

Total Skin Electron Beam Therapy (TSEBT) in the Management of Mycosis Fungoides: Single Institution Experience

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ABSTRACT

Purpose: To describe a protocol for total skin electron beam therapy (TSEBT) for the treatment of patients with mycosis fungoides (MF). We report the results of treatment and prognostic factors affecting the disease-free survival (DFS).

Patients and methods: A total of 40 patients with the diagnosis of T1/T2 mycosis fungoides have been referred to the Department of Radiation Oncology at National Cancer Institute of Cairo University from August 1997 till March 2002. They were treated with TSEBT provided via a 6-Mev Linac to a total absorbed dose of 35 Gy over 10 weeks. Response rate, disease-free survival and treatment toxicity were assessed.

Results: The average age was 50 years and the median duration of skin lesions prior to any specific treatment was 4 years. Thirty-four patients (85%) had T1-T2 tumors. Only 17.5% of patients did not receive any specific treatment prior to TSEBT. Response 4-5 weeks after end of TSEBT showed complete clinical response (CR) in 87.5% of patients. The median follow-up was 19.5 months, only 11 patients (27.5%) with initial CR continued to be free of disease until last follow-up. The overall 2-year disease-free survival (DFS) was 66%. Univariate analysis showed that age, performance status and T-stage were statistically significant prognostic factors affecting DFS. Multivariate analysis revealed that T-stage was the only independent significant factor affecting DFS.

Conclusion: For patients with MF confined to the skin, TSEBT is a safe treatment modality and is associated with high complete response (CR) rate and long DFS compared to other known modalities. The best results can be obtained in newly diagnosed patients without previous specific treatment and T1 disease.

Key Words: *Mycosis fungoides - Total skin electron beam therapy - Prognosis.*

INTRODUCTION

Cutaneous T-cell lymphoma (CTLC) characterizes a group of dermatologic disorders

including mycosis fungoides, which manifest themselves through a proliferation of epidermotropic neoplastic T cells [1-2]. Typical mycosis fungoides appears in the skin as patches or plaques and is often mistaken for benign dermatoses [3]. Patches and plaques eventually coalesce and may form cutaneous tumor nodules. In the later stages of disease, there may be spread to lymph nodes, peripheral blood and visceral organs. Circulating abnormal T cells with hyperconvoluted nuclei may be seen in the blood of those patients with Sezary syndrome [4].

Therapy for mycosis fungoides has included a variety of modalities, including topical and systemic chemotherapies, biologicals and both nonionizing and ionizing radiation. Examples include topical nitrogen mustard, oral psoralen plus ultraviolet light (PUVA), total skin electron beam therapy (TSEBT), extracorporeal photochemotherapy (ECP, photophoresis), interferon, retinoids and monoclonal antibody therapy [5]. However, the only therapies that offer long-term control of the disease have been TSEBT, PUVA and topical nitrogen mustard [6-9].

TSEBT was first reported in 1953 [10]. Subsequently, a number of centers in Europe and America began TSEBT. The best-known American series is from Stanford [11-12]. In the present work, we report the outcome of 40 patients with MF who were treated with TSEBT.

PATIENTS AND METHODS

This work was a prospective non-randomized study including 40 patients with histological

diagnosis of mycosis fungoides. They were all treated with TSEBT. At the National Cancer Institute, Radiation Oncology Department during the period from August 1997 to March 2002. Inclusive patients were evaluated by physical examination, chest X-ray, complete blood count and examination of the blood smear for Sezary cells. When clinically indicated, additional work-up was carried out, including bone marrow biopsy, lymph node biopsy, or studies to examine viscera. Patients were staged according to Bunn and Lamberg classification (Tables 1 & 2) [13]. Eligibility criteria included stage I and II patients (T1, T2, T3), with 0-1 ECOG performance status scoring [14]. Patients treated previously with systemic chemotherapy, PUVA, or limited fields radiotherapy were accepted for TSEBT.

