

Patient Dose Analysis Using Gafchromic™ EBT3 Film: A Retrospective Study with a Four Dual-Field Technique in Total Skin Electron Therapy

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Abstract

Objective: The Six dual-field is the most commonly used treatment technique in total skin electron therapy (TSET). Because of the prolonged treatment period, the patient may experience discomfort, and routine radiotherapy treatments may be affected. This reflects the idea of using a modified technique in TSET. The study aims to report our experience with the four dual-field technique and review the in-vivo dosimetry using gafchromic film. **Materials and methods:** The in-vivo dosimetry reports using gafchromic EBT-3 films of 12 patients who received TSET with the four dual-field techniques in our hospital were analysed in this study. The dosimetric parameter including percentage depth dose, dose homogeneity, flatness and symmetry were analysed in this study. **Results and discussion:** For all the patients, the mean dose to the skin was close to the prescription dose, and it was within 10% (99.3%–103%) of the prescription dose. The standard deviation was observed between 5.8 and 12.4 cGy. According to international standards, all of the measured dosimetric parameters were within the acceptable limit and thereby validating our technique. The in-vivo dosimetry study using radiochromic film in TSET is relatively uncommon. So, based on our results, gafchromic films are a viable choice. The objective of our four dual-field techniques is to reduce the overall treatment time on the machine, whereas our study shows a time reduction when compared to regular techniques, which aids in the smooth operation of daily routines. **Conclusion:** The preliminary results of this novel modified technique in TSET demonstrated favourable effectiveness with minimal skin toxicity. This four dual-field technique is simple and easy to implement. Comparatively, this study shows the dose homogeneity of $\pm 10\%$ and better dose in the underdose areas proving the reliability and homogeneity of four-dual field technique.

Keywords: Total skin electron therapy- In-vivo dosimetry- In-vivo dosimetry in Total skin electron therapy

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Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare neoplasm in the skin. Mycosis fungoides and Sezary syndrome are the common subtypes of CTCL. These diseases can affect a specific area of skin or the entire skin surface. Although these diseases are uncommon, they can have fatal to the sufferers (Korgavkar et al., 2013; Kron et al., 2018). The treatment options include topical steroids, photochemotherapy, and total skin electron therapy (TSET). According to the American Association of Physicists in Medicine TG-30 (AAPM) (Karzmark, 1987) and the European Organization for Research and Treatment of Cancer (Willemze et al., 1997), the recommended dose for CTCL treatment is 30–36 Gy. The treatment should use low-energy electrons, ensuring that at a depth of 2 cm, the dose should not exceed 20% of the prescribed dose and the depth at which 80% of the dose is absorbed should not be less than 4 mm (Karzmark, 1987).

So, the electron energy can be determined between 4 MeV and 8 MeV with a treatment distance of 3–8 m. The daily dose should range from 1–2 Gy. The dose homogeneity should be within $\pm 10\%$ of the prescribed dose (Willemze et al., 1997) and 8% vertically across central 160 cm, and 4% horizontally across central 80 cm (Karzmark, 1987). During treatment, the lens of the eyes and the finger and toe nails should be protected with shaped sheet lead.

TSET is a complex treatment procedure and differs from routine radiotherapy techniques as it is intended to deliver a homogeneous dose to the entire skin surface with maximal sparing of the underlying tissues (Kron et al., 2018; Dhivya et al., 2021). It can be performed using various methods and the two major are the large electron fields and the rotational method. In the large field method, two to eight dual-fields can be used (Karzmark, 1987). Traditionally, TSET is treated with six dual-field, which come under the large field method as proposed by Page et al., 1970. The treatment technique is chosen

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based on factors such as the size of the treatment room, patient comfort, available equipment, etc. (Piotrowski et al., 2003). In some centres, there used to be a dedicated Linear Accelerator (linac) in which some mechanical and electronic adjustments were made solely to deliver TSET. This makes the linac unavailable for regular treatments. Also, the reproducibility and execution of this technique will take a very long time. In a busy clinical setup like ours, routine treatments may be affected due to prolonged treatment times with regular techniques. Furthermore, the objective of TSET is to deliver a uniform dose to the entire skin surface, and proper patient positioning is required throughout the procedure to achieve this uniformity. Moreover, it is desirable to provide maximum comfort for the patient during the procedure (Piotrowski et al., 2013). Piotrowski et al., 2003 stated that it was preferable to provide maximum patient comfort during the procedure. The patient's weight pressure and arm pain from maintaining the arms' position for long duration could affect the patient's position in regular techniques (Fahimi et al., 2021). This reflects the idea of using a modified technique in TSET. This four dual-field technique is intended to address the issues in the traditional Stanford technique.

