the change in optical density per Gy of dose was recorded.

Energy	6MV	15 MV	6MeV	9 MeV	12 MeV	16 MeV
ΔOD/Gy	0.0105	0.0106	0.0105	0.0105	0.0105	0.0104
Mean:	0.0105	Std. Dev:	8.09E-05	COV (%):	0.770	

Intra-batch consistency is shown in table 2 where five sheets from the same batch were all irradiated to 4 Gy with the same set-up on the same day. The change in OD for the 5 sheets is recorded in table 2. The mean change in OD value was 0.0452, the standard deviation was 0.0003, the coefficient of variation was 0.7073%, and the greatest percentage difference between any two readings was 1.77%.

Table 2: Variation in change in OD response within one batch of sheets irradiated to 4 Gy in the same conditions.

Sheet #:	1	2	3	4	5
ΔOD:	0.0448	0.0456	0.0451	0.0455	0.0453
Mean:	0.0452	Std.Dev:	0.0003	COV (%):	0.7073

3.5 Thermal Characteristics

Unirradiated sheets were found to be insensitive to temperature change. After 20 hours of water bath submersion at 34°C and then 3 additional hours of submersion at 40°C, there was no significant change in OD from the room temperature pre-scans.

The effect of Presage temperature at the time of irradiation is shown in figure 9. The change in OD tended to increase with increasing sheet temperature at time of irradiation, with the equation for the line of best fit given in figure 9. This test is important for applications where the sheets will be used for absolute dosimetry. In these applications, differences in sheet temperature must be noted and measurements must be adjusted to account for these changes.

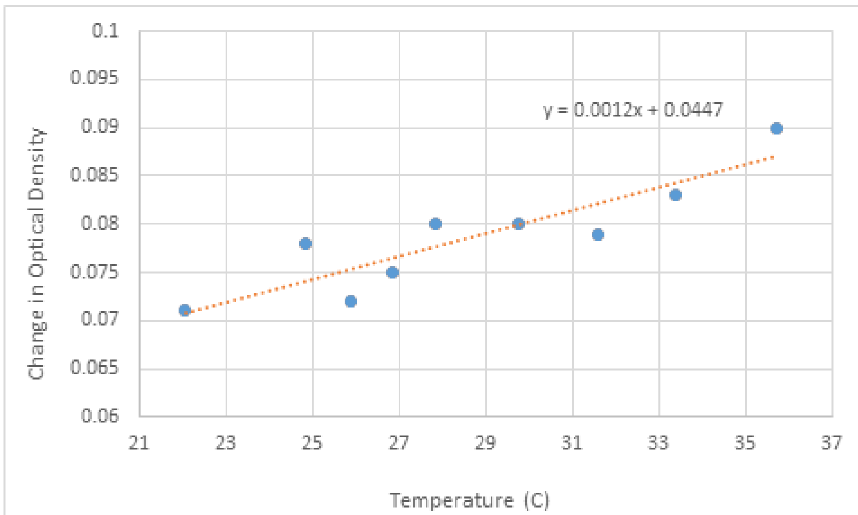


Figure 9: Reusable Presage optical density dependence on temperature at the time of irradiation. Temperatures from 22°C (cool room temperature) to 36°C (two degrees above typical skin temperature) were tested. The orange line represents the trend line for the change in OD measurements as sheet temperature varied.

Several points may be noted. First, in the broad skin temperature range (33-35°C), which is narrower than the full range of temperatures studied, the signal does not vary by more than +/- 3%. Additionally, the sheets were completely submerged in water, and the sheets were submerged at the relative temperature for 10-15 minutes before irradiation. In most clinical applications, it is unlikely that the entire sheet would be completely submerged on all sides in this way, and may not be fully equilibrated to the skin. If this test is to be compared to clinical applications where the reusable Presage is directly applied to the skin, the thermal environment may not have as strong of an effect on the sheets.

3.6 Characterization Summary

Throughout the discussion of sheet characterization, different applications (relative versus absolute dosimetry) and use in conjunction with other tools (OSLD and TLD) have been discussed. Table 3 details an analysis of the relative errors associated with sheet measurement as a result of the overall characterization analysis. This is broken down into use with absolute dosimetry, relative dosimetry, and absolute dosimetry in conjunction with OSLD spot measurements. Values represent an estimated typical to a practical worst case scenario range where sheet temperature is raised by 2°C above room temperature and temperature range within and across the sheet varies by 2°C in the worst case scenario.