Details of the TSEBT technique:

Patients were treated with TSEBT using the modified Stanford technique [9] but with variation of the gantry angles used. Therapy was provided via a 6-MeV linear accelerator (Varian clinic-1800) at a treatment distance of 292 cm. The average energy of the incident beam at skin was 4MeV. The patient was standing on a rotating platform that was designed to rotate 60° degree apart to facilitate the six patients position orientation. The patient was treated in 6 positions over a 2-day cycle, with three of the six fields [AP (Anterior-Posterior), LPO (Left-Posterior-Oblique) and RPO (Right-Posterior-Oblique)] treated on the first day and the remaining three [PA (Posterior-Anterior), LAO (Left-Anterior-Oblique) and RAO (Right-Anterior-Oblique)] on the second day. Three fields were used along each of the six positions, one portal with gantry angle directed 90 degrees to the patient and another superior and other inferior portals directed 20 degree above and below the horizontal axis using angles 70 and 110 degrees respectively. These gantry angles were defined to give the best dose homogeneity all over the body. Figs. (1 & 2) demonstrate the patient's position during TSEBT. The eyes, nails and toes were protected during irradiation using 2 mm thick lead shields that were designed in the mould room. Only in patients with skin affection of their eyelids, internal gold eye shields covered with wax were used instead of the external eye shields.

The total planned dose to skin was 35 Gy/10 weeks, using 1.75 Gy per fraction and giving

3.5 Gy/week in two cycles over 4 days. Additional boost dose of 20 Gy/2 wks with separate localized fields was added to hidden areas (scalp, perineal area, both soles of feet and inframmary region in females) and markedly infiltrated lesions after the end of TSEBT.

Follow-up:

After radiation treatment, the patients were followed monthly for the first six months then every two months for the next year and then every 3 months thereafter. Skin biopsy from the site of previous pretreatment area biopsied was done two months after end of treatment. Patients were scored as having either complete response (CR) (complete clinical regression of all cutaneous lesions), or a partial response (PR) (any regression less than complete). Relapse was recorded at the time of either biopsy-proved recurrence or initiation of therapy for clinical relapse even in the absence of pathologic confirmation.

Patients with PR were scored as having disease free survival of zero days. Disease-free survival was measured from end of radiation treatment. Actuarial curves were generated utilizing the Kaplan-Meier method [15] comparison of survival curves was done by Log Rank test. Multivariate analysis using Cox proportional hazard model was also used.

Radiation treatment morbidity were assessed according to RTOG/EORTC Early and Late Radiation Morbidity Scoring Scheme [16].

RESULTS

Patient characteristics:

Forty patients were eligible for treatment with TSEBT. The clinical characteristics for the patients are shown in Table (3). The median age was 50 years with a range of 24 to 63 years. The duration of skin lesions before any previous specific treatment ranged from 1 to 10 years with a median of 4 years. Thirty-four patients (85%) had T1-T2 tumors and 6 patients had T3 lesions.

Prior therapy to TSEBT:

Only 7 out of 40 (17.5%) patients did not receive any specific treatment prior to TSEBT and thirty-three patients (82.5%) had received one or more forms of specific therapy before

their presentation for TSEBT. Prior therapy included systemic chemotherapy (27.5%), PUVA (25%), localized external beam radiotherapy (7.5%) and combined treatment modalities including either systemic chemotherapy and PUVA in 10% of patients or systemic chemotherapy and localized beam irradiation in 12.5% of patients (Table 4). In all cases, prior therapy did not influence the regimen of TSEBT.

Initial response after TSEBT:

All patients showed subjective clinical response after the first 2-3 weeks of TSEB. The response was in the form of alleviation of itching and fading of the colour of some of the skin lesions. Evaluation of response 4-5 weeks after end of TSEB showed complete clinical response (CR) of all skin lesions in 35 out of 40 patients (87.5%) and partial response (PR) in the remaining 5 patients (12.5%). This response was documented by histological diagnosis of multiple skin biopsies from the previously involved sites. Patients with CR showed disappearance of the dermal infiltrate with no mycosis cells found but only non-specific inflammatory infiltrate. Patients with PR showed epidermal collection of lymphocytes with atypical nuclei. All patients were followed up after ending their treatment for a period of 6 to 48 months with a median of 19.5 months. Only 11 patients (27.5%) with initial CR continued to be free of the disease until their last follow up. The remaining 24 patients showed relapses which were limited to skin.