In-vivo dosimetry is mandatory, to determine the dose distribution to the patient's skin and verify that the prescribed dose to the patient's skin is correct (Karzmark, 1987). The most widely used in-vivo dosimeters for TSET treatments are the thermoluminescent dosimeter (TLD) and the semiconductor diode (Misson-Yates et al., 2019; Dhivya et al., 2021). The study using radiochromic film is extremely rare in TSET (Page et al., 1970; Dhivya et al., 2021). Some studies claim that the main disadvantage of TLD is that it is a time-consuming dosimeter due to the longer annealing, calibration, and reading durations (Ganapathy et al., 2012; Dhivya et al., 2021). Radiochromic film, on the other hand, is a more convenient dosimeter, and the preparation and reading procedures require less time than TLD. Because of its wide dosage range (1- 40 Gy), energy independence, directional independence, response independent of radiation incident angle, and tissue-equivalent, the improved version of GafchromicTM EBT-3 is a suitable choice for in-vivo dosimetry (Moylan et al., 1970). Thus, this study aims to report our experience with the four dual-field techniques in TSET and to review the in-vivo dosimetry using gafchromic film.

Materials and Methods

Treatment protocol

In our hospital, we treat TSET with a modified technique that uses four dual-field (right anterior oblique and left posterior oblique on day 1 and left anterior oblique and right posterior oblique on day 2). For treatment, a 6 MeV electron beam from a linac, Artiste (Siemens, Erlangen, Germany), was used at a high dose rate of 900 MU/min with a 25 x 25 cm applicator. A stand with a perspex degrader and a platform for the patient to stand on was designed. The stand was placed on a beam path at a distance of 330 cm from the isocenter, as shown in Figure 1. The degrader's thickness was 7 mm. The

patient surface to degrader distance was 19 cm. Then oblique angles with 45-degree intervals to the central axis representing the field portals were drawn on a sheet and pasted on the platform of the stand. Two L-shaped angles were fixed to the wall, from which sling-like suspensions were hung to facilitate the patients' keeping their arms in the proper position. The gantry angles for the dual field were chosen based on the patient's height using field light with a 10–12 cm gap between the two field edges as per guidelines (Karzmark, 1987). During treatment, the eyes, fingernails, and toenails were shielded with shaped sheet lead of a thickness of 2 mm.

Percentage depth dose (PDD) and Output Measurement

For PDD measurement, a virtual water phantom of different thicknesses was used. The phantom surface was positioned at a distance of 350 cm from the isocenter. The degrader with a thickness of 7 mm was placed on the beam path at a distance of 19 cm from the phantom surface. For measurement, a 6 MeV electron beam with a gantry angle of 270° and a 25x25 cm applicator were used. The dosimetry was performed with the Markus ion chamber (PTW, Freiburg, Germany) and the UNIDOS E electrometer. For 1000 MU/min, measurements were performed at different depths (surface, 2, 4, 5, 6, 7, 8, 10, 13, 15, 20, 25, 30 mm). The most probable energy (E_p) on the phantom surface was calculated using equation 1 (Semwal, 2020) and the mean energy (E_0) on the phantom surface was calculated using equation 2 (Semwal, 2020).

$$E_p = C_1 + C_2.R_p + C_3.R_p^2 \quad \text{Equation 1}$$

Where $C_1 = 0.22$ MeV, $C_2 = 1.98$ MeV/cm, and $C_3 = 0.0025$ MeV/c, R_p is the practical range.

$$E_0 = C_4.R_{50} \quad \text{Equation 2}$$

Where $C_4 = 2.33$ MeV/cm, R_{50} is the depth at which the dose is 50% of maximum dose

AAPM TG-21 protocol recommended C_1 , C_2 , C_3 , and C_4 values as 0.22 MeV, 1.98 MeV/cm, 0.0025 MeV/c, and 2.33 MeV/cm. The output was measured with the same setup at a depth of 5 mm with a Markus ion chamber and film. The IAEA TRS-398 formalism for output measurement of the electron beam was used to calculate the output, taking into account the ion recombination, polarity correction, temperature, and pressure corrections.

Along with the PDD, the horizontal and vertical profiles for the central axes were measured using films. Horizontal profile measurements were taken at 5 cm intervals, while vertical profile measurements were taken at 10 cm intervals. Furthermore, the horizontal profile was measured for dual-field for gantry angle $\pm 10^\circ$, $\pm 15^\circ$, $\pm 20^\circ$.