Table 3: Table of estimated uncertainty associated with each characterization test. These uncertainties are totaled depending on their effect on relative dosimetry applications, absolute dosimetry applications, and absolute dosimetry applications when the dose distribution is scaled by OSLD spot measurements.

Estimated Precision			
	Relative Applications	Absolute App	Absolute OSL ref.
Thermal*	0.84%-3.3%	1.18%-4.6%**	------
Energy	------	0.77%	------
Reusability	------	1%	------
Batch	------	0.71%	------
Total:	**0.84%-3.3%**	**1.6%-4.8%**	**1.5%**[29]
Typical-Worst Case Estimation *assume Δ0.5-Δ2° **Both uneven within sheet and overall temp change			

Along with the errors associated with our characterizations, another important source of error to consider is the uncertainty that arises as a result of sheet thickness and averaging measured dose over a non-negligible thickness. For the 5mm thick sheets, the is estimated to be around 1.3% for 6MV photon applications, and approaching 5% for 9MeV electron applications, the two energy levels studied most thoroughly in this work. When the dose is applied tangentially, this uncertainty is expected to be less pronounced than the estimates above, listed for normal incidence.

3.7 Diverse Clinical Applications

Following the sheet characterization, the sheets were tested in several clinical applications.

3.7.1 Application as an Economic Alternative to Film

Figure 10 displays the sheets employed as an IMRT QA tool. While patient-specific QA is completed using more advanced technology, such as EPID Portal Dosimeters, MapCheck diode arrays, or 3D diode arrays such as the Delta4 or ArcCheck, these are all quite expensive tools. Considering the low-income country perspective, IMRT QA is just as necessary to verify treatment plans in these clinics as in the US, but expensive arrays are not affordable. For this reason, testing the reusable Presage sheets as a patient-specific QA device is essential in order to explore a very large avenue of use for this dosimeter in the global perspective. A prostate IMRT QA test from the Duke clinic was delivered to both the reusable Presage sheet and an EBT film. The results from both of these measurements are pictured in figure 10A and 10B with a gamma map comparison displaying the results for 3% 3mm (C) and 5% 3mm (D). Within the IMRT field, the pass rate was 97% for 3% 3mm and 99% for 5% 3mm. Common features can be identified between the Presage sheet and the EBT, with the Presage yielding a slightly sharper measurement. Additionally, the EBT film required calibration scans and the application of a calibration curve to the dose distribution, where the Presage OD reading scales linearly with dose.