Sites of first relapse after TSEBT:

All relapsing cutaneous skin lesions occurred at sites of previously involved areas or nearby them (Table 5). Cutaneous relapses of nine of twenty-four patients (37.5%) occurred at upper medial aspect of thigh. Relapse at sites of previously involved tumours lesions was seen in 6/24 (25%), at the axillary fold region in 5/25 (20.83%) of patients and on the dorsal surface of forearm in 3/24 (12.5%) patients. There was one isolated skin relapse at inframmary region of a female patient (4.17%).

Salvage therapy:

When a partial response or relapse occurred following TSEBT, salvage therapy with other treatment modalities was frequently utilized to re-establish a second remission (Table 6). Only 11 patients (27.5%) with initial CR continued

to be free of the disease until their last follow up. The remaining 29 patients were salvaged by either, localized electron fields in 10/29 patients (34.50%) or the use of PUVA in 14/29 patients (48.25%). The remaining 5/29 patients with initial partial response, received salvage systemic chemotherapy. The choice of the type of salvage therapy depended mainly upon the extent, type of skin relapse and type of previous therapy to TSEBT.

All salvaged patients were followed up for a period ranging from 3-20 months with a median of 8 months. Seven out of 10 patients who received radiation dose of 1000 cGy over 5 fractions as localized electron fields attained a second CR whereas the other three patients just achieved PR. As regards the fourteen patients salvaged by PUVA, 3 patients were lost during their follow up while the remaining 11 patients achieved PR as they were maintained on PUVA till the time of analysis of data.

The five initially partial responder patients treated with systemic chemotherapy received either single agent oral methotrexate tablet 25-50 mg weekly in one patient or combination chemotherapy in the other four patients in the form of COP regimen (cyclophosphamide 200 mg²/day for 5 days. Vincristine 1.4 mg/m² IV on the first day and prednisone 100 mg/day orally for 5 days to be repeated every three weeks). Only one patient under COP regimen remained in partial remission whereas the other two patients developed progressive disseminated pattern of the disease. The last patient did not show back after the first cycle of chemotherapy. Table (7) shows the final response rate.

Disease free survival (DFS):

All patients were followed up after ending their TSEBT for a period of 6 to 48 months with a median of 19.5 months. The disease free interval ranged from 4 to 36 months with a median of 10.5 months. The overall 2-year DFS was 66% for the whole group (Fig. 4). The shape of DFS curve showed an initial sharp decline followed by an apparent plateau suggesting that the patients were at great risk of failure within the first year following TSEBT.

Univariate analysis:

Univariate analysis of DFS was done in relation to sex, age, performance status, stage and duration of skin lesions prior to TSEBT.

Female patients had a better DFS than males (58% vs 18%), however this was statistically non significant ($p = 0.07$). Patients with age < 50 years were associated with much better DFS than patients ≥ 50 years (56% vs 12%). The difference was statistically significant ($p = 0.005$). As regards PS, patients with PS 0 showed better DFS compared to patients with PS I (40% vs 10%) with statistically significant difference ($p = 0.007$). When analyzed by T stage, patients with T1 disease (IA) showed best DFS (67%) These patients were considered potentially curable with TSEBT. All T2 patients (stage IB) showed cutaneous relapse during their follow up period whereas those with T3 (stage IIB) had no DFS recorded for them since 5/6 of the T3 patients had an initial PR after TSEBT, showing a highly statistically significant difference ($p = 0.0001$) (Fig. 5). As regards duration of skin lesion prior to TSEBT, patients with duration of skin lesions < 4 years (median) were associated with nearly the same DFS compared to patients with ≥ 4 years (29% vs 27%). This was not statistically significant ($p = 0.61$).

Multivariate analysis:

Multivariate analysis was done to all significant factors defined by univariate analysis and revealed that the T-stage was the only independent prognostic factor with p value = 0.002. Patients with T1 disease were associated with CR in 93.75% whereas the overall response rate for T2 disease was 88.89% (16.67% CR and 72.23% PR). The worst rate was that for T3 patients with only 16.67% were in PR.

Adverse effects:

TSEBT was generally well tolerated. Acute adverse effects included mild erythema GI in 22/40 (55%) of patients and skin dryness GI in 27/40 (67.5%) of patients. These acute radiation dermatitis usually became evident 2 to 3 weeks after treatment and was intensified as treatment continues. It usually resolve within 3 to 4 weeks after completion of treatment. Apart from grade 1 leucopenia in 15% of patients, no significant changes in blood parameters were observed during radiation therapy. Subcutaneous ankle oedema GII was seen in 19/40 (47.5%) and was mostly related to the booster dose to the foot in some patients. It resolved within 10-15 days after end of boost therapy.