Film calibration

The GafchromicTM EBT-3 film (The Ashland Inc., Bridgewater, USA) was used as an in-vivo dosimeter in this study and it was handled by the AAPM Task Group 55 and the manufacturer's recommendations. According to the manufacturer, the upgraded version of EBT3

avoids the scanning-side dependency in EBT2 due to its symmetric construction, and the matte polyester substrate avoids Newton ring development. The film is made up of a nominally 28 μ m thick active layer sandwiched between two 125 μ m matte polyester substrates. The active layer contains the active component, a marker dye, stabilizers, and other components that contribute to the film's near-energy independence. Each new batch of films requires film calibration, and the films were cut into 2x2 c dimensions for the calibration process. In a solid water phantom measuring 30x30x30 cm³ at a depth of 5 cm, the films were exposed to 6 MV photon beams with a field size of 10x10 c. The distance between the source and the film was 100 cm. The films were irradiated at various dose levels ranging from 0.05–4 Gy to acquire a calibration curve. The irradiated films were scanned after 24 hours using the flatbed scanner Epson Expression 10000XL and its corresponding software, EPSON SCAN ver. 3.49E. For reading, the RIT 113 v.5.2 analysis software (Radiological Imaging Technology, Inc., USA) was used. The scanner was set to 48-bit RGB (red, green, blue) mode, and each film was read at 300 dpi resolution. Following scanner warm-up, the films were placed in the centre of the scanner in the orientation marked. The scanned films were stored in TIFF format. For reading, the RIT 113 v.5.2 analysis software (Radiological Imaging Technology, Inc., USA) was used. The optical density (OD) value was generated from the saved TIFF image. The OD is a logarithmic ratio of the intensity of the unexposed film to the intensity of the exposed film. The region of interest of each film was selected to avoid sources of inaccuracy. Because the film's edges may be damaged during the cutting process, or dust particles may become trapped in the film. This can be avoided by selecting ROI. In the reading software, the calibration option was selected. The pixel number was measured for each exposed film, and the system generates a table for the corresponding measured value. After creating the table, the calibration file was saved, and the OD curve was generated and used in the further steps

Demographic

This study received approval on January 6, 2023, by the Apollo Cancer Hospital's Institutional Ethics Committee - Biomedical Research with App. No.: ASH-C-S-002/01-23. This study analyzed the in-vivo dosimetry result of 12 patients (11 male (91.7%), and 1 female (8.3%)) who received TSET treatment between 2022. Among the 12 patients, 9 were diagnosed with Mycosis fungoides (75%), and the remaining 3 patients were diagnosed with Sezary syndrome (25%). The median age at diagnosis was 65 years (range: 28-75 years). Four patients were treated with 36 Gy in 30 fractions, five with 33 Gy in 33 fractions, and three with 30 Gy in 30 fractions.

In-vivo dosimetry

In-vivo dosimetry measurements were executed at the anatomical sites such as the scalp, forehead, anterior and posterior chest, right and left axilla, umbilicus, pelvis, groin, anterior thigh, medial thigh, and calf. During treatment, gafchromic EBT-3 films with a 5mm bolus were taped to the patient skin surface at the measurement sites.

For a female patient, measurements were also performed in inframammary folds. Because TSET is a fractionated treatment, in-vivo dosimetry was carried out every day for the first ten fractions and on alternate days for the remaining fractions for all patients.

Statistical analysis

For analysis, the Statistical Product and Service Solutions, version 10, was used. The paired t-test p-values for the total mean dose and measured dose at each site were calculated. P-values of 0.000 show that there was a significant difference and a number greater than 0.000 implies that the difference was not statistically significant.

Results

As per the PDD curve Figure 2, the percentage surface dose (Ds) was 89.7% and the maximum dose point position (Zmax) was 5 mm. The Rp was 2 g/c, and the depth at which the dose is 50% of the maximum dose (R50) was 1.4 g/c. Thus, Ep and E0 were obtained as 4.19 MeV and 3.26 MeV, respectively. Table 1 summarises the dosimetric parameters measured on the phantom.

From Figure 3, it is observed that the symmetry field at 350 cm was $\pm 0.57\%$ for the horizontal profile and $\pm 1.83\%$ for the vertical profile. Similarly, the flatness obtained was $\pm 5.29\%$ for the horizontal profile and $\pm 4.95\%$ for the vertical profile. From Figure 4, for a dual beam with a gantry of ± 100 , the flatness was $\pm 5.3\%$ and the symmetry was $\pm 1.86\%$. For the gantry ± 150 , the flatness was $\pm 6.04\%$ and the symmetry was $\pm 1.21\%$. For the gantry ± 200 , the flatness was $\pm 5.97\%$ and the symmetry was $\pm 1.33\%$.