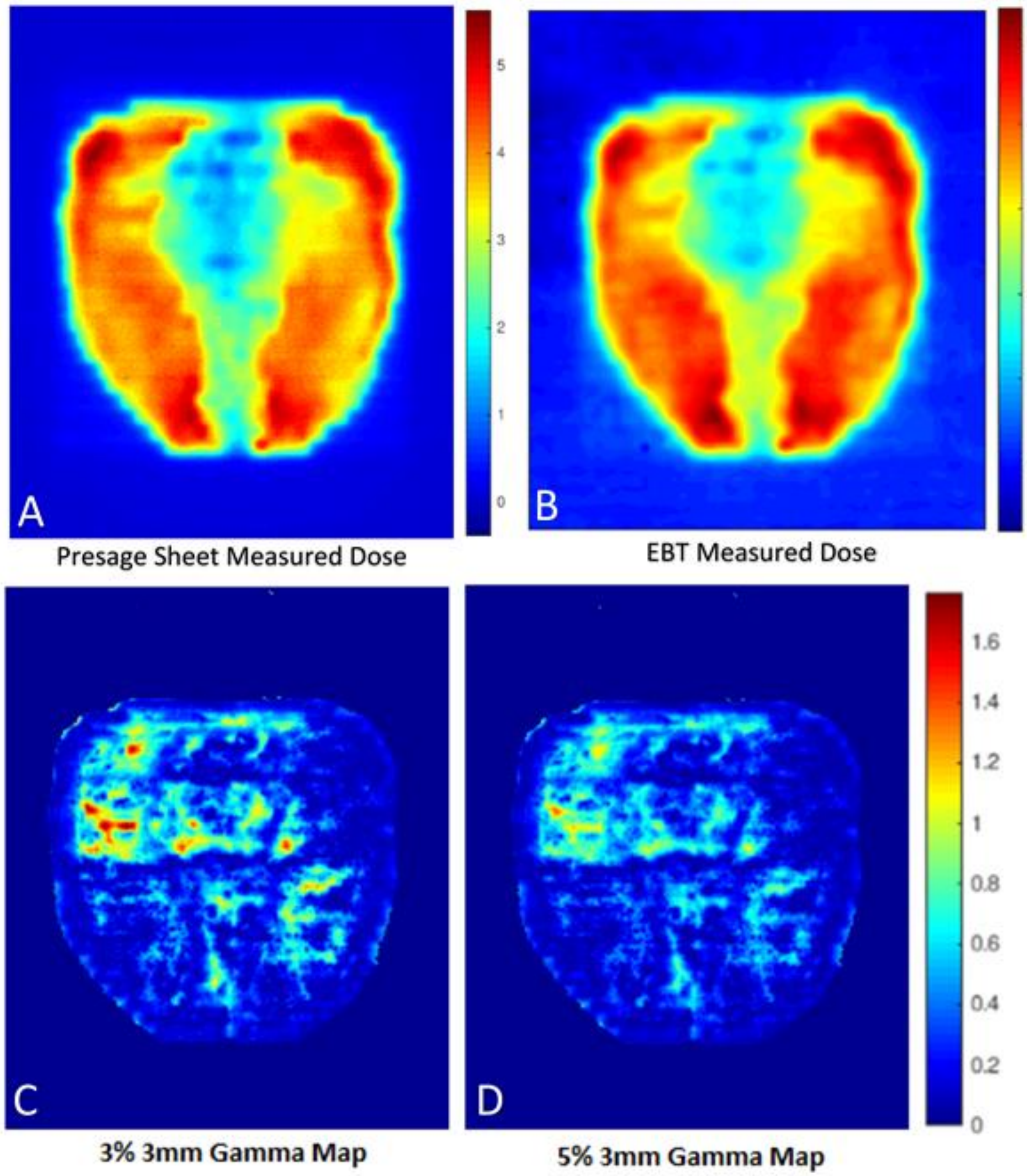


Figure 10: IMRT QA Prostate plan delivered to both the reusable Presage sheet (A) and an EBT film (B). The gamma map comparison between the two measurements at 3% 3mm yielded a 97% pass rate in the IMRT field region (C) and the comparison at 5% 3mm yielded a 99% pass rate (D).

To further explore the patient-specific QA application, a larger field plan was tested on a slightly modified formulation of the reusable Presage sheet. This formulation had a different softener employed than previous batches of sheets. For this trial, a pelvic QA plan was delivered to the Presage sheet and an EBT film and the dose distributions were compared with each other and the Eclipse treatment plan through gamma analysis. This formulation of Presage did not perform well in the higher dose regions of the delivery, which were in the 4.5Gy-5 Gy range. The gamma comparison between the Presage and the EBT film measured dose distributions at 3% 3mm with a 10% threshold yielded an 81% pass rate (figure 11F). The gamma comparison between the Presage sheet and the Eclipse treatment plan yielded a pass rate of 77% (figure 11 E). The gamma comparison between the Eclipse plan and the EBT film with the same constraints yielded a pass rate of 96% (11D). When the gamma comparison restraints were relaxed to 5% 3mm the pass rate for the comparison between the Eclipse plan and EBT film became 98%, between the Presage and the Eclipse Plan became 86%, and between the Presage and the EBT film became 88% (figure 11 G-I).

This formulation of Presage was found to have lower sensitivity for a dose of 4 Gy than the formulation used throughout this work, indicating that it may struggle to deliver a linear dose response in this dose range. Additionally, a large portion of the failure regions in this large field example were in the penumbra of the pelvic field. As the beam descends on the phantom at a wider angle from the target than for the small prostate field previously investigated, the delivered dose spread through the 5mm thick presage sheet is more pronounced. For large fields, future work should explore averaging the Eclipse plan in the 5mm thick region containing the Presage sheet, and comparing this averaged field to the Presage readout transmission scan (which inherently averages across this region).

