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In-vivo dosimetry in total body irradiation using GafchromicTM EBT-3 film: A retrospective analysis for quality assurance

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► ***Original article***

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ABSTRACT

***Background*:** Total Body Irradiation (TBI) is a specialized radiotherapy technique and it varies from routine radiotherapy techniques that involve a complex treatment procedure. It is therefore mandatory to perform an *in-vivo* dosimetry check to ensure dose accuracy and homogeneity during treatment. There is also a clear demand for *in-vivo* dose validation which must be reliable. The primary objective of this work is to review *in-vivo* dosimetry measured for our TBI patients using Film. ***Materials and Methods*:** In this study, *in-vivo* dosimetric data of 185 patients who received TBI during 2015 to 2021 were evaluated. The measurements were performed at 14 anatomical sites using Gafchromic™ EBT-3 film (The Ashland Inc., Bridgewater, USA). For mid-plane dosimetry, a special TBI phantom was designed and used for measurements. ***Result*:** For most of the patients, the *in-vivo* dosimetry result and the mean dose to the whole body were within ±10% (90.1% - 110%) of the prescription dose. The standard deviation was calculated for all the patients and the values were observed between 2.4cGy to 24cGy. Also, the analysis shows that both surface and mid-plane dosimetry were within the acceptable limits of ±10% of prescription dose. The mean mid-plane dose with film and ionization chamber shows 1.5% variation at the umbilicus. ***Conclusion*:** This extensive patient data analysis, as well as the reproducibility of patient dosimetry values and dose homogeneity of ±10% from the prescription dose, proves that the TBI treatments at our center meet the acceptable limits and EBT3 films are reliable in TBI *in-vivo* dosimetry.

INTRODUCTION

Total Body Irradiation (TBI) is a specialized radiotherapy technique performed prior to bone marrow transplantation in the treatment of diseases such as leukemia, lymphoma, and multiple myeloma. TBI is the significant part of the condition regimen for patients undergoing hematopoietic stem cell transplantation (HSTC). In combination with intensive chemotherapy, TBI enables the destruction of tumor cells and immune-suppression in patients undergoing HSTC. Though chemotherapy alone can be used in HSTC, TBI is considered favorable for certain clinical conditions. TBI varies from routine radiotherapy techniques as it is intended to deliver a uniform dose to the entire body that involves a complex treatment procedure such as extended Source to surface distance (SSD), larger field size, lower dose rate, and the use of spoiler [1-3]. It is therefore mandatory to perform an *in-vivo* dosimetry check to ensure dose accuracy and dose homogeneity during treatment [1, 4]. There is also a clear demand for *in-vivo* dose validation which must be reliable and suitable for delivery.

In radiotherapy, TBI can be performed by various techniques. The treatment technique in a specific hospital depends on a number of factors such as photon beam energy, treatment room size, available equipment etc. [1, 3]. Similarly, *in-vivo* dosimetry can be performed with different dosimeters such as thermoluminescent dosimeter (TLD), radiochromic film, semiconductor diodes, optically stimulated luminescence devices, and metal oxide semiconductor field effect transistors (MOSFET) etc. Although a number of TBI studies have been published, the treatment techniques and the dosimeters used were not completely similar. The studies based on anteroposterior-posteroanterior (AP-PA) techniques are very few [4]. In addition, TLD is the most commonly used dosimeter in TBI [5-8] and studies using other dosimeters are very rare. However, the main disadvantage of using TLD is time consuming because the preparation and reading process takes longer. In addition to the complexity of the TBI technique, *in-vivo* dosimetry using TLD may complicate treatment [9]. Alternatively, radiochromic film is less time consuming and more convenient than TLD [9]. Furthermore, there are few uncertainty in using diode and MOSFET as *in-vivo* dosimeter [10-12]. In a busy clinical setup, a dosimeter which is convenient for *in-vivo* dosimetry is preferable for routine quality assurance checks. Despite the fact that radiochromic films have more advantages than TLDs, *in-vivo* dosimetry study using radiochromic films are

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limited.