In this study, the in-vivo dosimetry reports of 12 patients who received TSET in our hospital using gafchromic EBT-3 films were analyzed. As previously stated, in-vivo dosimetry was performed on all patients on a daily basis for the first ten fractions and on alternating days for the remaining fractions. For analysis, the dose is normalised to 100%. Table 2 shows the minimum, maximum, median and average dose measured at each location for all patients. Figure 5 shows the percentage deviation from the prescribed dose at each location. The average dose measured at the forehead and scalp was 101% and 92%. The average doses on the shoulder, anterior, and posterior chest were 93%, 108%, and 112% respectively. In the right and left axilla, the dose measured was 99% and 106%, respectively. In the umbilicus, posterior pelvis, and groin, the doses measured were 110%, 101%, and

Table 1. Summarise the Dosimetric Parameters Measured on the Phantom.

Dosimetric Parameters	Measured values
Percentage Surface dose (Ds)	89.70%
Maximum dose point (Zmax)	0.5 cm
Practical range (Rp)	2 g/cm ²
Depth at which the dose is 50% of maximum dose (R50)	1.4 g/cm ²
Most probable energy (Ep)	4.19 MeV
Mean energy (E0)	3.26 MeV

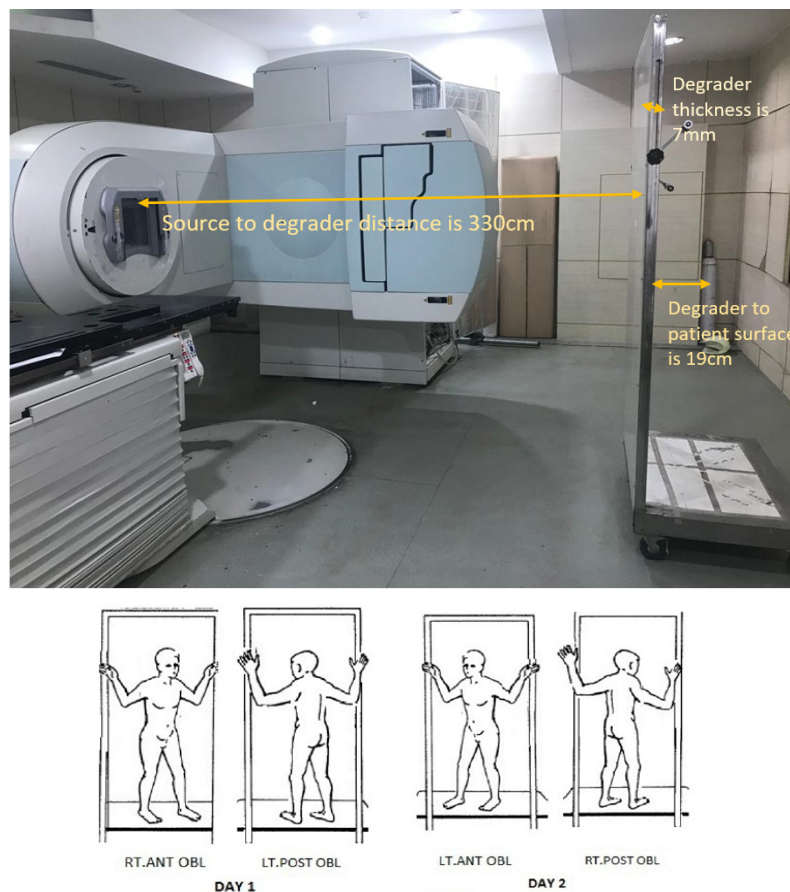


Figure 1. Shows the Total Skin Electron Therapy Treatment Set-up and Orientation

88%, respectively. In the anterior thigh, medial thigh, and calf, the dose measured was 111%, 91%, and 107%, respectively. For a female patient, the inframammary fold dose was 91%. For all the location, the standard deviation was calculated, and the values were observed between 5.1 and 11.1 cGy.

Table 3 shows the mean and standard deviation values calculated for each patient. The main objective of TSET

is to deliver a uniform dose to the entire skin. To ensure dose homogeneity, the mean dose was calculated for each patient. For all the patients, the mean dose to the skin was close to the prescription dose, and it was within $\pm 10\%$ (99.3%–103%) of the prescription dose, as shown in Figure 6. Along with this analysis, the standard deviation was calculated, and the values were observed between 5.8 and 12.4 cGy.