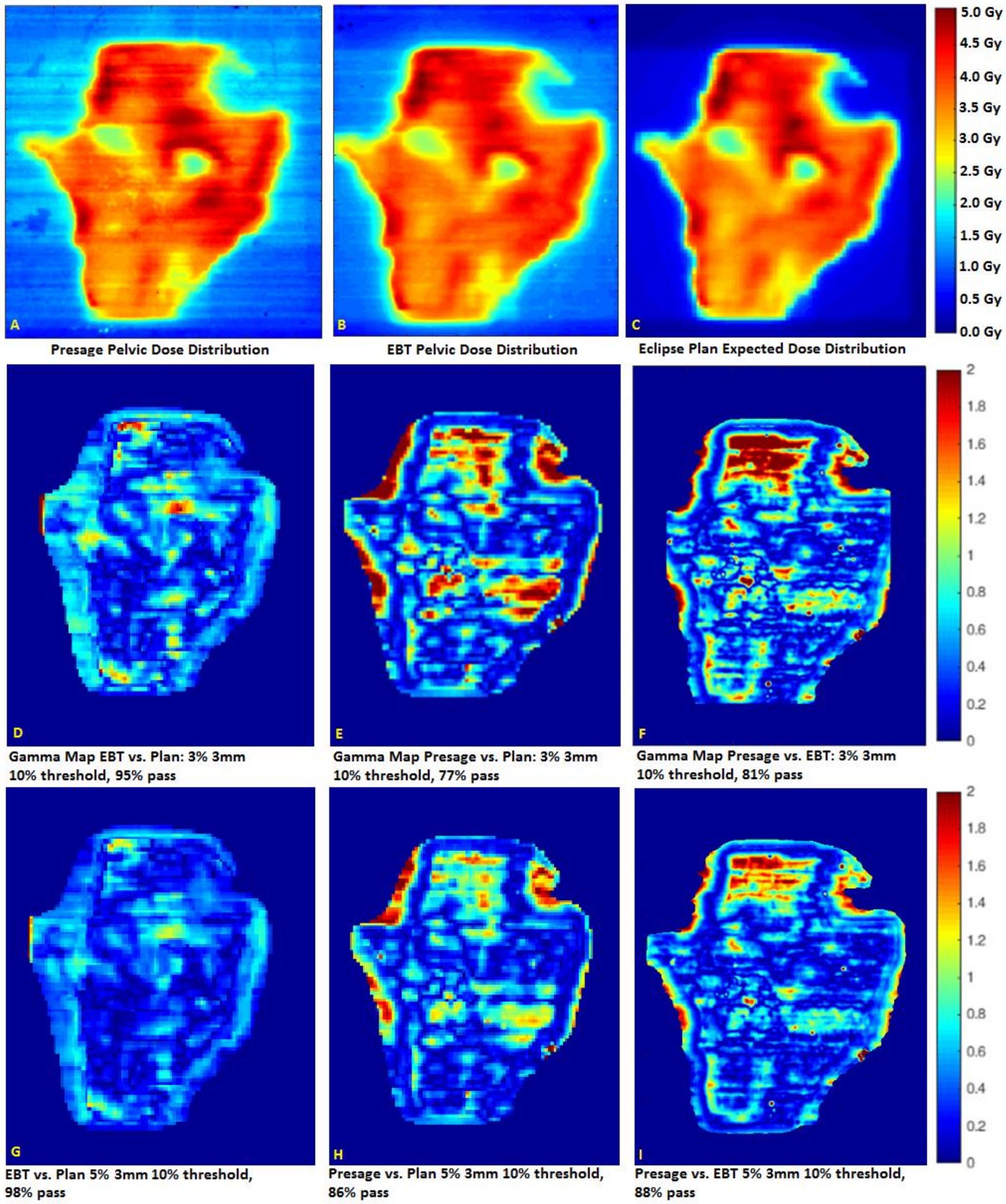


Figure 11: Results from the large-field pelvic IMRT-QA test. Image (A) is the Presage dose distribution scaled by dose, (B) is the EBT dose distribution of the delivered field, and (C) is the Eclipse treatment plan expected dose distribution.

Image (D) is the gamma map comparison between the EBT measured dose and the Eclipse plan, (E) between Presage measured dose and the Eclipse plan, and (F) is between the Presage measured dose distribution and the EBT measured dose distribution. Images G-I are the gamma map comparisons with 5% 3mm tolerance between Eclipse and EBT, Eclipse and Presage, and Presage and EBT, respectively.

