Comprehensive evaluation and new recommendations in the use of Gafchromic EBT3 film

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Keywords: EBT3, radiochromic film, temporal dependence, film dosimetry

Abstract

Background: Gafchromic film's unique properties of tissue-equivalence, dose-rate independence, and high spatial resolution make it an attractive choice for many dosimetric applications. However, complicated calibration processes and film handling limits its routine use.

Purpose: We evaluated the performance of Gafchromic EBT3 film after irradiation under a variety of measurement conditions to identify aspects of film handling and analysis for simplified but robust film dosimetry.

Methods: The short- (from 5 minutes to 100 hours) and long-term (months) film response was evaluated for clinically relevant doses of up to 50 Gy for accuracy in dose determination and relative dose distributions. The dependence of film response on film-read delay, film batch, scanner type, and beam energy were determined.

Results: Scanning the film within a 4-h window and using a standard 24-h calibration curve introduced a maximum error of 2% over a dose range of 1–40 Gy, with lower doses showing higher uncertainty in dose determination. Relative dose measurements demonstrated <1 mm difference in electron beam parameters such as depth of 50% of the maximum dose value (R_{50}), independent of when the film was scanned after irradiation or the type of calibration curve used (batch-specific or time-specific calibration curve) if the same default scanner was used. Analysis of films exposed over a 5-year period showed that using the red channel led to the lowest variation in the measured net optical density values for different film batches, with doses >10 Gy having the lowest coefficient of variation (<1.7%). Using scanners of similar design produced netOD values within 3% after exposure to doses of 1–40 Gy.

Conclusions: This is the first comprehensive evaluation of the temporal and batch dependence of Gafchromic EBT3 film evaluated on consolidated data over 8 years. The relative dosimetric measurements were insensitive to the type of calibration applied (batch- or time-specific) and in-depth time-dependent dosimetric signal behaviors can be established for film scanned outside of the recommended 16-24 hour post-irradiation window. We generated guidelines based on our findings to simplify film handling and analysis and provide tabulated dose- and time-dependent correction factors to achieve this without reducing the accuracy of dose determination.

Keywords: EBT3, radiochromic film, temporal dependence, film dosimetry

1 INTRODUCTION

Radiochromic film is commonly used for dosimetry in radiation therapy owing to its excellent spatial resolution, large dynamic dose range, tissue equivalence, dose-rate independence, and energy independence.[1] Radiochromic film can be used to measure dose and relative dose distributions, including percent depth dose (PDD) curves, dose homogeneity, and 2D isodose distributions; it is exceptionally valuable for conformal treatments that involve high dose gradients as well as small field dosimetry.[1,2] Moreover, film does not require physical or chemical processing and can be robustly handled in ambient lighting and room temperature conditions[1]. Radiochromic film works as a radiation dosimeter in that irradiation prompts a polymerization reaction that causes a color change in the irradiated region of the film. The initial color change is instantaneous upon exposure to ionizing radiation. However, the color's intensity grows and plateaus after irradiation. Color changes in film are measured quantitatively in terms of optical density (OD) by using a commercially available flatbed color scanner and analysis software to measure the amount of light transmitted through irradiated and nonirradiated film.

However, radiochromic film is a passive dosimeter, limited by the need for a complicated and time-consuming calibration and delayed time to readout (recommended 16-24 hours) to allow the polymerization reaction to stabilize upon irradiation[1,3]. The extent of color changes produced in film also does not correlate linearly with dose, except when PRESAGE sheets are used.[4,5] Rather, film requires a time-dependent calibration to convert the measured OD reading to a dose value, because the polymerization reaction never fully stabilizes[6]. For this reason, it is important to ensure the delay (irradiation to scanning) to be the same as used for film-calibration, which further limits film usability. Rapidly emerging new technologies, such as FLASH radiotherapy, are heavily reliant on film dosimetry for beam calibration and experimental verification of dose due to radiochromic film's established dose-rate independence of up to 10^{12} Gy/s[7-11]. For radiotherapy with ultra-high dose-rates or "FLASH", traditional dosimeters (except for radiochromic film) are not usable due to saturation effects. For such ultra-high dose-rates and dose-per-pulse conditions, as well as extremely short irradiation times, real-time dose monitoring is nontrivial. The read-out delay in film may be unacceptably long for experiments that rely on quick calculations or rapid adjustment of beam parameters for which other commercially available dosimeters that can measure radiation in real-time cannot be used due to large saturation effects.[12]

To address the limitations of film dosimetry, we undertook a comprehensive evaluation of how the signal in Gafchromic EBT3 film varies when measured over short timespans (minutes and hours) and long timespans (months), when scanned using different film scanners at different institutions, the consistency of dose response in the use of different batches of Gafchromic EBT3 film over several years, the energy dependence for different batch formulations, as well as the dependence of relative dose distribution measured on film depending on when film was scanned or the type of calibration that was applied. The data presented in this work provides substantial improvement to the field of film dosimetry by addressing the limitations in the dosimetric recommendations presented in TG-235. In this work, we propose simplified novel methods of Gafchromic film dosimetry for point dose measurements and relative dose distribution measurements that allows for rapid film processing without compromising the accuracy of film dosimetry

2. MATERIALS AND METHODS

2.1 Short-term evaluation

2.1.1 Evaluation of dose response

Gafchromic EBT3 films (Ashland, Bridgewater, NJ, USA) were cut into 3.8 × 3.8 cm^2 squares, with each square labeled with the dose to be delivered: 0–40 Gy. Film squares were irradiated with a 16-MeV electron beam from a Varian Clinac 2100 (Varian, Palo Alto, CA, USA). The machine was calibrated to deliver 1 cGy/MU at the depth of maximum dose (d_{max}) in water for a 10×10 cm^2 field at a source-to-surface distance (SSD) of 100 cm, according to the TG-51 protocol.[13] Six films were designated for each dose group. After irradiation, a first set of three films per group were scanned at the following times: 5–30 minutes and 1–100 hours after irradiation. The second set of three films per group were scanned only once at 24 hours after irradiation. This analysis was done to examine if and how repeated scans obtained intermittently over a 24-hour period (additional illumination to film) would affect the measured optical density in the irradiated EBT3 film.

An Epson Expression 10000XL flatbed scanner (Seiko Epson Corporation, Nagano, Japan) was used to scan all films. Each scanned image was acquired in transmission mode, landscape orientation, 48-bit color, 72 dpi, and without color correction. The films were placed on the scanner at the same location with the aid of a cardboard cutout. The scanned film data were analyzed by measuring the netOD of the irradiated film square relative to an unirradiated (0 Gy) film square from the same batch. The red channel was used unless otherwise noted for single-channel dosimetry measurements. The mean pixel value of each scanned EBT3 film square was obtained from ImageJ from a 2.5 × 2.5 cm^2 square region of interest placed at the center of the film square. The mean pixel values measured for the three films in each dose group were averaged to acquire an averaged mean pixel reading. The netOD reading was determined by taking the base-10 logarithmic ratio of the averaged mean pixel reading from the unirradiated film squares, $Pixel_{background}$, with the averaged mean pixel reading from the film squares irradiated to an absorbed dose, $Pixel_{dose}$, using the following equation: netOD = $\log_{10}(\frac{Pixel_{background}}{Pixel_{dose}})$.

