



Original Research Article

In-vivo dosimetric analysis in total skin electron beam therapy

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ABSTRACT

Background and purpose: Thermoluminescent dosimetry (TLD) is an important element of total skin electron beam therapy (TSEBT). In this study, we compare radiation dose distributions to provide data for dose variation across anatomic sites.

Materials and methods: Retrospectively collected data on 85 patients with cutaneous lymphoma or leukemia underwent TSEBT were reviewed. Patients were irradiated on two linear accelerators, in one of two positions (standing, $n = 77$; reclined, $n = 8$) and 1830 in vivo TLD measurements were obtained for various locations on 76 patients.

Results: The TLD results showed that the two TSEBT techniques were dosimetrically heterogeneous. At several sites, the dose administered correlated with height, weight, and gender. After the first TLD measurement, fourteen patients (18%) required MU modification, with a mean 10% reduction (range, -25 to $+35$). Individual TLD results allowed us to customize the boost treatment for each patient. For patients who were evaluated in the standing position, the most common underdosed sites were the axilla, perineum/perianal folds, and soles (each receiving 69%, 20%, and 34% of the prescribed dose, respectively). For patients evaluated in a reclining position, surface dose distribution was more heterogeneous. The sites underdosed most commonly were the axilla and perineum/perianal folds (receiving less than one third of prescribed dose). Significant variables were detected with model building.

Conclusion: TLD measurements were integral to quality assurance for TSEBT. Dose distribution at several anatomical sites correlated significantly with gender, height, and weight of the treated individual and might be predicted.

1. Introduction

Total skin electron beam therapy (TSEBT) is a radiation modality for patients with diffuse cutaneous lymphoma and skin manifestations of leukemia [1,2]. The use of TSEBT for cutaneous lymphoma differs widely among treatment centers. The most commonly used technique for radiation treatment is performed with the patient standing [3,4]. Patients who are unable to stand during treatment receive treatment in a reclining position [5,6]. Though several reports on dose variation have been published, no previous study has included a systematic evaluation of dosimetric differences among techniques [7–9]. Due to anatomical or technical variations, certain areas of the body may be “shadowed” or underdosed during TSEBT [10–12]. In vivo dosimetry allows for the identification of areas that should receive significantly less radiation. A thermoluminescent dosimeter (TLD) is typically used for in vivo dosimetry during TSEBT. Areas that often receive boosts include the top of the scalp, perineum/perianal region, upper inner

thighs, and soles of the feet [4,8,9,13]. Additionally, inframammary folds in women and other skin folds (e.g., panniculus in obese patients) must be considered [8,11].

Currently, low-dose TSEBT is commonly used because this approach involves a short course of radiation, and patients report superior tolerability [14–17]. While TSEBT is one of the most effective modalities for treatment of cutaneous lymphoma, measuring TLD is time consuming and limits the availability of TSEBT at many institutions.

In this study, we compare patient dose distributions as a quality assurance check for patients receiving TSEBT in order to provide dose recommendations for boosts in the era of low-dose TSEBT.

2. Materials and methods

2.1. Radiation technique

From January 2000 to June 2017, eighty-five courses of TSEBT

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radiation for cutaneous lymphoma (T-cell, $n = 74$; B-cell, $n = 7$) and leukemia cutis ($n = 4$) have been completed. For this study, 68% of those who participated were male. We used modified Stanford technique to deliver TSEBT to 77 patients (91%) [3,18,19]. The remaining eight patients (9%) were not able to stand during the course of radiation; they underwent TSEBT for multiple segmental fields in a reclining position. The high dose rate electron beams with 6 or 9 MeV electron energy from a Siemens primus ($n = 44$) or Varian truebeam linear accelerator ($n = 41$) were used. External eye shields were routinely used during wide-field skin irradiation to protect the cornea and lens. Nails of the hands and feet, other than the shielded regions involved with lymphoma manifestations, were usually shielded to preserve nail growth.

2.2. In-vivo dosimetry

TLDs are considered the most appropriate dosimeters due to their small size, reusability, and nearly tissue equivalent density. In this study, TLD-100 rods (LiF:Mg,Ti; diameter: 1×6 mm) were used for TSEBT measurements. The readout was done using a Harshaw 5500 automated TLD-Reader. To double-check the evaluation, ten TLDs from the same batch were used as control dosimeters. They exposed to a single dose of 2 Gy with the same energy. Reading of first group of the control dosimeters was done at the beginning and the second group at the end of the cycle. This enabled us to determine if fading or other unexpected changes applied to the batch. The thermal treatments of the TLDs were done for bleaching of the previous dose information in TLD PTW annealing oven heats on 400°C for 10 min.