Table 2. Shows the Average Dose Measured at Each Location for All Patients. For analysis, the dose is normalized to 100%.

Location	Number of measurements	Minimum	Maximum	Average	Median	Standard deviation	Interquartile range	p value
Forehead	243	88.2	110.1	101.2	100.2	6.5	8.3	0.072
Scalp	235	86	112.4	92.3	92.6	10.3	12.5	0.006
Shoulder	251	91.4	115.7	92.9	92.5	5.3	7.2	0
Anterior chest	241	91.8	117.2	108.3	108.0	8.2	9.2	0.213
Posterior chest	238	95.3	115	111.9	111.2	7.3	8.4	0.012
Right axilla	245	91.2	108.6	99.1	98.1	9.1	10.2	0.031
Left axilla	238	92.5	108.2	106.2	104.8	6.2	7.5	0.213
Umbilicus	245	90.2	114.6	110.3	111.2	7.2	8.4	0.312
Posterior pelvis	241	93.4	118.4	100.8	101.8	6.3	8.2	0.412
Groin	238	82.3	93.8	87.9	89.0	7.3	7.8	0.002
Anterior thigh	235	95.6	117.3	111.4	112.1	6.7	7.3	0.001
Medial thigh	238	84.6	107.1	90.6	91.3	10.4	11.8	0
Calf	240	92.8	113.2	107.4	106.4	11.2	12.1	0.042
Inframammary Fold	24	81.2	92.3	88.6	89.8	5.1	7.3	0.213

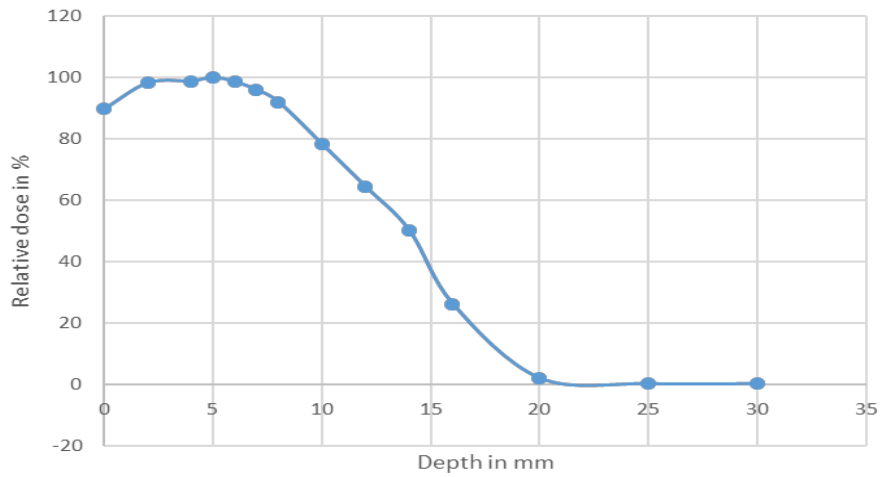


Figure 2. Shows the Measured PDD Curve

Discussion

The recommended Z-max range is 0.5 to 1.5 cm. In our technique, the Z-max value measured was 0.5 cm. Platoni et al., (2012) in their study with a 6 MeV electron in TSET, reported a Z-max of 7 mm. Also, the R50, Rp,

Ep, and E0 values were 1.5 cm, 2.1 cm, 4.4 MeV, and 3.4 MeV, respectively. Similarly, for a flattened 6 MeV electron, Reynard et al., (2008) observed that the Z-max, R50, and Rp were 0.9 cm, 1.8 cm, 2.8 cm, 5.6 MeV, and 4.1 MeV, respectively. Furthermore, Fahimi et al., (2021) reported the Z-max, R50, Rp, Ep, and E0 values as 0.7