2.1.2 Evaluation of relative dose distributions

The effects of time delay (irradiation end to film-scanning) on relative dose distributions from EBT3 films were evaluated on acquired PDD curves. Three film strips measuring 4.5 × 9.0 cm^2 were used. Each film strip was placed inside an acrylic water tank that had a 2-degree tilt with the film oriented parallel to the beam and its edge at the water's surface by using a clamp to situate the film in place. The apparatus used is described by Arjomandy et al. for mounting films for a depth-dose irradiation in a water tank.[14] Each EBT3 film strip was irradiated with a 16-MeV electron beam at 100 cm SSD and a field size of 25 × 25 cm^2 with a d_{max} dose of 20 Gy. After irradiation, the films were dried off with paper towels and scanned at timepoints ranging from 5 minutes to 100 hours post-irradiation using an Epson 10000XL flatbed scanner. For each image scanned, the netOD was obtained, which was then converted to dose using a script written in MATLAB based on a dose calibration curve. The calibration curve was generated from the netOD measured in the scanned film squares from the first set of films in the same batch (described in section 2.2.1) that were irradiated to 1–40 Gy at 5 minutes to 100 hours post-irradiation (5 min, 1 h, 24 h. and 100 h). The three PDDs were then averaged to produce a single PDD curve for each scanned timepoint investigated.

The time-delay and batch dependent changes on the relative dose distributions of the PDD curves was investigated. The films used for PDDs were scanned at the four timepoints noted above that had their respective timepoint-specific calibration applied (e.g. film scanned 1 hour post-irradiation had a calibration applied based on film scanned at 1 hour post-irradiation); in a separate analysis, the film PDDs were compared with each other by using a calibration obtained at a single timepoint (24 hours after irradiation). The calibrations used were from the calibration curve generated specific to the scanned image's respective timepoint (5 minutes to 100 hours), plus the calibration curve at 24 hours, for the film squares irradiated to 1–40 Gy. To explore EBT3's batch-dependence, the films for 3 PDDs, scanned at the 24-hour timepoint, had calibrations applied from five separate EBT3 batches purchased within the same year (labeled Batch A-E). The calibration curve from each batch had been scanned at 24 hours after irradiation to doses of 0–50 Gy.

2.2 Long-term evaluation

2.2.1 Evaluation of film response over several weeks

EBT3 films irradiated for batch calibration purposes were scanned at 24 hours after irradiation and then rescanned at 2 –39 weeks after irradiation to evaluate how the response of the irradiated EBT3 film changes over longer periods. The calibration films included EBT3 film squares irradiated to a dose of 0–50 Gy, with three films used for each dose point, and irradiated as described for the short-term evaluation (2.1.1). The netOD measured at 2–39 weeks was normalized to the netOD measured at 24 hours. This provided quantification of OD evolution with scanning delay.

2.2.2 Film batch comparison over a 5-year period

Calibration curves of EBT3 film from 14 different batches were acquired over a period of 5 years, from May 2016 to May 2021. The films had been irradiated to doses ranging from 0–50 Gy, with three films irradiated per dose. The films were scanned between 18 and 24 hours after irradiation and analyzed separately based on the red, green, and blue channels. To quantify the variation in netOD between different film batches over time, the coefficient of variation (COV), also known as relative standard deviation, in the netOD measured for each dose level was calculated by dividing the standard deviation of the netOD measured for each dose group from all 14 batches by the mean netOD value for each dose group measured from all 14 batches.

2.3 Scanner dependence

To determine the influence of choice of scanner on the netOD response, EBT3 film irradiated to an absorbed dose of 1, 4, 10, and 20 Gy was scanned with one Epson 10000XL, two Epson 11000XL (referred to as Epson 11000XL-1 and 11000XL-2), and one Epson V800 film scanner. The same films were scanned on the Epson 10000XL and the Epson 11000XL-1 at the same institution. The film scanned at collaborating institutions on the Epson 11000XL-2 and Epson V800 came from different EBT3 film batches that were irradiated at their respective institutions within the same year, with three films used per dose investigated.

2.4 Energy dependence for different film batches

To investigate the energy dependence of EBT3 film, films from four separate batches were irradiated with radiation sources of different energies. The dose range investigated was 0–12 Gy. The radiation sources were Cs-137 (0.662 MeV) and Co-60 (1.25 MeV) and the radiation beam energies produced from a clinical linear accelerator were 6 MV and 18 MV photons, and 20 MeV electrons.

3. RESULTS

3.1 Short-term evaluation

3.1.1 Evaluation of dose response

The measured netOD in films that were scanned only once (at 24 hours after irradiation) were compared with the netOD measured in films that had been scanned ten times total at the 24-hour timepoint post-irradiation (Table S1). A negligible difference (<1%) was noted between the measured netOD (at the 24-hour timepoint) for film that had been scanned multiple times over a 24-hour period (measured at 0.08 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 16 h, and 24 hours after irradiation) versus films that had been scanned only once, at 24 hours.

Figure 1A presents temporal evolution of netOD for films irradiated to absorbed doses 1–40 Gy. Figure 1B presents the data of Figure 1A in terms of relative netOD (normalized to netOD for 24-hour delay). The data in Figure 1B is also tabulated in Table S2. The rapid readout of film at 5 minutes after irradiation to absorbed doses of 1–40 Gy led to measured netOD values that were 2%-8% lower than the netOD value measured in film scanned at 24 hours after irradiation on the same scanner.

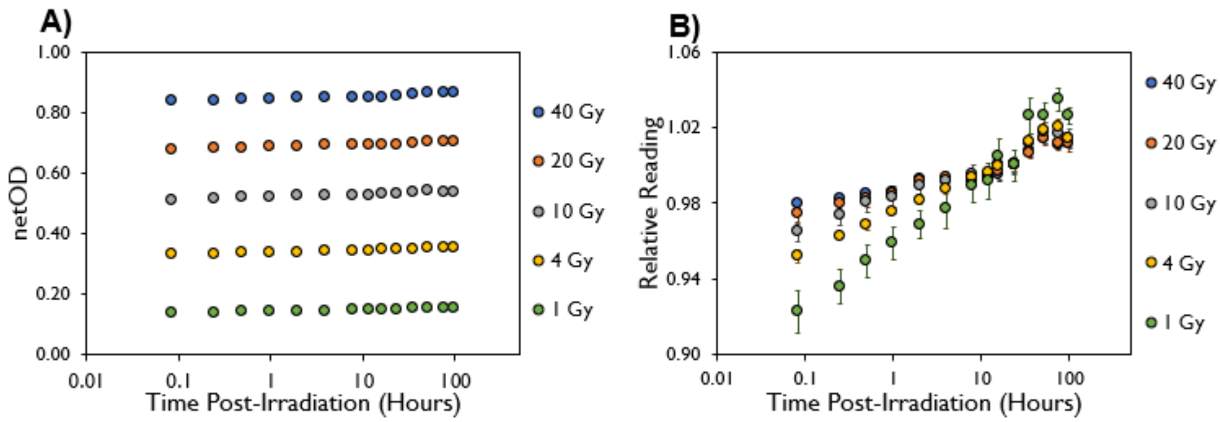

Figure 1. (A) Temporal dependence of EBT3 film response measured over a period of 100 hours and (B) netOD normalized to 24 hours after irradiation. Error bars represent one standard deviation from three films irradiated to each dose delivered.