The plan created to follow the IMRT TG-119 prompt was delivered to the reusable Presage sheet and the red channel of the readout image was compared to the Eclipse treatment plan expected dose distribution (figure 12). Figure 13 shows the results of the delivered treatment plan and the Eclipse treatment plan for the C-Shaped IMRT TG-119 delivery test. A 2D gamma comparison (C) shows the differences, and a global passing rate of 93% pass at 5% 3 mm, 10% threshold. The pass rate at 3% 3mm was 81%. Regions of failure arose from markings applied to the sheet for registration and alignment (top left, bottom left) and edge artifacts where the comparison falls off of the Presage sheet (right). Some regions of disagreement were identified to correspond to imperfections where optical fluid contaminated the upper surface of the sheet, highlighting the importance of clean scanning techniques. The overall agreement and clear similarities between features in both images indicates that the Presage sheets show promise as a radiochromic film alternative.

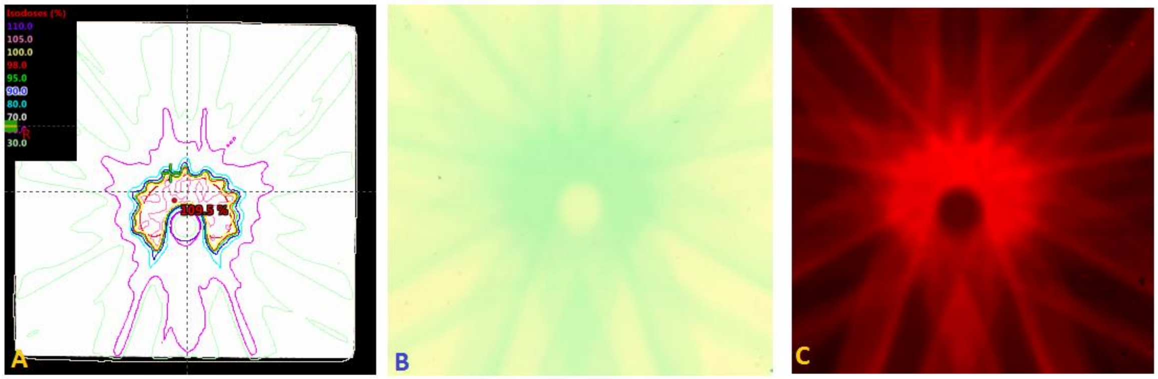


Figure 12: (A) pictures the TG-119 C-Shape IMRT treatment plan. (B) is the reusable Presage sheet readout scan. (C) is the red channel of the RBG readout scan, which is used for analysis.