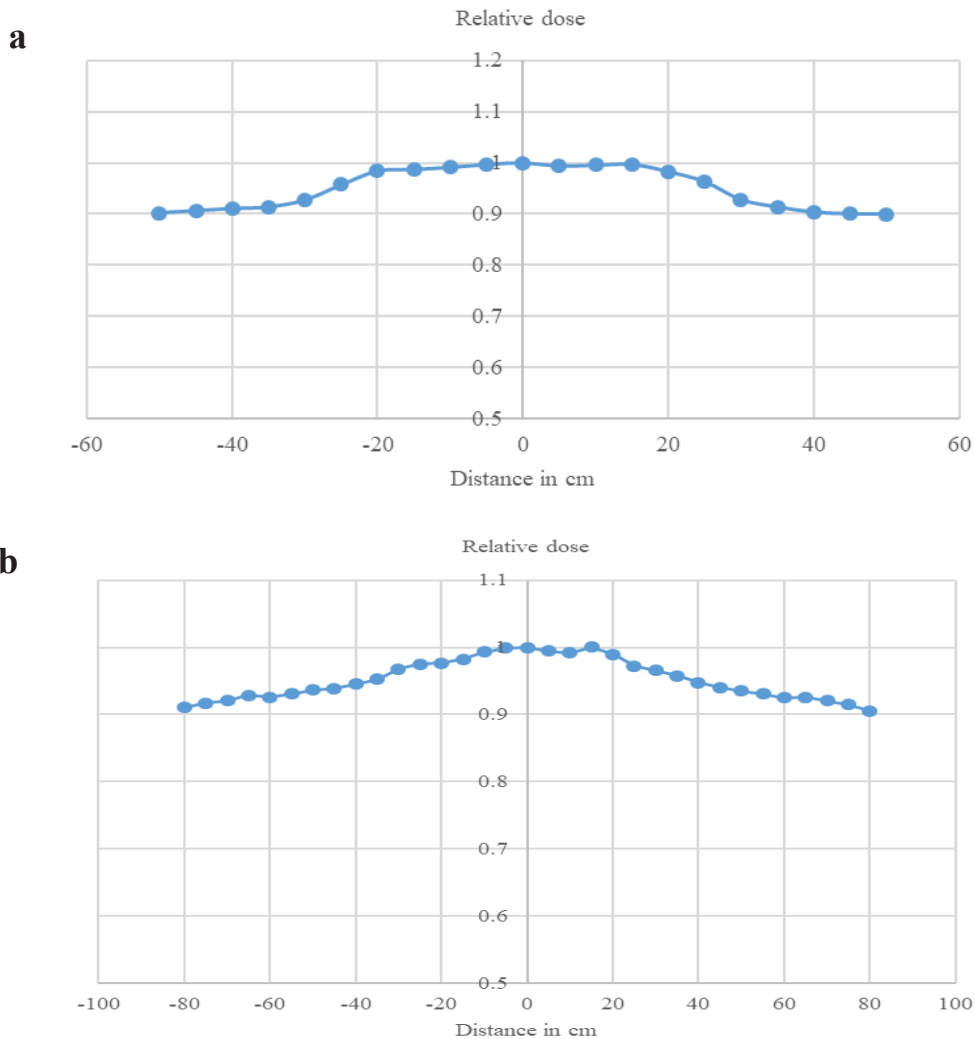


Figure 3. Shows the Measured Dose Profile for the Vertical and Horizontal Central Axes

Table 3. Shows the Mean and Standard Deviation Values Calculated for each Patient

No. of Patients	Average dose (%)
Patient1	101.5 ±8.9
Patient2	100.8 ±12.4
Patient3	100.8 ±11.8
Patient4	100.9 ±7.5
Patient5	102 ±9.5
Patient6	101.5 ±5.8
Patient7	102.5 ±9
Patient8	99.3 ±10.7
Patient9	101.1 ±11.5
Patient10	103 ±10.1
Patient11	101.7 ±9.4
Patient12	101.2 ±6.5

cm, 1.5 cm, 2.1 cm, 4.4 MeV, and 3.4 MeV, respectively. The PDD values in our study were well correlated with those in the Platoni et al., (2012) and Fahimi et al., (2021) studies. Alternatively, the lowest agreement was observed with Reynard et al., (2008) since the measurements were performed with a filter.

All three of our measured composite beams meet the requirements of the acceptable vertical uniformity of 8% and the acceptable horizontal uniformity of 4%. Furthermore, Pagnan-González et al., (2015) observed a horizontal uniformity of 3.62% and a vertical uniformity of 14.2% at 500 cm SSD. Similarly, El-Khatib et al., (1995) reported a vertical uniformity of 8% for a single beam in their treatment approach. Our measurement shows a vertical uniformity of 5% for a single beam. For dual beams, the maximum observed vertical uniformity was 6.04%. The photon contamination was estimated