Furthermore, the dose was prescribed to the mid-plane depth of average patient thickness in TBI treatment and routine *in-vivo* dosimetry provides details on surface dose alone. The actual mid-plane dose is therefore not evaluated. Many studies have shown that the measured entrance and exit doses are used to predict the delivered mid-plane dose [11]. However, this is challenging since surface doses vary with patient thickness and beam energy. The predicted mid-plane might also be overestimated than the actual delivered dose [11]. But, this study will provide details of the actual mid-plane dose along with surface dose. Thus, the primary objective of this work is to review *in-vivo* dosimetry measurements made with Gafchromic™ EBT-3 Film (The Ashland Inc.). This study is noteworthy because quality assurance is an important aspect of radiotherapy since it ensures that patients receive the accurate dose [13].

MATERIALS AND METHODS

Treatment techniques

The AP-PA treatment technique with 6 MV photon beam is used for TBI in our hospital. At an extended SSD of 350/400 cm, the patient was positioned at the lateral decubitus position. During treatment, both arms were placed across the chest to compensate for tissue homogeneity in the lung. A field size of 40×40 cm^2 at isocenter with the collimator rotated through 45 degree was used. A beam spoiler made of 2 cm thick polymethylmethacrylate was used to increase the surface dose. The spoiler is placed in the beam path at a distance 50 cm from the patient surface. For manual dose calculation, the patient anteroposterior (AP) separations at 9 locations such as forehead, neck, chest, abdomen, umbilicus, pelvis, thigh, knee, calf were measured. The treatment set-up is shown in figure 1.

Figure 1. TBI treatment set-up for anteroposterior-posteroanterior technique and the patient was positioned at the lateral decubitus position.

Film calibration

In this study, the Gafchromic™ EBT-3 film (The Ashland Inc., Bridgewater, USA), a commercially available radiochromic film, was used as an *in-vivo* dosimeter. Gafchromic™ EBT film by Ashland is the widely used radiochromic film, with the advantages such as permanent recording, insensitivity to room light, self-developing, energy independence, water resistance, more stability in room light, and high spatial resolution, thus reduces uncertainty. In 2009, the EBT film was replaced by the EBT2 film with a basic change in structure. Later in 2011, the EBT2 film was replaced with the EBT3 film. As per the manufacturer, the improved version of EBT3 avoids the scanning side dependency in EBT2 because of its symmetric structure and prevents Newton ring formation due to the matte polyester substrate. Generally, film calibration has to be done with each new batch of films. The films were cut into 2×2 cm^2 dimensions for the calibration process. Before irradiation, the orientation of the films was marked with a marker in each piece of film. The films were irradiated with 6 MV photon beams of field size 10×10 cm^2 in a solid water phantom of 30×30 cm^2 with thickness 5cm above and below the film. The source-to film distance was 100 cm. The films were irradiated at different dose levels from 0.05-4 Gy, to acquire a calibration curve. As recommended by the manufacturer, after 24 hours, the irradiated films were used for scanning and reading. The flatbed scanner, Epson Expression 10000XL (Epson Inc., USA) and its corresponding software, Epson scan ver.3.49E, were used for scanning. The RIT 113 v.5.2 analysis software (Radiological Imaging Technology Inc., USA) was used for reading. For scanning, the films were placed centrally in the scanner one by one, consistently oriented in the same manner as to eliminate any orientation-based source of error [13]. The films were scanned and digitally converted to .tiff image using scanner. In reading software, with the measured pixel values, the calibration curve has been generated and used for further process.

In-vivo dosimetry

For *in-vivo* dosimetry, the EBT-3 films with 5mm bolus were taped on the patient's skin surface during treatment. The measurement was performed at 13 anatomical sites including the head, neck, thorax, abdomen, pelvis, thigh and calf. At the sites, such as chest, thigh and calf, measurements were performed either on the right or left side of the patient's site of convenience. In our department, a test dose of 20cGy was usually given to a patient for dosimetric verification prior to treatment. Patients were taken for treatment, only after ensuring acceptable dose results from the test dose report. For fractionated treatment (12Gy in 8 fractions /4days,), *in-vivo* dosimetry was performed at every day morning

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fraction.