TLD measurements of the prescribed skin dose were obtained for 76 patients (89%). To document dose measurements, TLD rods were taped to the surface of the patient's skin at various locations on the body. All TLDs were affixed and measured by the same physicist. Each TL dosimeter was heated by hot nitrogen gas stream to 135°C for 15 s – this minimize the fading effect of the dosimeters. After the temperature increased to 240°C with a heating ramp of 10°C/s with a 33 s hold. During this time the light emission was measured, which is related to the absorbed dose by the TLD (Fig. 1). TLDs were typically measured on the first or second day of treatment, and all results were reported as a percentage of the prescribed dose. The reference point for the given dose was located at the anterior abdominal wall. Variation in TLD measurements was analyzed to determine the dose variation during TSEBT for various areas of the body. Several areas were underdosed according to EORTC criteria [20]. Scatter plots of measured dose vs. patient height, weight, and body mass index (BMI) were generated, and correlation coefficients were calculated. Dosimeters were placed symmetrically when applicable. For female patients, extra dosimeters were

placed in the inframammary region when needed. Various other locations were measured individually, as determined by clinical situation and physical characteristics.

2.3. Patients characteristics

Median age of the patients was 64 yr (range, 26–87). Heights ranged from 154 to 192 cm; weights ranged from 51 to 130 kg. Male patients had greater median height [176 (IQR: 10) vs. 160 cm (IQR: 6), $P < 0.001$] and median weight (78 vs. 70 kg, $P = 0.003$). Median BMI was 26 (range, 19–39; IQR, 4.4), without significant difference between males and females (25 vs. 27, $P = 0.14$). Median surface dose was 30 Gy (range, 6–40 Gy). The entire wide-field skin surface received a median fraction dose of 1.6 Gy (range, 0.5–2 Gy) in a given day. All patients treated after 2011 ($n = 41$) received low-dose regimens (median dose: 12 Gy; median fraction dose: 1.5 Gy). Median monitor unit calculation was 575/Gy (range, 396–867). Boost or supplemental radiation was delivered to 70/85 patients (82%) to compensate for underdosing in shadowed body areas or for treatment of large lymph nodes/tumorous lesions. Dose required to deliver a full prescribed TSEBT dose was calculated from TLD measurements and delivered using daily median fraction dose of 2 Gy (range, 1–4). Fifteen patients (18%) did not receive additional radiation due to non-compliance or poor clinical conditions.

Median follow-up was 16 mo (range, 1–185). Three months after completion of radiotherapy, palliation was achieved in 71 patients (83%). A clinically complete response was documented in 47 patients (55%); partial response was documented in 24 patients (28%). Median time to skin progression (duration of clinical benefit) was 16 mo (95% CI: 10–22). After completion of TSEB, median overall survival (OS) was 23 mo (95%-CI: 0.7–45). Clinical outcomes are presented in Table 1.

2.4. Statistics

All statistical analyses were conducted with IBM SPSS Statistics 24.0 software. Mean change is reported with standard deviation (SD). Spearman's rank correlation coefficient (r) values were calculated to analyze TLD measurements. A χ^2 or Fisher exact test was performed to probe relationships between categorical variables. Two-sample U test was used to study the relationship between categorical and continuous variables. T -tests were used to analyze differences between paired samples. Differences were considered statistically significant at $p < 0.05$.