3.1.2. Evaluation of relative dose distributions

EBT3 film used to measure PDDs were scanned after delay of 5 minutes to 100 hours post-irradiation. Measured netOD were converted to doses employing the delay-specific calibrations. This allowed for determination of depth-doses, and consequently the depth-dose parameters of R_{30}, R_{50}, R_{80}, and R_{90}. These values are presented in Table S3. For reference, the corresponding values from the commissioning of the machine are shown. Table S3 also shows the relative percent difference in the measured beam parameter values in films scanned at their respective timepoints with their respective time-specific calibration applied versus what was measured when only the 24-hour calibration curve was applied. The depth-dose parameters of R_{30}, R_{50}, R_{80}, and R_{90} measured in EBT3 film when only a general 24-hour calibration curve was applied is listed in Table S4. The depths of the 16 MeV electron beam are within 1 mm of the values measured from the TPS and within 1 mm of each other at the respective scanned timepoints (5 minutes to 100 hours post-irradiation) regardless of which calibration curve was applied (Figure S1). Table S5 lists the beam parameter values measured from the same EBT3 PDD films but with different batch calibrations applied from calibration films scanned on the same scanner. That table also illustrates that the measured beam parameters were within 1 mm of each other and within 1 mm of the beam parameter values measured by the TPS, despite the use of different batch calibrations.

3.2 Long-term evaluation

3.2.1 Evaluation of film response over several weeks

Figure 2 compares the netOD reading measured at 2–39 weeks after irradiation in comparison with measurements obtained at 24 hours after irradiation, taken from a single batch of film irradiated to 0.5–50 Gy, with three films irradiated per dose investigated. Figure 2A shows calibration curves of films measured at their respective timepoints, and Figure 2B shows the relative difference between the measurement at 24 hours and the measurements scanned at 2–39 weeks after irradiation. The relative difference in the measured netOD scanned several weeks after irradiation were largest in films irradiated to low doses (< 6 Gy). In quantifying the relative increase in netOD, the netOD measured at 2 weeks after irradiation was between 1.6% and 5.5% higher over the investigated dose range. At the 6-week timepoint, the netOD in film continued to increase, with a percent increase in netOD (relative to the 24-h measurement) of 2.3% to 5.5%; at 11 weeks, the percent increase was 2.6% to 7.8%; at 19 weeks, the percent increase ranged from 2.8% to 7.8%; at 39 weeks, the percent increase ranged from 3.8% to 6.8%. At doses greater than or equal to 6 Gy, the percent relative difference in netOD between the 24-h measurement and the 2-, 6-, 11-, 19- and 39-week timepoints stabilized and averaged at 1.6 ± 0.11% (at 2 weeks), 2.3 ± 0.04% (at 6 weeks), 2.8 ± 0.12% (at 11 weeks), 3.1± 0.15% (at 19 weeks), and 4.3 ± 0.24% (at 39 weeks).

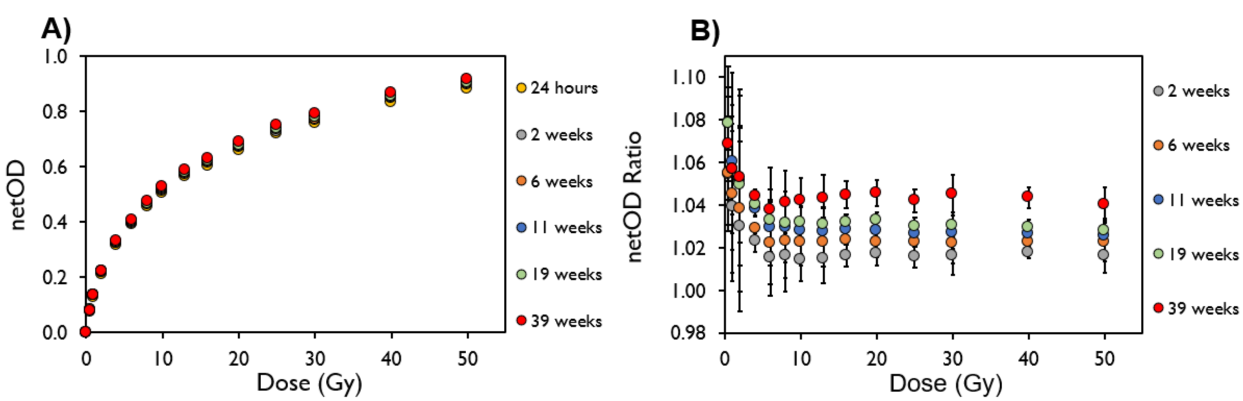

Figure 2. (A) Dose response curve and (B) netOD ratio relative to the 24-h measurement of EBT3 film scanned at 24 hours, 2 weeks, 6 weeks, 11 weeks, 19 weeks, and 39 weeks after irradiation to doses of 0.5–50 Gy. Error bars represent one standard deviation from three measurements.

3.2.2 Film batch comparison over a 5-year period

The dose response curves of EBT3 films scanned 18 to 24 hours after irradiation from 14 different batches of EBT3 film collected from 2016 to 2021 with the red, green, and blue channel are shown in Figure 3. The variation between different batch calibration curves from separate color channels was smallest for measurements taken with the red channel and was largest in netOD measured in the blue channel. Figure 3B-D show the netOD specific to each dose value with the date that each batch of calibration curves were scanned. No correlation was found between the variation in the measured signal for the different batches investigated between the red, green, and blue channels.

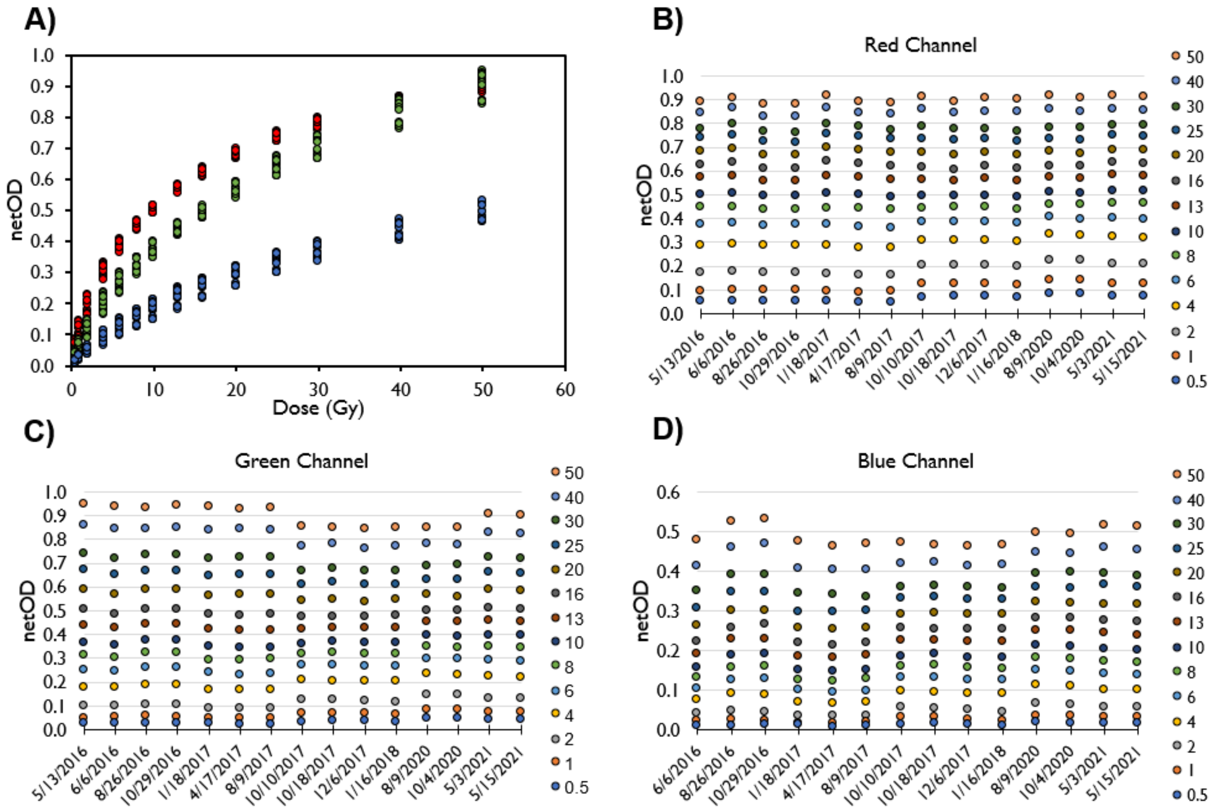

Figure 3. (A) Dose response curve of EBT3 film data (16 MeV electrons, 14 calibration curves total) scanned from 2016 to 2021 at 18 to 24 hours after irradiation to doses of 0.5–50 Gy with the red, green, and blue channels. (B-D) The netOD measured at each dose point, with the indicated scan date, for the (B) red, (C) green, and (D) blue channels.