Demographic

This study was reviewed by the Institutional Ethics Committee- Bio Medical Research at Apollo Cancer Hospital, Chennai and was approved on January 6, 2023 with App. No.: ASH-C-S-002/01-23. In this study, dosimetric data of 185 patients who had received TBI during 2015 to 2021 were included. The majority of patients treated in our center were children under the age of 15 (83.5% children, 16.5% adults). There were 12 men, 18 women, 82 boys, and 73 girls (6.5%, 10%, 44% and 39.5%, respectively) among the patients evaluated. Acute lymphoblastic leukemia (62 patients) was the most prevalent diagnosis, accounting for 33% of all cases. Thalassemia (36 patients), fanconi anemia (31 patients), aplastic anemia (29 patients), acute myelogenous leukemia (20 patients) accounted for respectively (19%, 17%, 16% and 11%). The remaining 7 patients (4%) were diagnosed with different types of lymphoma. Both single dose treatment (2Gy in 1 fraction) and fractionated treatment (12Gy in 8 fractions /4days) data were used in this study. Among the 185 patients, 123 received a single dose fraction while the remaining received fractionated treatment. For analysis, the prescribed dose is normalized to 100% and doses measured at each site in both treatment methods were pooled and evaluated. The patient demographics and diagnosis, are described in figure. Until November 2016, the TBI treatment in our hospital was performed in the linear accelerator (linac), Oncor Expression (Ms. Siemens, Erlangen, Germany). Later in December 2016, the Oncor machine was decommissioned and the TBI is performed in the linac, Artiste (Ms. Siemens, Erlangen, Germany). The study includes data on *in-vivo* dosimetry for patients receiving treatment on both machines. The demographics of patient includes gender and diagnosis is shown in figure 2.

Mid-plane dose measurement

For mid-plane dose measurements, an in-house TBI phantom was designed as shown in figure 3, to simulate the patient. The phantom contains the regions of the head, neck, mediastinum, chest and umbilicus. Head and neck region was designed with anthropomorphic phantom (Accuray Inc., Sunnyvale CA), mediastinum, and chest region with lung phantom (Accuray Inc., Sunnyvale CA), umbilicus region with virtual water phantom (MedTech Inc., Newyork) (density 1.3g/cc) of thickness 18 cm. This phantom was designed to evaluate both the surface and the mid-plane dose and during measurements, the films were taped in both mid plane and surface.

Data analysis

This study examined the minimum dose, maximum dose, mean dose, standard deviation, and P value at each location. Statistical Product and Service Solutions, version 10, was used for statistical analysis. The paired t-test P-values were obtained between the dose at each location and the total mean dose.

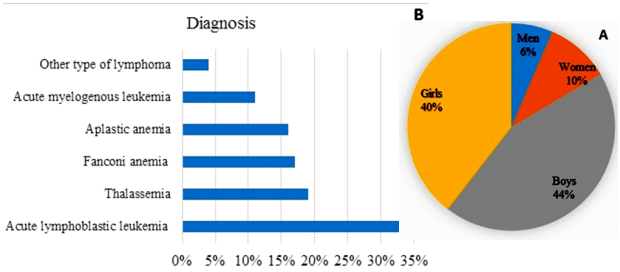

Figure 2. Pie chart showing the Patient gender **(A)**. Bar chart showing the Patient diagnosis **(B)**.

Figure 3. TBI phantom for mid-plane dosimetry.

RESULTS

A retrospective analysis of dosimetry measurements for 185 patients was carried out for the period of 2015 to 2021. The minimum dose, maximum dose, the mean dose, standard deviation, and P value measured at each location were shown in table 1.

For analysis, dose received in both treatment techniques were included and the prescribed dose was normalized to 100%. The mean dose measured at the forehead was 94.2%. The mean dose at the anterior and posterior neck was 100.4%, 99.6% respectively. The mean dose at the anterior and posterior mediastinum, anterior and posterior chest were 94.2%, 97.7%, 97.1%, 97.5% respectively. The mean dose at the umbilicus and posterior pelvis were 95.9%, 97.1% respectively. The mean dose at the anterior and posterior thigh, anterior and posterior calf were 100.8%, 99.9%, 104.5%, 105% respectively. The standard deviation was calculated for all the sites and the values were observed between 4.1 to 7.5%. P-values of 0.000 indicate that there was a significant difference between measurements with total mean dose. A value larger than 0.000 indicates that there

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was no statistically significant difference.