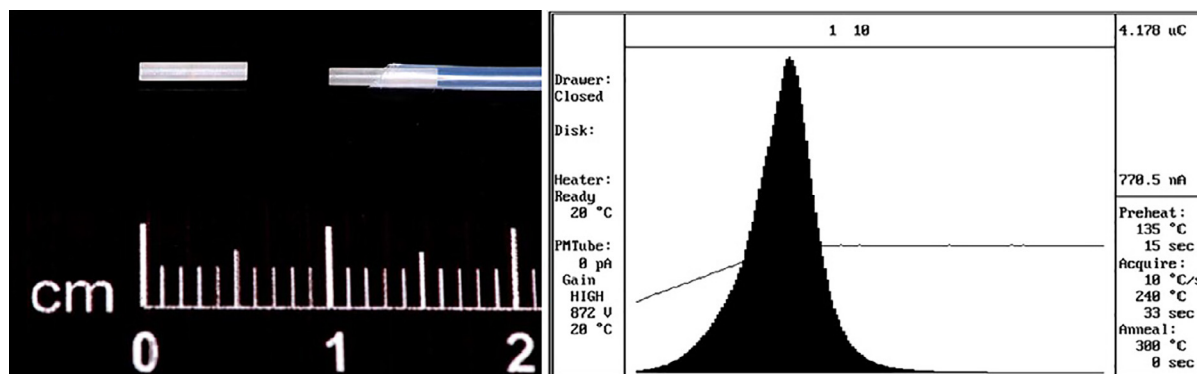


Fig. 1. The left picture points the TLD-100 size: a diameter of 1 mm and a length of 6 mm. The right side shows a typical glow curve of the TLD-100 during the evaluation of the light signal. Downright is written the thermal handling of the TLDs. The intensity of the emitted light is related to the dose absorbed by the TLD.

Table 1
Patient outcomes (n = 85) regarding diagnosis and treatment characteristics.

Characteristic	Nr. of patients	ORR (CR)%	Median PFS (months)	Median OS (months)
<i>Whole cohort</i>	85	83 (55)	16	23
<i>Diagnosis</i>		<i>P = 0.07</i>	<i>P = 0.01</i>	<i>P = 0.16</i>
CTCL				
Primary	72	85 (54)	16	21
Secondary	2	50 (0)	2	2
CBCL				
Primary	4	100 (75)	> 120	> 120
Secondary	3	33 (33)	3	> 50
LC	4	100 (100)	10	16
<i>Position</i>		<i>P = 0.6</i>	<i>P = 0.4</i>	<i>P = 0.6</i>
Standing	77	84 (56)	16	25
Reclined	8	75 (50)	6	18
<i>TLD</i>		<i>P = 0.6</i>	<i>P = 0.4</i>	<i>P = 0.9</i>
Yes	76	78 (54)	13	47
No	9	84 (67)	26	21
<i>Boost</i>		<i>P = 0.01</i>	<i>P = 0.4</i>	<i>P = 0.5</i>
Yes	70	89 (57)	16	20
No	15	60 (46)	16	51

ORR, overall response rate; CR, complete response; PFS., progression-free survival; OS, overall survival; CTCL, cutaneous T-cell lymphoma; CBCL., cutaneous B-cell lymphoma; TLD, Thermoluminescent dosimetry.

Table 2
Dose variation throughout the body during TSEBT in the standing and reclined positions.

TLD location	Nr. of measurements [†]	Mean % of prescription dose		
		Standing	Reclined	P-value**
Top of head [‡]	84	98 ± 21	80 ± 19	0.09
Forehead	84	101 ± 12	67 ± 13	≤0.01
Behind right ear [‡]	83	105 ± 16	68 ± 13	≤0.01
Behind left ear [‡]	81	106 ± 17	49	0.09
Sternal notch	87 [#]	100 ± 10	58 ± 17	0.03
Right axilla [‡]	92 [#]	69 ± 22	22 ± 31	≤0.01
Left axilla [‡]	93 [#]	69 ± 23	16 ± 24	≤0.01
Mid chest [‡]	93 [#]	103 ± 11	80 ± 20	≤0.01
Umbilicus	91 [#]	108 ± 11	85 ± 22	≤0.01
Right inguinal [‡]	85	93 ± 18	78 ± 14	0.02
Left inguinal [‡]	82	90 ± 21	77 ± 16	0.11
Right inner thigh [‡]	84	92 ± 21	80 ± 25	0.3
Left inner thigh [‡]	86 [#]	88 ± 25	85 ± 29	0.8
Behind the right knee	84	103 ± 12	71 ± 7	≤0.01
Behind the left knee	74	103 ± 13	83 ± 12	0.03
Upper back	93 [#]	107 ± 9	85 ± 21	≤0.01
Lower back [‡]	91 [#]	105 ± 7	92 ± 24	0.4
Perineum [‡]	74	20 ± 26	29 ± 19	0.2
Right sole [‡]	72	34 ± 20	71 ± 34	0.014
Left sole [‡]	62	31 ± 20	66 ± 38	0.1
Other regions	155	–	–	–

* Sites affected by changing variables as demonstrated in Table 3.
 ** P-value calculated with two sample T-test for 2 independent groups.
 # Sites may include doubled TLD measurements coming from the same patients
 † Sites require local boost radiations.
 ‡ Number of total TLD measurements analyzed for each site in both positioning techniques.