The COV of the measured netOD values at each dose point evaluated for the red, green, and blue color channels for all doses evaluated in 14 different batches of EBT3 film between 2016 and 2021 are shown in Figure 4 and Table S6. The measured netOD for each dose value in the red channel showed the smallest COV of all three color channels; a COV of 10% or less was observed in films irradiated to 6 Gy or higher in the red and green channels, and in films irradiated to 16 Gy or higher in the blue channel.

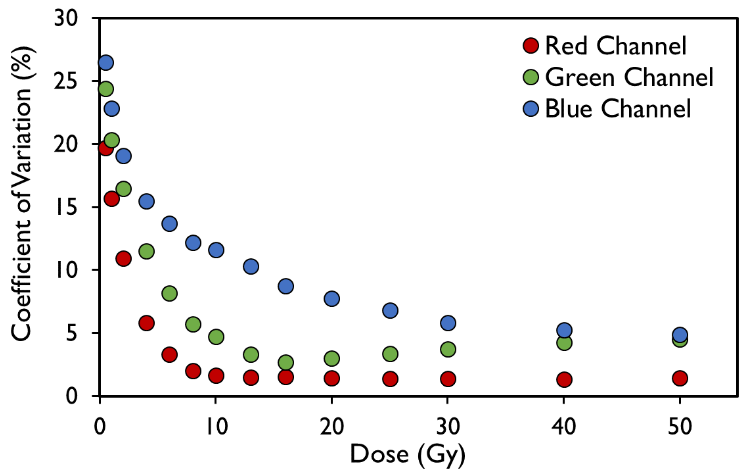

Figure 4. Coefficient of variation of EBT3 film data (14 calibration curves total) scanned at 18 to 24 hours after irradiation from 2016 to 2021 with the red, green, and blue channels.

3.3 Scanner dependence

Figure 5 and Table S7 compare the netOD measured in the same films scanned at 24 hours after irradiation with two different color scanners at the same institution (Epson 10000XL and Epson 11000 XL-1); also shown are comparisons with measurements from different film batches irradiated to the same dose but scanned at different institutions (Epson 11000XL-2 and Epson V800). The difference in the measured netOD of the same film scanned on two separate scanners at the same institution was within 1% for the Epson 10000XL and 11000XL-1, with the netOD measurement lower with the Epson 10000XL than with the 11000XL-1 (difference of 0.1% to 1.1%). The netOD measured with two Epson 11000XL scanners at two separate institutions were within 1.8% to 2.5% when using the same scanner type; the netOD measured in film scanned with the Epson 11000XL-2 was consistently lower than the netOD measured in film scanned with the Epson 11000XL-1. The netOD measured with the Epson V800 was substantially (2.6% to 19.5%) lower than that in films scanned with the Epson 11000XL-1.

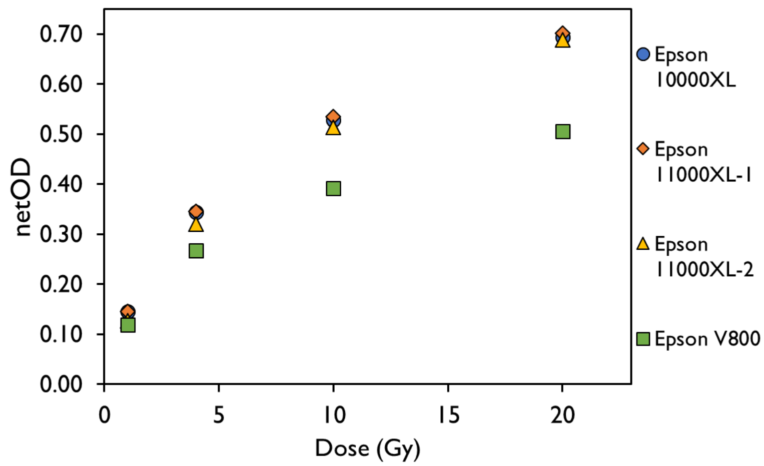

Figure 5. netOD values from EBT3 film scanned with Epson 10000XL, 11000XL, and V800 film scanners at different institutions, measured at 24 hours after irradiation to 1, 4, 10, and 20 Gy. Error bars represent one standard deviation from three films irradiated to each dose.

3.4 Energy dependence

Figure 6 shows the consolidated dose-response data points of EBT3 film from four different film batches irradiated with different x-ray and electron beams at energies of 0.6–20 MeV, plotted with a polynomial curve comprising of all the consolidated data (black line). The energy dependence and batch dependence in EBT3 film irradiated in the mega-voltage energy range (including Cs-137 and Co-60) regardless of modality type (photons/electrons) was found to be minimal with the relative percent difference between the delivered dose with the dose measured from the polynomial fit being <12% for all of the batches and energy combinations, with the highest relative difference observed in the datapoints acquired at 30-40 cGy dose points. At delivered doses higher than 100 cGy, the relative percent difference between the delivered dose and the dose measured from the polynomial fit was < 4% between the different batch and energy modality types.

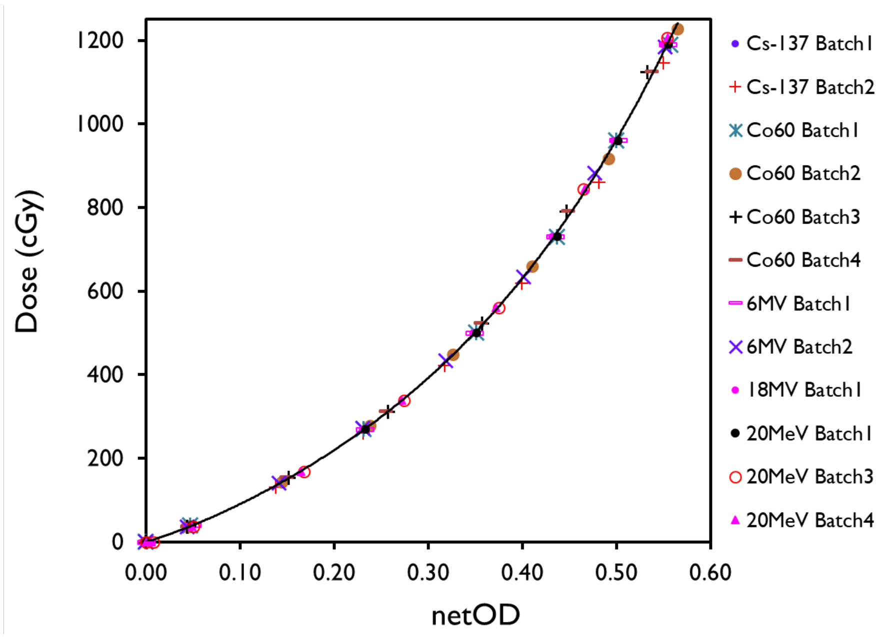

Figure 6. Dose response curve for EBT3 film from four different batches irradiated using Cs-137, Co-60, and mega-voltage x-ray and electron beams at a dose range of 0-12 Gy.