A separate analysis was performed for each site to evaluate dose measurements within ±10% of the prescribed dose and the results are tabulated in table 2. Although the percentage variation of prescribed dose at forehead was 94%, only in 77% of instances the dose range fall within ±10% of prescribed dose. At the anterior mediastinum, in 96% of instances the dose falls within ±10%. At the anterior chest, in 77% of instances the dose range falls within ±10%. Furthermore, at umbilicus, the dose falls within ±10% in 83% of the instances. At the posterior mediastinum, posterior chest, posterior pelvis, the dose was with in ±10% in 90%, 84%, and 89% instances respectively. In most of the cases, the dose at neck falls within ±10%. This same pattern was followed at the posterior and anterior thigh and in maximum instances the dose falls within ±10%. At the anterior calf, in 80% of instances the dose falls within ±10%. Similarly at the posterior calf, in 70% of instances the dose falls within ±10%. To gain a better understanding, a graph was plotted in figure 4 which depicts the number of instances the dose measurements were within ±10% of the prescribed dose.

The main objective of TBI is to deliver a uniform dose to the whole body. To ensure dose homogeneity, the mean dose was calculated for each patient. For most patients, the mean dose to the whole body was close to the prescription dose, and for all patients, it was within ±10% (90.1% - 110%) of the prescription dose. Along with this analysis, standard deviations were calculated for all the patients and the values were observed between 2.4cGy to 24cGy.

In order to further understand the variation in dose and also to check the reliability of the *in-vivo* dosimetry system, a separate analysis was carried out and tabulated in table 3. The mid-plane dose measurement was performed with EBT-3 films and ionization chamber in the TBI phantom. The phantom was placed in the treatment position and the same treatment condition was reproduced. The monitor unit was calculated at a depth of 6 cm and the calculated monitor unit was delivered to a phantom. We chose this depth at random based on our experience treating over 185 patients. Measurements were performed in the head, neck, mediastinum, chest, umbilicus, and pelvis using EBT3 film. In addition, a 0.6 cc farmer chamber (PTW) was placed in the mid plane of the umbilicus region. While measuring the mid-plane dose simultaneously, the surface dose was also evaluated. Thus, both surface dose and mid-plane dose were evaluated and tabulated. For analysis, the prescribed dose is normalized to 100%.

Table 1. Minimum, maximum, mean dose, standard deviation and P value measured at each location.

Location	Measured dose (prescribed dose is normalized to 100%)						
	Minimum	Maximum	Mean	Median	Interquartile range	Standard deviation	P-value
FOREHEAD	77.0	112.0	94.2	94.6	8.7	6.3	.000
ANT NECK	91.0	112.0	100.4	100.0	5.5	4.1	.013
POST NECK	89.0	111.0	99.6	99.3	4.7	4.4	.116
ANT MEDIASTINUM	79.3	113.5	94.2	94.1	10.6	7.5	.000
POST MEDIASTINUM	86.0	113.3	97.7	98.7	8.0	5.5	.030
ANT CHEST	80.2	114.8	97.1	98.0	6.9	6.6	.391
POST CHEST	77.0	112.4	97.5	98.1	6.7	6.6	.137
UMBILICUS	78.0	113.3	95.9	96.6	9.5	6.2	.000
POST PELVIS	84.0	117.0	97.1	97.0	8.0	6.0	.001
ANT THIGH	85.3	116.0	100.8	102.0	9.3	6.3	.002
POST THIGH	83.5	115.3	99.9	100.6	9.9	7.1	.000
ANT CALF	90.0	121.5	104.5	104.5	8.2	6.8	.000
POST CALF	90.0	118.7	105.0	106.7	10.5	6.8	.000

Table 2. Percentage of instance the dose measurements within acceptable range and out of the acceptable range.

Location	Number of instance(%) the dose ranges is		
	<10% of prescribed dose	within ±10% of prescribed dose	>10% of prescribed dose
FOREHEAD	22%	77%	1%
ANT NECK	0%	96%	4%
POST NECK	3%	93%	4%
ANT MEDIASTINUM	27%	71%	2%
POST MEDIASTINUM	8%	90%	2%
ANT CHEST	17%	77%	6%
POST CHEST	11%	84%	5%
UMBILICUS	15%	83%	2%
POST PELVIS	9%	89%	2%
ANT THIGH	9%	83%	8%
POST THIGH	6%	88%	6%
ANT CALF	0%	80%	20%
POST CALF	0%	70%	30%

Table 3. Mean surface doses and mid-plane dose measured in TBI phantom. . For analysis, the prescribed dose is normalized to 100%.