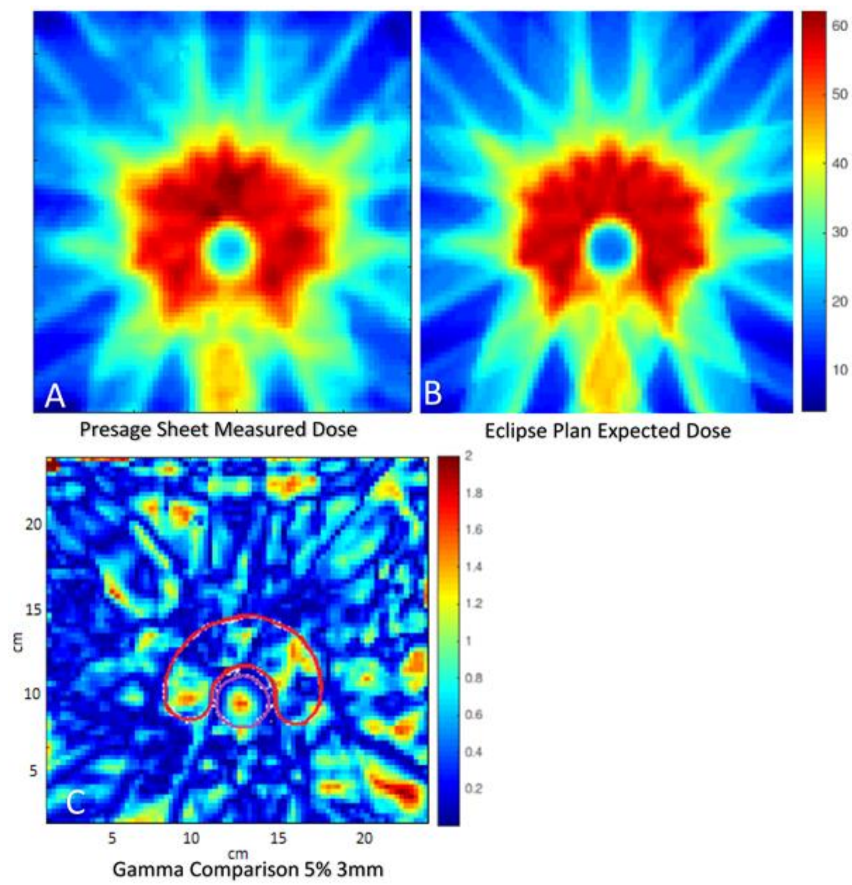


Figure 13: TG-119 C Shaped test for IMRT commissioning. (A) is the delivered color-map dose pattern in the Presage sheet. (B) is the Eclipse plan color-map. (C) is

the gamma map comparison between Eclipse plan and the delivered dose for 5% 3 mm. The resulting image had a 93% pass rate.

3.7.2 Application as a Reusable Radiochromic Bolus

Presage sheets were evaluated in two settings, both involving an electron cutout (figure 14A) and chest wall scar treatment. In the first setting, the field was delivered to a presage sheet lying flat on a solid water stack. This simplified setting allowed for a direct comparison of the dose delivered to the presage sheet, dose delivered to an EBT film with 5mm standard bolus, dose delivered to several OSLD points, and the expected dose distribution in the Eclipse treatment planning system. Dose contour maps were created for the field delivered to the sheet and for the Eclipse treatment plan and were overlaid in figure 14A. Figure 14B displays three line profiles through the same position, the black dotted line in 14A, spanning the length of the electron cutout field. One line profile was collected from the reusable Presage readout image, another from the EBT readout image, and the final line profile is the predicted dose pattern from the Eclipse treatment plan. The values were normalized to the OSLD readings.