3. Results

Measurements on the patient’s skin surface were conducted in 76 patients, with total TLD measurements of 1830; median number of measurements was 20 (range, 12–84) per patient. After the first TLD measurement, major modifications to the treatment unit were made for 14/76 patients (18%), with MU modification of –10% (range, –25 to +35). Fractional doses measured are presented as percentage values, normalized to prescribed fraction dose. Dosimetry readings are

Table 3
Correlations with dose distribution during TSEB in the standing position.

TLD location	Standing technique	
	Estimated change (95%-CI)	p-value
Top of head		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–0.754 (–1.272, –0.235)	≤0.01
Gender (male vs. female)	–11.34 (–22.62, –0.052)	0.05
Behind ear		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–0.433 (–0.79, –0.077)	0.02
Gender (male vs. female)	–	–
Mid chest		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–	–
Gender (male vs. female)	7.201 (1.09657,13.307)	0.02
Inguinal		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–0.535 (–1.002, –0.068)	0.02
Gender (male vs. female)	13.397 (3.402, 23.39)	≤0.01
Inner thigh		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–0.549 (–1.066, –0.031)	0.04
Gender (male vs. female)	14.96 ((3.712, 26.22)	≤0.01
Lower back		
Height (x vs. x – 1)	–	–
Weight (x vs. x – 1)	–	–
Gender (male vs. female)	4.34 (0.088, 8.595)	0.05

presented according to radiation technique in Table 2. Correlations with height, weight, and BMI were significant at several sites, as shown in Table 3.

3.1. TSEBT dose distribution with use of standing position

Dose variations during TSEBT for several regions of the body are listed in Table 2. Median dose in the perineum was 20 ± 26% of the prescription dose; however, readings ranging from 0% to 87% were also recorded. Large variation in axillary dose was documented, with a mean dose of 69 ± 22% of the prescribed dose, ranging from 19% to 149%. The mean dose administered to soles ranged from 31% to 34%, with surface dose ranging from 6 to 120%. Dose to the inner thigh region varied from 36% to 127%, with mean dose of 88 ± 25%.

In many cases, significant correlations were observed with BMI, weight, and height. BMI of patients treated in the standing position correlated with dose distribution at the inguinal region (r = 0.33, P ≤ 0.01), inner thigh (r = 0.43, P ≤ 0.01), and popliteal region (r = –0.28, P = 0.05). However, only correlations in the inguinal (P ≤ 0.01) and inner thigh regions (P ≤ 0.01) remained significant after linear regression. Patient height correlated with dose distribution at the vertex (r = 0.32, P = 0.012) and inner thigh (r = 0.34, P ≤ 0.01). Inframammary folds were usually underdosed in patients with pendulous breasts; panniculus was underdosed in obese patients. Variables identified as significant by model building with forward variable selection are presented in Table 3. Based on our analysis, predictions of dose distribution at several anatomical sites based on gender, height, and weight are provided in Table 4.

3.2. TSEBT dose distribution with use of reclining position

Dose variation for several regions of the body during TSEBT are listed in Table 2. BMI of patients treated in the reclining position correlated significantly with dose distribution at the anal folds/perineum (r = 1, P = 0.013). No significant correlation with variables was observed at other sites.

Table 4

Predicted radiation dose distribution at several anatomical sites based on gender, height, and weight. For dose distribution at inguinal and inner thigh regions, alternative formel based on BMI has been developed.

Site	Predicted radiation dose (%)
Top of the head	$162.8 - 11.34 \times \text{gender}$ (1 = male, 0 = female) – $0.754 \times (\text{weight in kg})$
Mid chest	$98.45 + 7.2 \times \text{gender}$ (1 = male, 0 = female)
Lower back	$102.1 + 4.34 \times \text{gender}$ (1 = male, 0 = female)
Inguinal	$125.27 + 13.397 \times \text{gender}$ (1 = male, 0 = female) – $0.535 \times (\text{weight in kg})$ OR $151.335 - 2.229$ (BMI)
Inner thigh	$122.3 + 14.97 \times \text{gender}$ (1 = male, 0 = female) – $0.549 \times (\text{weight in kg})$ OR $158.63 - 2.624$ (BMI)

4. Discussion

Based upon our TLD results, use of the TSEBT technique with the patient in the standing position represents a feasible treatment option for diffuse skin lesions, with an acceptable surface dose distribution of radiation.