Location	Mean surface dose in %	Mean Mid-plane dose in %	Percentage deviation
Forehead	98	95	3%
Neck	105	104	1%
Chest	103	99	4%
Mediastinum	102	-	-
Umbilicus	100	100	-

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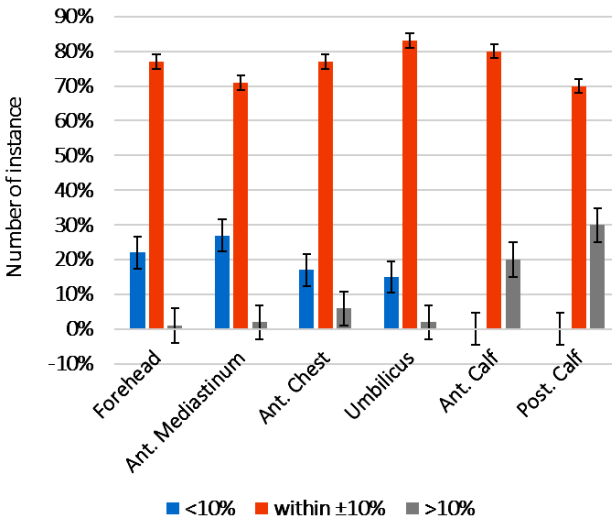

Figure 4. The graph depicts the number of instances the dose measurements were within ±10% of precribed dose at each site.

DISCUSSION

From the table 1 it is noted that the mean dose for majority sites is within the acceptable range of ±10%.

From table 2 and figure 4, it is noted that the analysis shows greater variation in dose at the forehead, anterior chest, anterior mediastinum and calf. At the anterior mediastinum, in 27% of instances the dose was below 10% acceptable limit. This is due to the patient's arm position during treatment. In some cases, the film taped in the mediastinum may be shielded under the patients arm. So this may have an impact on the reading of the film. At the anterior chest, in 17% of instances the dose was below 10% of the prescribed dose. The main reason for this dose variation is due to tissue in-homogeneity in the chest region. Furthermore, at the forehead, in 22% of the instances the dose was below 10%. This is mainly due to the significant difference between the forehead separation and average depth of the patient. The analysis also shows that the forehead separation in the majority of patients is noticeably greater than the average patient depth. The average difference observed was 11.5 cm. Similarly, at the umbilicus, the dose was below ±10% prescribed dose in 15% of the instances. This is also due to the significant difference in the umbilicus separation and average depth of the patient. For the majority of patients the separation is noticeably greater than the average patient depth and the average difference observed was 9.5 cm. Other sites such as neck, thigh in most cases the measured dose is within 10% of the prescribed dose, and the separation is almost equal to the average depth. At the anterior calf in 20% of instances the dose falls above 10% acceptable limit. Similarly at the posterior calf, in 30% of instances the dose falls above 10% acceptable limit. The dose measured is expected to be high, when the calf separation is greater than the average patient depth. The average difference observed was -1 cm. Apart from the above reasons, patient position, patient movements and film position during treatment may also have an impact on the measured dose.

The TBI phantom measurement shows that at the forehead, when the mean surface dose was 98%, the mean mid-plane dose was 95%. At the neck the mean surface dose was 105% and the mean mid-plane dose was 104%.At the chest, the mean surface dose was 103% and the mean mid-plane dose was 99%. The mean surface dose in the mediastinum was 102 %. Mid-plane dose cannot be performed at this site due to the phantom design. At the umbilicus, the mean surface dose was 100% and the mean mid plane dose was 100% with film and 98.5% with chamber. Su *et al.* [9] performed a mid-plane dosimetry in anthropomorphic phantom using EBT film. The dose recorded at the chest and umbilicus correlated well with our study. The lowest agreement was obtained at the forehead, where the dose was 101.5%. Similarly, Llanes Veiga *et al.* [14] also performed mid-plane dosimetry in an in-house TBI phantom using EBT3 film. The mid-plane dose measured at the head, chest, and umbilicus correlated well with our findings. Furthermore, the difference in surface dose to mid-plane dose at the chest and umbilicus is consistent with our results. The umbilicus had the lowest level of agreement. As a result of the analysis using TBI phantom, both surface and mid-plane dosimetry at all the sites using Gafchromic™ EBT-3 Film were within acceptable limits of ±10% of prescription dose and a graph is plotted in figure 5. This analysis proves the accuracy of treatment delivery for our TBI patients.