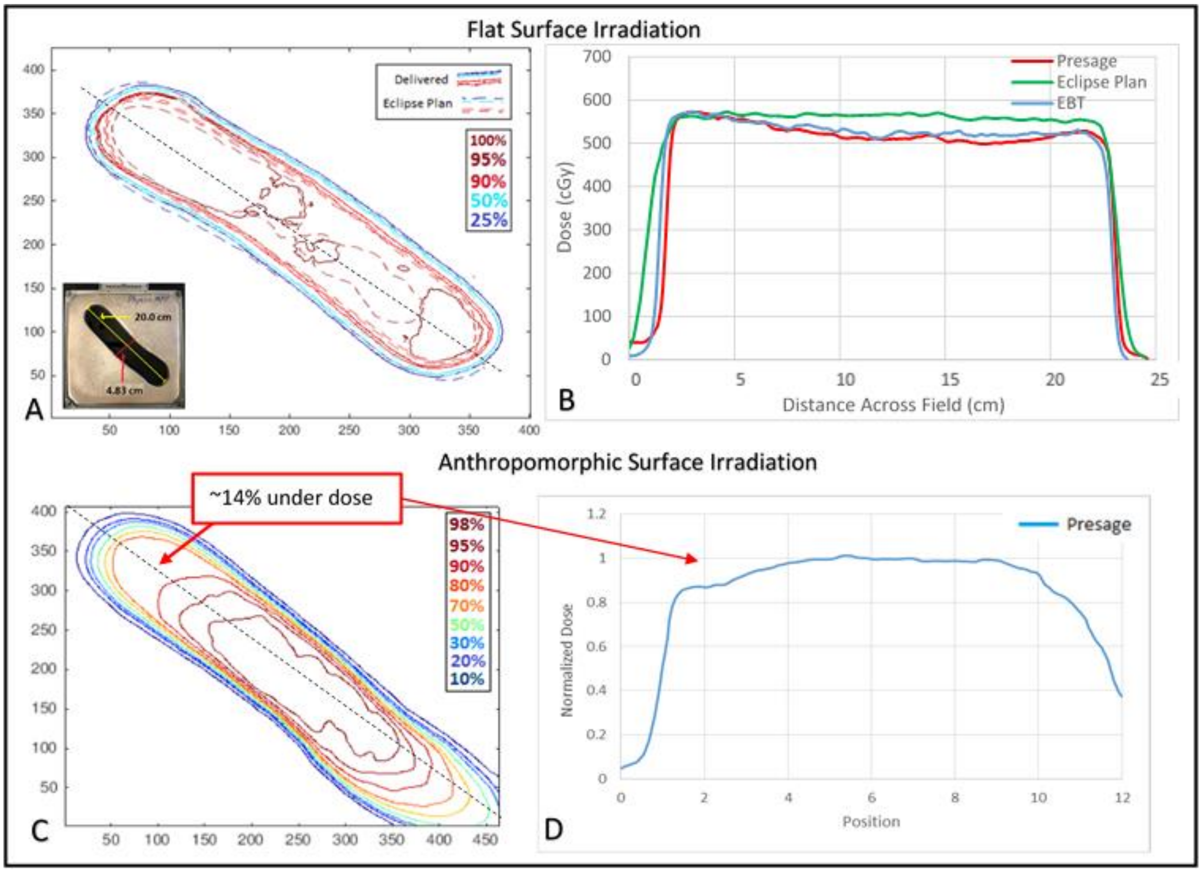


Figure 14: (A) depicts the dose contour map of the delivered plan overlaid with the Eclipse treatment plan expected results. (B) Compares a line profile through the long axis of this delivered plan, the long axis of the Eclipse treatment plan, and the long axis of an EBT film irradiated in place of the Presage sheet with a 5 mm standard bolus. The profiles are normalized to the corresponding OSLD readout dose values. Image (C) is the contour dose map from 10% to 98% and (D) is the line profile, recording normalized dose, along the black dashed profile line in (C).

From these line profiles we can see the same general trend, however, in the majority if the profile range the EBT and Presage profiles similarly diverge from the Eclipse pattern. The Eclipse plan predicts a more uniform profile, where the reusable Presage bolus and EBT film plus standard bolus detect a more uneven dose distribution in the true treatment. The OSLD readings paralleled the EBT and Presage trends, with an area of decreased dose on the right hand edge of the field. The root mean square error between the central cross-plane EBT film profile and the same profile in the Presage sheet is 11.7 cGy and the root mean square error between the Presage profile and the same profile in the Eclipse treatment plan's predicted dose distribution is 42.5 cGy. The strength in these initial experimental findings lies in the consistency of signal between the EBT and Presage sheets during the true irradiation trials, compared with the simulated plan.

To test the sheets and evaluate dose in a more clinically relevant scenario, the same test was conducted on a torso phantom with a chest wall scar. Figure 14C displays a dose contour map of the results and figure 14D shows the line profile through the electron cutout field (marked by the black dashed line in 14C). The dose contour map and line profile highlight a significant area of 14% under-dose in the field, identified by the use of the Presage radiochromic bolus. This finding from the clinical application emphasizes the need for a secondary verification of treatment setup and treatment modeling systems, and demonstrates the functionality of the Presage bolus. Comparison with EBT film was not practical in this scenario, as the film buckled and bulged when wrapped around the torso phantom, less accurately conforming to the surface contours.

Dumas and Rakowski noted issues with the use of the Epson flatbed scanner, citing difficulty obtaining clear readout scans due to the presence of bubbles and sheet irregularities and concern with UV light exposure to the sheets from the Epson scanner.

They also reported poor dose resolution and low sensitivity, resulting in a poor signal to noise ratio. These complications in their results arose from the simple equipment that they used to create the sheets, which resulted in air bubbles in their material, non-uniform chemical dispersion in the sheets, variation in thickness within each sheet, and other uniformity issues.

The current work has resolved and improved upon each of these concerns. The sheets were devoid of irregularities that may affect image quality, based on the commercial fabrication by Heuris, Inc. where vigorous mixing ensured uniform distribution of dye molecules throughout the sheet and consistency of sheet thickness was confirmed using an electronic caliper. Artifacts due to air bubbles between the sheet and the glass face of the scanner were eliminated using a drop of optical fluid which allowed the sheet to settle into the scanner uniformly. The current formulation of Presage also demonstrated increased sensitivity, resolving various signal to noise issues. Furthermore, the UV light from one pre-scan and one post-irradiation scan was not found to affect the sheet readout values in these sheets. While a slight increase in OD was observed when unirradiated control sheets were scanned many times repeatedly, this practice is not practical in any clinical applications.