4 DISCUSSION

4.1 Short-term evaluation

One key finding from this study was that repeat single scans of EBT3 film at different intervals within the first 24-hours after irradiation did not have a significant effect on the resulting netOD, thereby confirming the robustness and insensitivity of EBT3 film to the light produced from the Xenon cathode fluorescent lamp in the Epson 10000XL scanner when scanned intermittently over a 24-hour period. Because each film was scanned once at each timepoint considered (18 films), the lack of change in netOD indicates that the number of scans obtained at each timepoint was not sufficient to affect the temperature of the scanner, which can otherwise cause a change in the netOD reading.[1,2,15]

Increases in OD after irradiation limit the use of EBT3 film for film dosimetry, given that the user must follow a timepoint-specific calibration procedure for accurate dosimetry. AAPM TG-235 recommends a 16- to 24-hour wait time between irradiation and scanning to allow stabilization of any post-exposure increase in signal, within the bounds of a clinic's established protocol, or by adopting the one-scan protocol, a simplified protocol that allows rapid film scanning and dose calculation by using a recalibration method with patient film, reference film, and unexposed film as proposed by Lewis et al. in 2012.[1,16] Others have reported using shorter wait times after irradiation to allow the OD in film to stabilize. Sharma et al 2021[17] reported that the growth kinetics of EBT3 netOD stabilized as soon as 6 hours after irradiation of EBT3 film to doses of 1 Gy or higher, which is consistent with our findings. Borca et al. 2007[3] reported stabilization in netOD growth as soon as 2 hours after irradiation for film irradiated to 1–4 Gy. Sharma et al. defined stabilization of the netOD as being within 2% of the netOD value at 24 hours, whereas Borca et al. defined it as being within 2.5% of the netOD value at 24 hours after irradiation. The results of these past studies and ours show that netOD in EBT3 film stabilizes earlier than the 16- to 24-hour interval recommended by TG-235 and that stabilization in film is strongly dependent on the dose delivered to the film of interest and the time the film was scanned post-irradiation. In the current study, we found that to be within 2% of its 24-hour netOD value, film irradiated to an absorbed dose of 4 Gy must be scanned at anywhere between 1 hour and 76 hours after irradiation, and for film irradiated to an absorbed dose of 1 Gy, that interval was 4-24 hours after irradiation. Film irradiated to doses of 10 Gy or higher can be scanned within 30 minutes to 100 hours after irradiation and still be within 2% of its 24-hour netOD value.

For relative dosimetric measurements of dose distributions with EBT3 film, the use of (1) a time-specific calibration curve, (2) a standard 24-hour calibration curve from the same batch, or (3) a calibration curve from a different batch of film all showed insensitivity to the choice of calibration applied. Notably, this insensitivity was found for calibration curves generated from the same scanner that the measurement films were scanned on. Electron beam parameters at a depth beyond d_{max} where the PDD curve is 30%, 50%, 80%, and 90% of the maximum value measured in EBT3 film differed by no more than 1-2 mm relative to the PDD curves scanned at 24 hours after irradiation on the Epson 10000XL scanner, again demonstrating negligible effects from the use of time-specific and batch-specific calibration curves on relative dosimetry. Likewise, these beam parameter values deviated by ≤1 mm for the R_{50} value and ≤1-2 mm from the other electron beam parameter values reported by the TPS. However, use of calibration curves generated from different scanners would likely result in different PDDs, as we showed by the percent differences in netOD in Figure 5 and Table S7. From this we can conclude that the relative dose distribution is unperturbed based on when the user scans film as long as the dose calibration curve that was applied came from the same scanner that was used irrespective of film batch or the post-irradiation scan time of the measured film and calibration film.

Concerning the clinical use of film, with the development of patient specific QA equipment such as the ArcCheck (Sun Nuclear Corporation, Melbourne, FL, USA) and Delta4 (ScandiDos, Uppsala, Sweden), film is seldom used anymore in the evaluation of dose distributions of standard intensity-modulated radiation therapy plans[18]. However, their use in high-dose stereotactic treatments is still employed due to the unparallel spatial resolution that can be achieved with film. These treatments are most often delivered using high dose (> 8 Gy) per fraction with emphasis on spatial performance and accuracy in the high-dose region of the dose distribution[19]. For a dose delivery of 8 Gy and utilizing a 24 hour calibration curve as the comparison, these films could be read out between 4 hours and 36 hours post irradiation with only an added uncertainty in dose determination of ≤ 1% (Figure 1 and Table S2). Higher doses would expand this window further. Time specific calibration curves could also be employed which would then reduce this uncertainty further but with the increased effort of having to create specific calibration curves for multiple time points post irradiation. However, we show that the use of (1) a time-specific calibration curve, (2) a standard 24-hour calibration curve from the same batch, or (3) a calibration curve from a different batch of film all showed insensitivity to the choice of calibration applied in the relative dose distribution determination for doses above 6 Gy.

4.2 Long-term evaluation

Our analysis of one batch of EBT3 film that was irradiated, scanned 24 hours later, and then rescanned 2–39 weeks after revealed that the EBT3 film continued to darken for several weeks after irradiation, with the netOD increasing by 1.5% to 7.8% relative to the original value scanned at 24 hours after irradiation at a dose range of 0.5–50 Gy. TG235 reported a 2.5% increase in the measured OD between 24 hours and 14 days after irradiation, and another 2.5% increase 6 months later.[1,20] However, that report and the literature cited within it did not specify the dose range that yielded the 2.5%; our study showed that the increase in netOD several weeks after irradiation to be in fact dose-dependent with a greater percent increase in netOD measured in low doses (< 6 Gy) delivered to film. Palmer et al. found that darkening of EBT3 film after irradiation was a logarithmic function that continued to grow over their 3-month investigation period after doses ranging from 0 Gy to 14 Gy.[21] Their characterization of the absolute change in netOD over time showed that film irradiated to higher doses had a greater absolute change in netOD over time. Pocza et al.[22] evaluated darkening long-term of EBT2 film after irradiation to up to 2 Gy and found that OD increased by up to 15% for films scanned with the red channel at 18 months after irradiation relative to the original scan at 24 hours. Fuss et al. [23] reported that EBT film irradiated to 0.9–8.1 Gy and scanned 4 months later showed a 5.4%-12.4% increase in netOD relative to the netOD measured at 24 hours. From these data, we can conclude that beyond 24 hours, the extent of darkening in irradiated film is less severe than during the first few hours after irradiation. However, we found that the netOD continued to increase beyond 24 hours (Figure 1) and that this will continue for several months after irradiation (Figure 2). We further found that the relative increase in netOD was highest in films irradiated to lower doses, but the absolute increase in netOD was highest in films irradiated to higher doses. However, beyond 24 hours post irradiation, a constant relative increase in netOD as a function of time was found for doses of ≥ 6 Gy (Fig. 2B), thus allowing for the scanning and determination of the relative dose distribution at any time post 24h after irradiation without the use of correction factors for high dose plans.