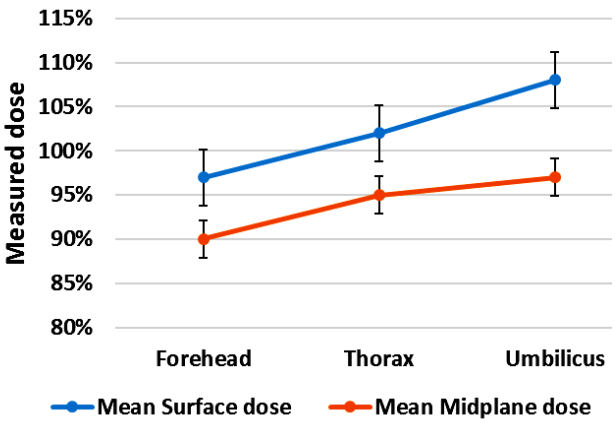

Figure 5. The graph depicts the mean surface dose and mean mid-plane dose measured at each site in the TBI phantom. For analysis, the prescribed dose is normalized to 100%.

As previously stated, while there are several studies in TBI, *in-vivo* dosimetry studies are extremely rare. Additionally the majority of TBI studies were performed on human-like phantoms, which have limitations in providing actual patient dose. Alternatively, our large-scale patient data

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analysis proves the significance of this study. Sengupta *et al.* [12] performed an *in-vivo* dosimetry study in TBI using a MOSFET detector. The dose measured at the chest, umbilicus, and leg were correlated well with the study. The forehead had the lowest agreement, with an average deviation of 8.4% to the prescribed dose. However, the study does not discuss in detail about the dose report beyond these four regions. The study also stated that the accuracy and short life duration of a MOSFET were the major drawbacks of using it in *in-vivo* dosimetry. Additionally, the dose at the fore head correlated well with the results of Lancaster *et al.* [5] measurements using semiconductor diodes. Lowest agreement was observed at the umbilicus, pelvis, and chest. The dose at the umbilicus and pelvis in our measurements were 95.9% and 97.1% respectively, were better compared to 92.8% and 94.8% in their AP-PA technique. Furthermore, the dose measured at the forehead, mediastinum, and umbilicus correlated well with Palkoskova *et al.* [8] Lowest agreement observed at the pelvis and neck.

Though there are various TBI techniques, the bilateral field technique is the most commonly used [4-5]. However, it may increase the dose to the peripheral areas, and the dose will be less homogeneous owing to the significant thickness difference in the patient's lateral position compared to the AP-PA position [15]. So, the dose to the mediastinum is more homogenous in the AP-PA technique than in the lateral field technique.

In general, the study using films in TBI are extremely rare. There is uncertainty in using a diode as an *in-vivo* dosimeter since the sensitivity decreases over time [10]. Similarly, there are certain inherent uncertainties in TLD, such as annealing, calibration method, and TLD readout [4, 9]. According to Best *et al.* [16] handling TLD is labour demanding and needs expensive equipment and a specialized workstation. Furthermore, Choi, *et al.* [11] mentioned that because the MOSFET device requires a cable and a specific reader device, taping the detector for measurement to the patient's skin is quite difficult. These uncertainties may be overcome by utilising gafchromic film, which is very easy to handle and reliable. Su *et al.* [9] mentioned that gafchromic films have advantages over TLD since they are easier to handle and may be moulded to fit the patient's body contour. Furthermore, the film's features, such as self-processing, constant and uniform responses, nearly water-equivalent density, water resistance, insensitivity to ambient light, and energy independence, make it a particularly suited *in-vivo* dosimeter. The mean mid-plane dose with film and chamber shows 1.5% variation at the umbilicus, indicating that our *in-vivo* dosimetry with Gafchromic™ EBT-3 Film is reliable.

The purpose of this retrospective study of 185 patients who received TBI at our center during the period 2016-2021 is to determine the accuracy of dose delivery using Gafchromic™ EBT-3 Film. This extensive patient data analysis, as well as the reproducibility of patient dosimetry values and dose homogeneity of ±10% from the prescription dose, proves that EBT3 films are reliable in TBI *in-vivo* dosimetry. With this observation, we have begun to broaden the mid plane dosimetry measurements to reproduce the entire body, including the thigh and calf regions, and the results will be analyzed in the future to standardize our TBI technique. Based on the results obtained with 185 patients, we also concluded that the TBI treatments at our center meet the acceptable limits of dose variation.

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***Authors Contribution*:** Sundaramoorthy Dhivya wrote the manuscript, Chandrasekaran Anuradha reviewed and revised the manuscript.

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