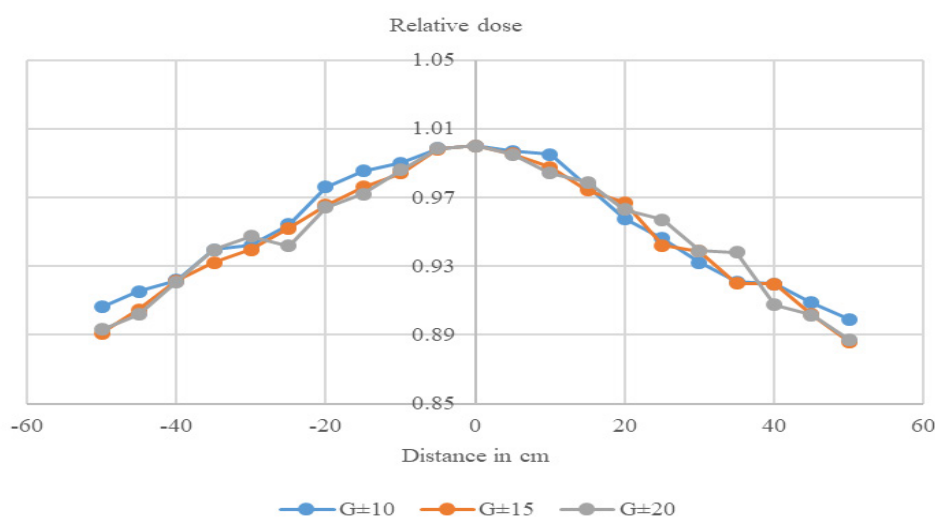


Figure 4. Shows the Measured Dose Profile for the Gantry Angle ±10°, ±15°, ±20°.



Figure 5. Shows the Percentage Deviation from the Prescribed Dose at Each Location

Table 4. Shows a Comparison of Four Dual Field Technique with Six Dual Field Technique

Techniques	Prescribed dose per fraction in (cGy)	Set-up time for per field (min)	Irradiation time for per field (min)	Average time for total treatment per day (min)
Four dual-field	100	5	2.15	32
Six dual-field	100	5	2.15	48

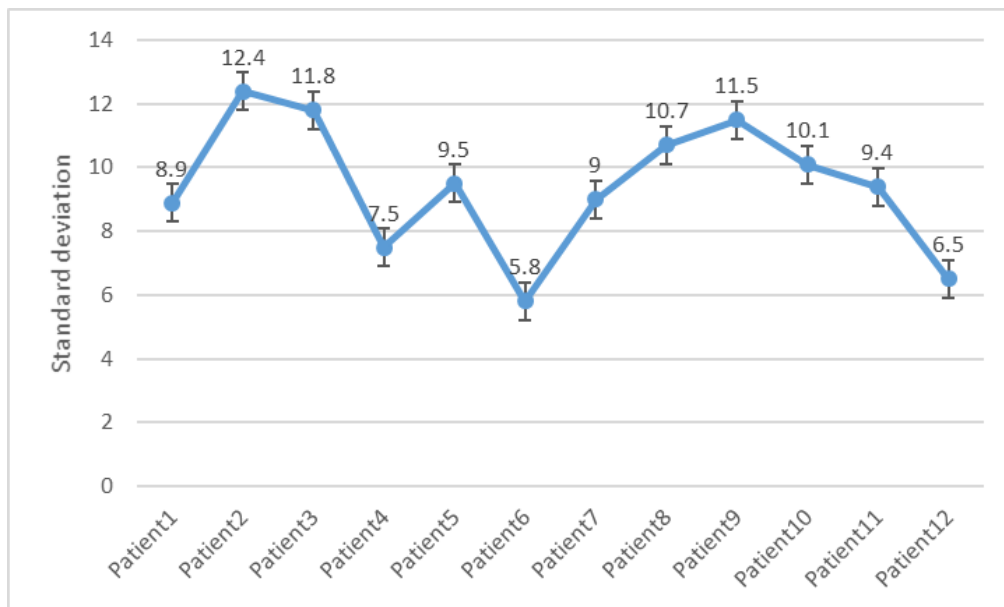


Figure 6. Shows the Measured Mean Dose for All the Patients

Table 5. Shows the Average Dose Measured at Each Location for a Patient in Six Dual Field Technique. For analysis, the dose is normalized to 100%

Location	Average dose (%)
Forehead	108
Scalp	95
Shoulder	97
Anterior chest	125
Posterior chest	119
Right axilla	105
Left axilla	102
Umbilicus	123
Posterior pelvis	122
Groin	90
Anterior thigh	118
Medial thigh	89
Calf	116

by dividing the dose in the phantom at the depth behind the practical range by the surface dose (Nevelsky et al., 2016). The complete treatment photon contamination was estimated by multiplying the measured contamination from one field by eight fields. As per this method, the measured photon contamination for a single field was 0.11%, and for the complete treatment, it was 0.88%. The recommended photon contamination should be less than 1%. All of the dosimetric parameters we measured were within the acceptable limit, thereby validating our technique.