3.8 Cost Analysis

The reusable Presage sheets have been described throughout this work as a low-cost alternative to various standard tools and technologies that are currently in place in the clinic. This section walks through a cost analysis detailing the degree to which this new dosimeter helps to reduce expenses. Each value presented marks the current price of tools and technology as of March, 2019.

3.8.1 Film Application

A box of 25 Gafchromic EBT3 films is sold for approximately $690 [30]. This means that each individual film costs $27.60. On top of this cost, these films are single-use. A box of 100 sheets of Kodak Carestream radiographic film is less expensive, costing around $225, but requires post-processing and a film processor, which can cost up to $8,000, and require maintenance [31]. These films are, again, single-use.

The reusable Presage sheets have been shown to be reusable for 10 consecutive irradiations, with no sign of ceasing to function for many more irradiations. While a retail price has not been officially set for the sheets, an estimate places the price at about $100. This means that if the sheets were only reusable for 10 trials, the price per use would be $10, a significant improvement on EBT film. There is no reason to believe that these sheets could not be reused many more times, but this portion of the research is ongoing.

For the purposes of these experiments, the sheets were read out on an Epson Expression 10000 XL flatbed scanner, which costs approximately $3000. The benefit, however, of this readout technique is that most clinics are equipped with a functioning scanner already, for use with EBT Gafchromic film or general paper scanning.

Additionally, flatbed scanners come in a variety of different levels of quality, and therefore expense, so that they can be more readily adapted in lower-income clinics, assuming minor sacrifices in image quality can be accepted.

3.8.2 Patient-Specific QA Application

For patient-specific QA, the reusable Presage sheets would replace advanced LINACs with built in EPID portal dosimeters, MapCheck diode arrays, VMAT-capable diode arrays such as ArcCheck and Delta4, and other advanced tools for IMRT-QA. Each of these systems are potentially preferable because of their almost instant results and lack of a need for readout scanning. However, in the context of care in lower-income countries, the cost for these systems, at thousands of dollars, is prohibitively expensive. In addition to this consideration, the resolution in the reusable Presage sheets is significantly better than the diode arrays and other such dosimetry systems, as it does not require interpolation.

3.8.3 Bolus Application

For the bolus application, the comparison is less about cost and more focused on utility. A sheet of Superflab bolus costs about $150 and does not contribute any form of dose recording to the treatment analysis [30]. This Presage sheet would function in all of the ways in which a Superflab bolus would, yet would add the benefit of being able to perform a secondary verification of the dose delivery, and would be less expensive.

4. Conclusion

This work presents investigations into the first reusable 2D radiochromic sheet dosimeter. Promising performance is shown for film and bolus applications, and the potential for reusability confers substantial economic savings. Evaluation in the present work was restricted to sheets of 5mm thickness, but potential exists for substantive customization in terms of stiffness, thickness, sensitivity, clearance time, and number of repetitions for reusability. Key observations from the Presage sheets studied include no evidence of the memory of prior irradiation and also consistent sensitivity in dose response.

This body of results suggests that these sheets have the potential to push the frontier of care in the most advanced clinics of the world, making improvements in cost, safety, and quality throughout the treatment process. The economic advantage in the film application may be able to, for the first time, challenge the use of established films. The novel development of a radiochromic bolus has the potential to provide an important verification of treatment setup and treatment planning system modeling.

Alternatively, the sheets also have the potential to provide a much needed, versatile resource in mid- to low-income countries. They have the three necessary qualities to become useful in clinics with the fewest resources as they are fast, inexpensive, and easy to use. In these respects, they can be used for patient specific QA – greatly improving the quality and safety of current treatments, as an economic film alternative, and as a radiochromic bolus. This diversity of applications in a system that will save a clinic thousands of dollars has the potential to be a much needed resource filling a large gap in quality of care.

This work is still a preliminary study of feasibility, with exciting opportunities for future work and development. The current limitations include the narrow nature of testing with analyses limited to only a handful of clinical applications. In addition to this, inter-batch comparisons must be studied in more detail, as consistency of manufacturing is often a concern is this realm of research. Additional work is recommended to further study use in a wide variety of clinical applications, of most interest in the DEAR electron arc therapy studies, where the use of the reusable Presage sheets as a bolus has the most potential for direct implementation. Additionally, future work should establish a material more closely reflecting flexible bolus and study the extent of the potential for reusability in the sheets until this characteristic is exhausted. To this point, the extent of the reusability has not been reached through experimentation.

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