In examining the calibration curves produced over the same dose range from multiple batches of EBT3 film over a period of 5 years, we found that the calibration was batch-dependent but overall had the least variation when the red channel and higher doses (≥10 Gy) were used indicating that the red channel is the most suitable and most robust channel to use for applications related to single-channel dosimetry.

Some substantial variations in the green and blue channels seem to appear abruptly and remain consistent thereafter, as evidenced by the batches scanned in 10 October 2017 to 4 October 2020 with the green channel and batches scanned in 18 January 2017 to 16 January 2018 with the blue channel. The variation in calibration between batches depended on the color channel used, and no correlation was found between the variation in one channel and that of another between batches. Based on this data, one may argue against triple channel dosimetry for situations where the calibration curves are used across batches, given that introducing the green and blue channel introduces additional uncertainties as presented in this work. We acknowledge some limitations in the retrospective data such as uncertainties in the assumption that the doses delivered for all batches investigated were precisely matched; user-to-user scans of the film were negligible over that timeframe; and that the time of scanning after irradiation may not have been exactly as stated. However, the timeframe of scanning for these 14 batches (18 to 24 hours after irradiation) suggests that the relative change in netOD should be negligible (Table S2).

To the best of our knowledge, this is the first evaluation of multiple batches of EBT3 film irradiated to the same dose range over a period of several years with the goal of tracking variation in netOD across batches over a wide dose-range that is clinically relevant. However, batch homogeneity of EBT2 film was evaluated by Mizuno et al.,[24] who examined homogeneity in the netOD response on EBT2 film from five separate batches that had been irradiated at a single dose of 2 Gy. In comparing the netOD in EBT2 film irradiated with the same dose but from different batches, the differences in netOD were as high as 10% for the investigated dose. This finding is consistent with our observation of a COV of 10.9% in separate film batches analyzed with the red channel. Overall, the results of our study confirm the general recommendation regarding the use of calibration curves specific to each batch of film when EBT3 film is used for dose determination. However, because the shape of the calibration curve remains consistent for EBT3 film over a span of several years as shown in this study, the possibility of generating a "public" calibration curve that can be refitted based on fewer dose measurements specific to a film batch should be explored more closely as a way to simplify radiochromic film dosimetry.

4.3 Scanner dependence

The important take-away from these experiments is the need for consistency in the type of scanner used for irradiated EBT3 film. The same film irradiated on the Epson 10000XL and Epson 11000XL showed a difference in netOD values of up to 2% at the extremes of the dose range investigated, despite the similarities between the two scanners. These differences may have arisen from differences in optical scanning resolution or differences in how scanned images are processed from the internal components of the respective scanners. Regardless, these results highlight the need for consistency in the type of scanner used to acquire the scanned image from film for absolute dose conversions from film, because the error in netOD between scanners will propagate and magnify in dose conversion in the application of calibration curves, thereby obfuscating the dose delivered to film. This experiment could have been improved by a cross-comparison of the same irradiated films, scanned at the same time after irradiation, on scanners of identical make and model (Epson 10000XL) and scanners of different design (such as the Epson V800) to compare variation between scanners of similar and different designs rather than relying on separate film measurements and scans obtained at different institutions.

4.4 Energy dependence

Here, we have shown that the dose-response curves are minimally energy dependent at clinically relevant energy ranges from 0.662-20 MeV, confirming the observations from previous studies[1,25,26], not only in the same batch of EBT3 film but also in different batches purchased in the same year. This demonstrates that film-calibration can be performed for any beam energy in the mega-voltage energy range provided that the film is also used for dosimetry in mega-voltage beams.

4.5 Recommendations

Our findings on how time after irradiation, radiation dose, and type of scanner influence the results of using EBT3 film for dosimetry led us to propose the following general conclusions and guidelines (summarized in Table 1):

The dose response measured in EBT3 film between batches was found to have the smallest variation for red-channel analyses, and that higher doses showed less variation between batches, suggesting that use of the red channel for dose measurements is advantageous when dose is being measured from different batches of film. Furthermore, it is recommended that in calibrating film, the beam energy in the mega-voltage range for x-rays and electrons have no effect in the measured netOD even when measured between batches. We acknowledge that our findings on dose-response ranges are different from those of TG-235, which indicated that the useful clinical dose range for EBT3 film is 0.01–20 Gy[1]. However, in our study we have demonstrated the usability of EBT3 film beyond 20 Gy (up to 50 Gy) for single channel dosimetry, without indication of saturation, which is of considerable utility for novel treatment modalities such as FLASH radiotherapy where the usable dose range may extend beyond that recommended by the manufacturer, especially in treatments involving single fraction deliveries. We found that doses in excess of 10 Gy had substantially smaller uncertainty as to when the netOD was measured after irradiation relative to the measurement at 24 hours. Table 1 is listed below to provide a summary of observations made and their corresponding recommendations.

TABLE 1 Summarized Observations and Recommendations

Observation	Recommendation
Number of intermittent scans (scanner illumination) has a negligible effect on netOD.	No correction factor needed for ≤10 scans.
Scanner dependence is within 3% for scanners of similar make and model but is higher between scanners of different models.	Use the same scanner for calibration and dose readout.
No saturation in film response is observed within a dose range of 0-50 Gy.	Gafchromic EBT3 film is suitable for dosimetry measurements up to 50 Gy even for red channel.
NetOD measured with the red channel has lowest variation of the three channels between batches.	Use red channel to allow easier comparison of doses between batches.
No difference in shape of relative dose distribution regardless of whether time-specific or batch-specific calibration curves are used. This is only applicable if the same scanner was used for the measurement and calibration.	For relative dose measurements using higher doses, films can be scanned at any time without affecting accuracy, and the use of time-specific or batch-specific calibrations are not necessary.
Films with an absorbed dose of >4 Gy can be scanned between 1 hour and 100 hours after irradiation to be within a 2% uncertainty when analyzed with a standard 24h calibration curve. The corresponding numbers to be within 1% uncertainty would be between 4 hours and 36 hours post-irradiation.	If an extra uncertainty in dose readout is unacceptable in film measured outside its calibration time window, the tabulated correction factors can be applied.
Film scanned at a much longer timepoint post-irradiation (e.g. several weeks/months) were found to have a netOD approximately 2-8% larger than their 24-hour measurement at a dose range of 0.5-50 Gy.	Though not recommended, the netOD in film measured several weeks/months post-irradiation can be used to estimate the 24-hour post-irradiation netOD using correction factors presented in this study.
Calibration of EBT3 film with x-ray or electron beams in the mega-voltage energy range yields small difference in the netOD measurement even in different batches	The film response is independent of energy and modality (electrons/photons) in the mega-voltage range.

5 CONCLUSIONS

This analysis of the short-term, long-term, and inter-batch characteristics of EBT3 Gafchromic film irradiated to the full range of clinically relevant absorbed doses showed that the relative response in EBT3 films scanned at different times can be used as a rule of thumb to estimate a correction factor for the netOD of EBT3 films measured at 24 hours after irradiation. We have shown that EBT3 film irradiated to low doses (<10 Gy) required substantially longer post-irradiation wait times than films irradiated to higher doses (>10 Gy) to be within 2% of the netOD value measured at 24 hours after irradiation. Likewise, when irradiated EBT3 film is stored in an environmentally stable location before its expiration, the netOD in the film continues to increase, with film irradiated to lower doses showing greater relative increases in netOD. However, we were able to characterize the dose dependent increase in the netOD over several months and demonstrate a consistent percent increase in signal over-time for delivered doses at 6 Gy or higher, which may be useful for relative dose distribution measurements at this dose range and timeframe. The relative dose distribution of film in terms of normalized PDDs was shown to be robust when the same type of calibration specific to the default scanner was applied, regardless of which timepoint the calibration curve was specific for, or when the film was scanned, or which batch the calibration curve came from. Inter-batch differences in EBT3 film evaluated over a 5-year period revealed lower uncertainty in measured netOD values when film was irradiated to higher doses and analyzed with the red channel. In summary, we conclude that EBT3 film is a robust dosimeter for which the netOD value can be estimated when the time of scanning is known (relative to 24-hours after irradiation); that relative dose response curves remain largely unaffected when a scanner-specific calibration factor is applied; that EBT3 can be calibrated with any beam in the mega-voltage energy range; and that film response shows the least variance when the red channel is used for analysis and the films are irradiated to higher doses (up to 50 Gy).