The non-homogeneity of dose distribution in the treatment plane air should not exceed $\pm 10\%$ (Willemze et al., 1997). As per our study, the mean dose measured at the majority of sites was within $\pm 10\%$ of the prescription dose. The variation was observed at the scalp, groin, and

medial thigh. In many studies, these sites were referred to as “underdose areas” (Dhivya et al., 2021). In general, in-vivo dosimetry studies in TSET are limited, and studies using gafchromic film are extremely rare. Misson-Yates et al., (2019) performed an in-vivo dosimetric study in six dual-field technique using TLD. The dose was well correlated with our study, in the majority of sites. The lowest agreement was observed in the axilla and medial thigh. The study reported an average dose of 71% in the axilla and 50% in the medial thigh. The dose at the scalp and groin showed the lowest agreement with Piotrowski et al., (2003). The study has reported that the doses to the scalp and groin were 52% and 38%, respectively, using TLD. Similarly, Elsayad et al., 2018 reported that the dose to the axilla was 69%. Furthermore, the dose to the inframammary folds in a female patient shows the lowest agreement with the study by Weaver et al., (2005) using TLD. The study reported an average dose of 40%, whereas our study shows an average dose of 88.6% to the inframammary fold. Thus, the dose measured at the underdose area in our study was better than in other studies, and the mean dose in the majority of sites was within $\pm 10\%$, proving the high homogeneity of our study.

According to Fahimi et al., (2021) the patient’s weight pressure and pain in the arms from retaining the arms’ position during treatment may influence the patient’s posture in the standing method. Furthermore, Platoni et al., (2012) stated that the drawback of the standing TSET method was patient exhaustion from the prolonged treatment duration. For an older patient, a static posture for at least 20 minutes may be uncomfortable. In addition to the complexity of the treatment process, movement during treatment may affect delivery. Thus, the goal of our four dual-field technique is to reduce the overall treatment time on the machine as well as the patient’s discomfort. In Table 4, a comparison of treatment techniques is shown. Based on the table, the estimated total treatment time

per day for the six dual-field technique is 48 minutes, and for the four dual-field techniques is 32 minutes. In a busy clinical set-up like ours, where 50–70 patients are being treated on a machine, this time reduction of 16 minutes per fraction helps in the smooth functioning of the daily routine. To understand better, we used the Stanford technique on a patient for four fractions. It consists of a six dual-field technique with six positions spaced at 60-degree intervals. When compared to the four dual-field techniques, we observed field overlapping in the six dual-field technique. The dosimetric analysis revealed a more heterogeneous dose distribution with this technique. When compared to other sites, dose variations of more than 20% of the prescribed dose were observed in the anterior chest, posterior chest, umbilicus, and posterior pelvis, and the results were tabulated in Table 5. So we stopped using the six dual-field technique and completed the remaining fractions with the four dual-field technique on the patient. As a result of this analysis, our technique had less skin toxicity.

Output measurement with the Markus ionisation chamber and film shows a deviation of less than 0.5%, demonstrating the reliability of the film. TLD is a labor intensive dosimeter that requires expensive equipment and a specialised workstation (Best et al., 2005). Furthermore, annealing, calibration, and readout have some inherent uncertainties in TLD (Weaver et al., 1995; Ganapathy et al., 2012). Additional to the complexity of the treatment technique, TLD as an in-vivo dosimeter may complicate the treatment. Gafchromic films are a more convenient dosimeter, and the preparation and reading processes are also less time-consuming compared to TLD. But only limited studies were available for dosimetry with film in TSET. So based on our result, gafchromic films are a viable replacement for TLD in TSET in-vivo dosimetry. The current study has a limitation in that we failed to correlate the obesity index with dose despite many studies proving the correlation between dose and weight and height.

The preliminary results of this novel modified technique in TSET demonstrated favourable effectiveness with minimal skin toxicity. The four dual-field technique in TSET is simple and easy to implement. All our measured dosimetric parameters were within the recommended range. Comparatively, this study shows the dose homogeneity of $\pm 10\%$ and better dose in the underdose areas proving the reliability and homogeneity of four-dual field technique. With this outcome, we have expanded our in-vivo dosimetry work by correlating the obesity index with the dose.

Author Contribution Statement

Sundaramoorthy Dhivya wrote the manuscript, Chandrasekaran Anuradha reviewed and revised the manuscript..

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Ethical Considerations

The Institutional Ethics Committee- Bio Medical Research at Apollo Cancer Hospital approved this study on January 6, 2023, with App. No.: ASH-C-S-002/01-23.

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