There are few reports describing in vivo TLD results for multiple patients treated with the Stanford technique. The data reported for scalp vertex, posterior neck, axilla, abdomen, upper medial thigh, soles, and perineum using a similar technique with an acrylic screen are consistent with our findings [7,8]. Moreover, several authors [8,9] reported overdose to the dorsum of the foot reaching 140% of the prescribed dose, suggesting that shielding should be used after 10 Gy to avoid an adverse reaction. Antolak et al. [9] reported underdosing at the top of the shoulder (mean dose, $67\% \pm 15\%$ of prescribed dose). Radiation dose administered to the dorsum of the foot was not measured in this study, but the toes were shielded in all cases (if not involved). In accordance with our findings, several researchers observed a significant correlation of variation in radiation dose across sites (e.g., scalp vertex) with patient height or BMI [8–10,21]. Additionally, our data analysis indicated a correlation with patient weight or gender in other regions of the body. We therefore sought to predict radiation surface dose at various sites according to patients' gender and physical characteristics in order to individualize boost radiation doses.

Doses to the inner thigh and axilla were also quite variable, likely because of patient positioning and physical characteristics. Therefore, careful consideration must be given to positioning of the arms and legs during TSEB. Perineal dose varied as well, likely because of changes in TLD position during rotation, which would result in higher readings. Therefore, patient positioning should be evaluated when abnormal dose deviations are observed [8]. In contrast, dose distribution for the sternal notch, middle chest, umbilicus, upper back, and lower back showed relatively low standard deviation ($\leq 11\%$ of the prescribed dose). This small range of variation most likely reflects insufficient self-shielding and reproducibility of TLD positioning on the skin [9]. Therefore, we suggest reducing the number of TLDs in these locations to one or two dosimeters.

Van Der Merwe [6] and Gerbi et al. [5] reported on TSEBT with the patient in a reclining position. The dosimetric differences between the findings reported by these authors and our results in Table 2 likely reflect differences in the particular TSEBT techniques used.

We further recommend routine use of TLD measurements for TSEBT as part of quality assurance programs. However, we may recommend reducing the number of TLD measurements, which does not increase the risk of underdosing for TSEB. Interestingly, dose distribution at several anatomical sites during TSEBT in the standing position correlated with gender, height, and weight of treated individuals and may be predicted.

Based on our TLD measurements, in the era of modern low-dose TSEBT using 12 Gy [15,17,22], we may recommend delivery of total radiation with a daily fraction of 2 Gy to the following anatomic sites to ensure homogenous skin surface dose distribution: axilla (skin): 4 Gy ($\sim 31\%$ of prescribed dose), soles: 8 Gy ($\sim 66\%$ of prescribed dose), perineum/perianal region: 10 Gy ($\sim 80\%$ of prescribed dose). Inframammary folds are usually underdosed in patients with pendulous breasts; panniculus might be underdosed in obese patients. Therefore, boost radiation with 8 to 12 Gy to these sites may be necessary. The use of a breast sling in order to avoid boost delivery and undertreatment of the inframammary fold in patients with pendulous breasts may be recommended [23]. In addition, pathologically enlarged lymph nodes and plaques/tumors should be treated with the full prescribed dose of electrons or photons (as determined by the region involved and the size and depth of lesions). Decisions regarding use of eye and nail shields during TSEBT should be decided on an individual basis, considering the patient's clinical circumstances and the extent of his or her skin manifestations.

Limitations of the current study include its retrospective nature and the lack of TLD measurements for several sites. There were few data points coming from the same patients for most endpoints reported in Table 2. These might not be considered statistically independent. However, the information presented expands an important area of research to improve radiation dose distribution during TSEBT.

In conclusion, highly variable readings were obtained from several body surface sites (e.g., top of vertex, extremities, axilla, and perineum). Therefore, we recommend routine use of TLD measurements for TSEBT as part of quality assurance programs for TSEB. If TLD is not available, boost radiation to axilla, soles, and perineum can be applied at 31%, 66%, and 80%, respectively, of prescribed TSEBT dose. After consideration of the patient's clinical circumstances, sequential or concurrent RT to other regions (i.e. inframammary folds or panniculus) or lesions (i.e. enlarged lymph nodes or large skin lesion) may be recommended.

Declarations

Ethics approval and consent to participate

Patients signed consent prior to treatment being initiated and data being collected. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and comparable ethical standards.

Conflict of interest

Khaled Elsayad, Christos Moustakis, Manuela Simonsen, Dagmar Bäcker, Uwe Haverkamp, and Hans Theodor Eich state that there are no conflicts of interest.

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