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REFERENCES

1. Niroomand-Rad A, Chiu-Tsao ST, Grams MP, et al. Report of AAPM Task Group 235 Radiochromic Film Dosimetry: An Update to TG-55 [published online ahead of print 2020/09/30]. *Med Phys.* 2020;47(12):5986-6025.
2. Marroquin EY, Herrera Gonzalez JA, Camacho Lopez MA, Barajas JE, Garcia-Garduno OA. Evaluation of the uncertainty in an EBT3 film dosimetry system utilizing net optical density [published online ahead of print 2016/09/30]. *J Appl Clin Med Phys.* 2016;17(5):466-481.
3. Borca VC, Pasquino M, Russo G, et al. Dosimetric characterization and use of GAFCHROMIC EBT3 film for IMRT dose verification. *Journal of Applied Clinical Medical Physics.* 2013;14(2):158-171.
4. Liu K, Wang YF, Dona Lemus OM, Adamovics J, Wuu CS. Temperature dependence and temporal stability of stacked radiochromic sheets for three-dimensional dose verification [published online ahead of print 2020/10/01]. *Med Phys.* 2020;47(11):5906-5918.
5. Wang YF, Dona O, Liu K, Adamovics J, Wuu CS. Dosimetric characterization of a body-conforming radiochromic sheet [published online ahead of print 2020/02/27]. *J Appl Clin Med Phys.* 2020;21(3):167-177.
6. Devic S, Tomic N, Lewis D. Reference radiochromic film dosimetry: Review of technical aspects. *Physica Medica-European Journal of Medical Physics.* 2016;32(4):541-556.
7. Bazalova-Carter M, Liu M, Palma B, et al. Comparison of film measurements and Monte Carlo simulations of dose delivered with very high-energy electron beams in a polystyrene phantom. *Medical Physics.* 2015;42(4):1606-1613.
8. Karsch L, Beyreuther E, Burris-Mog T, et al. Dose rate dependence for different dosimeters and detectors: TLD, OSL, EBT films, and diamond detectors [published online ahead of print 2012/05/09]. *Med Phys.* 2012;39(5):2447-2455.
9. Romano F, Bailat C, Jorge PG, Lerch MLF, Darafsheh A. Ultra-high dose rate dosimetry: Challenges and opportunities for FLASH radiation therapy [published online ahead of print 2022/04/12]. *Med Phys.* 2022;49(7):4912-4932.
10. Schuler E, Trovati S, King G, et al. Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator. *International Journal of Radiation Oncology Biology Physics.* 2017;97(1):195-203.
11. Schuler E, Acharya M, Montay-Gruel P, Loo BW, Jr., Vozenin MC, Maxim PG. Ultra-high dose rate electron beams and the FLASH effect: From preclinical evidence to a new radiotherapy paradigm [published online ahead of print 2022/01/09]. *Med Phys.* 2022;49(3):2082-2095.
12. Ashraf MR, Rahman M, Zhang RX, et al. Dosimetry for FLASH Radiotherapy: A Review of Tools and the Role of Radioluminescence and Cherenkov Emission. *Front Phys-Lausanne.* 2020;8.
13. Almond PR, Biggs PJ, Coursey BM, et al. AAPM's TG-51 protocol for clinical reference dosimetry of high-energy photon and electron beams. *Medical physics.* 1999;26(9):1847-1870.
14. Arjomandy B, Tailor R, Zhao L, Devic S. EBT2 film as a depth-dose measurement tool for radiotherapy beams over a wide range of energies and modalities [published online ahead of print 2012/02/11]. *Med Phys.* 2012;39(2):912-921.
15. Lewis D, Devic S. Correcting scan-to-scan response variability for a radiochromic film-based reference dosimetry system. *Medical Physics.* 2015;42(10):5692-5701.
16. Lewis D, Micke A, Yu X, Chan MF. An efficient protocol for radiochromic film dosimetry combining calibration and measurement in a single scan. *Medical Physics.* 2012;39(10):6339-6350.

17. Sharma M, Singh R, Dutt S, Tomar P, Trivedi G, Robert N. Effect of absorbed dose on post-irradiation coloration and interpretation of polymerization reaction in the Gafchromic EBT3 film. *Radiat Phys Chem.* 2021;187.
18. Miften M, Olch A, Mihailidis D, et al. Tolerance limits and methodologies for IMRT measurement-based verification QA: Recommendations of AAPM Task Group No. 218 [published online ahead of print 2018/02/15]. *Med Phys.* 2018;45(4):e53-e83.
19. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101 [published online ahead of print 2010/10/01]. *Med Phys.* 2010;37(8):4078-4101.
20. Andres C, del Castillo A, Tortosa R, Alonso D, Barquero R. A comprehensive study of the Gafchromic EBT2 radiochromic film. A comparison with EBT [published online ahead of print 2011/02/10]. *Med Phys.* 2010;37(12):6271-6278.
21. Palmer AL, Bradley D, Nisbet A. Evaluation and implementation of triple-channel radiochromic film dosimetry in brachytherapy [published online ahead of print 2014/09/11]. *J Appl Clin Med Phys.* 2014;15(4):4854.
22. Pocza T, Zongor Z, Melles-Bencsik B, Tatai-Szabo DZ, Major T, Pesznyak C. Comparison of three film analysis softwares using EBT2 and EBT3 films in radiotherapy. *Radiol Oncol.* 2020;54(4):505-512.
23. Fuss M, Sturtewagen E, De Wagter C, Georg D. Dosimetric characterization of GafChromic EBT film and its implication on film dosimetry quality assurance. *Phys Med Biol.* 2007;52(14):4211-4225.
24. Mizuno H, Takahashi Y, Tanaka A, et al. Homogeneity of GAFCHROMIC EBT2 film among different lot numbers. *Journal of Applied Clinical Medical Physics.* 2012;13(4):198-205.
25. Chiu-Tsao ST, Duckworth T, Zhang C, et al. Dose response characteristics of new models of GAFCHROMIC films: dependence on densitometer light source and radiation energy [published online ahead of print 2004/10/19]. *Med Phys.* 2004;31(9):2501-2508.
26. Bekerat H, Devic S, DeBlois F, et al. Improving the energy response of external beam therapy (EBT) GafChromicTM dosimetry films at low energies (</= 100 keV) [published online ahead of print 2014/02/11]. *Med Phys.* 2014;41(2):022101.

Supplementary Material

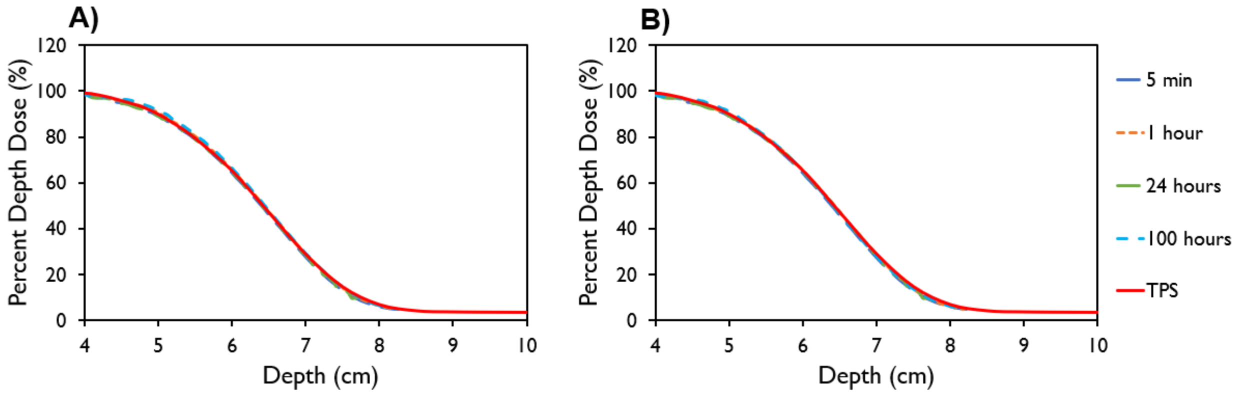

Figure S1. The Percent Depth Dose (PDD) curve of a 16 MeV electron beam beyond the depth of d_{max} measured on EBT3 film with (A) time-specific calibration correction applied to film scanned at 5 min – 100 hours post-irradiation and (B) a general calibration correction (24-hour calibration) applied to film scanned at 5 min – 100 hours post-irradiation.

TABLE S1 Percent difference in net optimal density (netOD) from EBT3 films scanned once at 24 h after irradiation vs films scanned 10 times before the 24-hours-after-irradiation time point. Films were irradiated to 1-40 Gy

Dose, Gy	Percent Difference in netOD, %
1	–0.40
4	0.85
10	0.19
20	–0.16
40	0.23

TABLE S2 Measurements of netOD obtained at designated timepoints normalized to the netOD measurement obtained at 24 hours

	Dose				
Time, h	**40 Gy**	**20 Gy**	**10 Gy**	**4 Gy**	**1 Gy**
0.08	0.98	0.97	0.96	0.95	0.92
0.25	0.98	0.98	0.97	0.96	0.94
0.5	0.98	0.98	0.98	0.97	0.95
1	0.99	0.99	0.98	0.98	0.96
2	0.99	0.99	0.99	0.98	0.97
4	0.99	0.99	0.99	0.99	0.98
8	0.99	0.99	1.00	0.99	0.99
12	0.99	0.99	1.00	1.00	0.99
16	0.99	1.00	1.00	1.00	1.00
24	1.00	1.00	1.00	1.00	1.00
36	1.01	1.01	1.01	1.01	1.03
52	1.01	1.01	1.02	1.02	1.03
76	1.01	1.01	1.02	1.02	1.03
100	1.01	1.01	1.01	1.01	1.03

TABLE S3 Electron beam parameters for EBT3 films, scanned at various times after irradiation, with timepoint-specific calibration curves applied, and parameters entered into the treatment planning system (TPS) based on machine commissioning data. Also shown are the standard deviations of the parameters from three irradiated films, and the percent difference relative to the measured values when a single timepoint-specific (24-hour) calibration curve was applied

	R_{30}, cm	**R_{50}, cm**	**R_{80}, cm**	**R_{90}, cm**
5 minutes	6.93 ± 0.07 (0.4%)	6.38± 0.04 (0.6%)	5.47 ± 0.04 (0.7%)	4.96 ± 0.06 (0.2%)
1 hour	6.95 ± 0.06 (0.4%)	6.43 ± 0.06 (0.2%)	5.49 ± 0.03 (0.2%)	4.93 ± 0.05 (0.4%)
24 hours	6.96 ± 0.04	6.44 ± 0.02	5.47 ± 0.03	5.00 ± 0.06
100 hours	6.96 ± 0.07 (0.1%)	6.42 ± 0.07 (0.5%)	5.51 ± 0.06 (0.4%)	5.03 ± 0.02 (0.4%)
TPS	6.99	6.40	5.50	5.00

R_x, Depth in water of x% of the maximum dose value

TABLE S4 Electron beam parameters for EBT3 films, scanned at various times after irradiation, with a general 24-hour calibration curve applied, and parameters entered into the treatment planning system (TPS) based on machine commissioning data. Also shown are the standard deviations of the parameters from three irradiated films.

	R_{30}, cm	**R_{50}, cm**	**R_{80}, cm**	**R_{90}, cm**
5 minutes	6.96 ± 0.09	6.42 ± 0.05	5.51 ± 0.05	4.95 ± 0.07
1 hour	6.98 ± 0.04	6.44 ± 0.03	5.50 ± 0.04	4.95 ± 0.06
24 hours	6.96 ± 0.04	6.44 ± 0.02	5.47 ± 0.03	5.00 ± 0.06
100 hours	6.95 ± 0.06	6.45 ± 0.04	5.49 ± 0.04	5.01 ± 0.06
TPS	6.99	6.40	5.50	5.00

R_x, Depth in water of x% of the maximum dose value

TABLE S5 Electron beam parameters for EBT3 films, scanned at the same time after irradiation, with different batch calibration curves applied and parameters entered into the treatment planning system (TPS) based on machine commissioning data. Also shown are the standard deviations of the parameters from three irradiated films.

	R_{30}, cm	**R_{50}, cm**	**R_{80}, cm**	**R_{90}, cm**
Batch A	7.02 ± 0.01	6.43 ± 0.06	5.53 ± 0.03	4.98 ± 0.03
Batch B	6.97 ± 0.01	6.44 ± 0.06	5.53 ± 0.03	4.99 ± 0.06
Batch C	6.98 ± 0.05	6.45 ± 0.01	5.54 ± 0.03	4.99 ± 0.06
Batch D	6.94 ± 0.05	6.42 ± 0.02	5.44 ± 0.00	4.97 ± 0.07
Batch E	6.96 ± 0.04	6.42 ± 0.02	5.52 ± 0.01	4.97 ± 0.02
24 hours	6.96 ± 0.04	6.44 ± 0.02	5.47 ± 0.03	5.00 ± 0.06
TPS	6.99	6.40	5.50	5.00

TABLE S6 Coefficients of variation of EBT3 film data (14 calibration curves total) scanned at 18 to 24 hours after irradiation from 2016 to 2021 for the red, green, and blue channels

Dose, Gy	Red, %	Green, %	Blue, %
0.5	19.7	24.4	26.5
1	15.7	20.3	22.8
2	10.9	16.5	19.1
4	5.8	11.5	15.5
6	3.3	8.2	13.7
8	2.0	5.7	12.2
10	1.7	4.7	11.6
13	1.5	3.3	10.3
16	1.6	2.7	8.8
20	1.4	3.0	7.8
25	1.4	3.4	6.8
30	1.4	3.7	5.8
40	1.3	4.2	5.2
50	1.4	4.5	4.9

TABLE S7 Percent differences in netOD response between EBT3 film scanned on the Epson 11000XL-1 vs other film scanners at 24 hours after irradiation to 1, 4, 10, and 20 Gy

Dose, Gy	Epson 10000XL, %	Epson V800, %	Epson 11000XL-2, %
1	–0.13	–2.63	–1.87
4	–0.42	–7.73	–2.54
10	–1.21	–14.37	–2.11
20	–1.10	–19.55	–1.37