Total alopecia GII including eye lashes and eye brows became evident 3 to 4 week after completion of therapy in 98% of patients, but it was reversible 3-6 months after end of therapy in all patients. Only 25% of patients (10/40) suffered from pigmentation GI with slight skin atrophy GI was seen in 5/40 (12.5%) of patients. There were no signs of fibrosis or telangiectasia seen (Table 8).

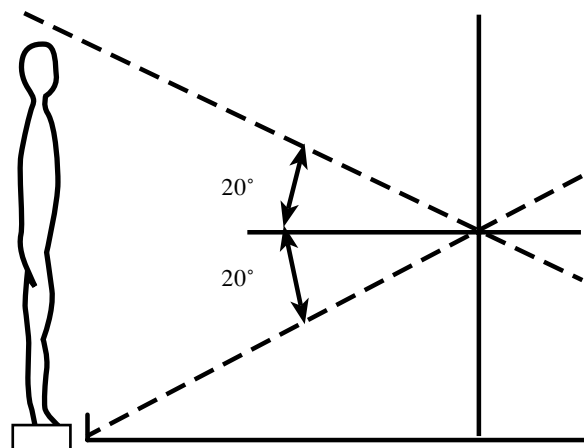


Fig. (1): Patient standing at a distance of 292 cm from the rotation axis of the accelerator.

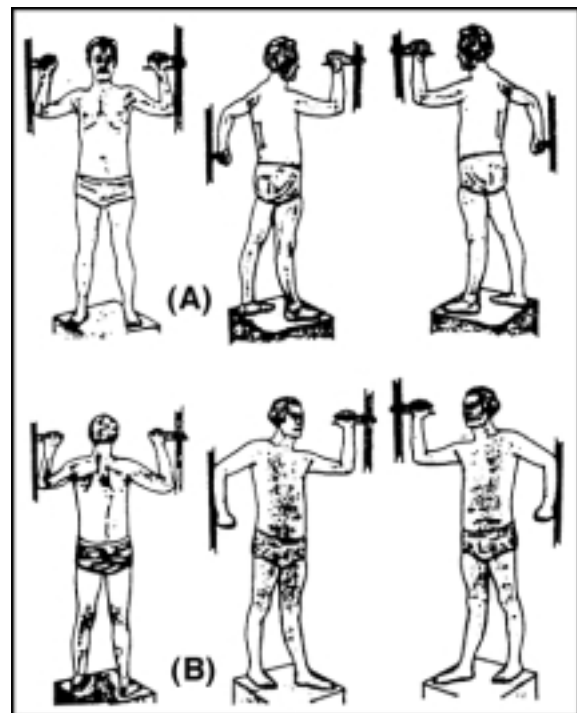


Fig. (2): (A) Positions of the patient in first day. (B) Positions of the patient in second day and etc.



Fig. (3): Male patient with patch and plaque phase MF.

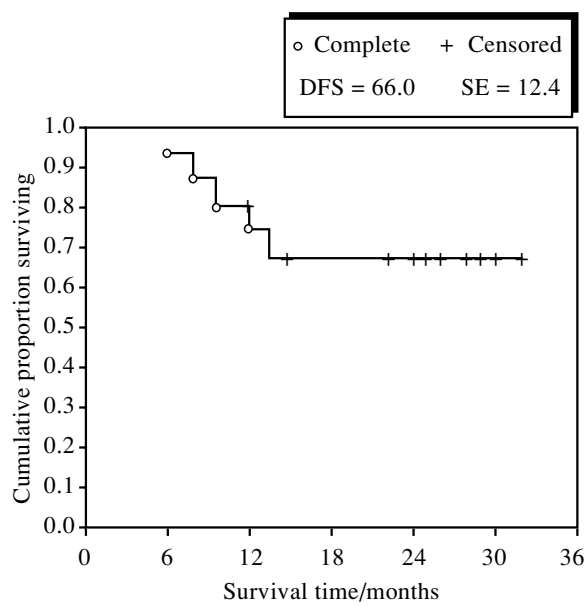


Fig. (4): DFS among the whole MF group.

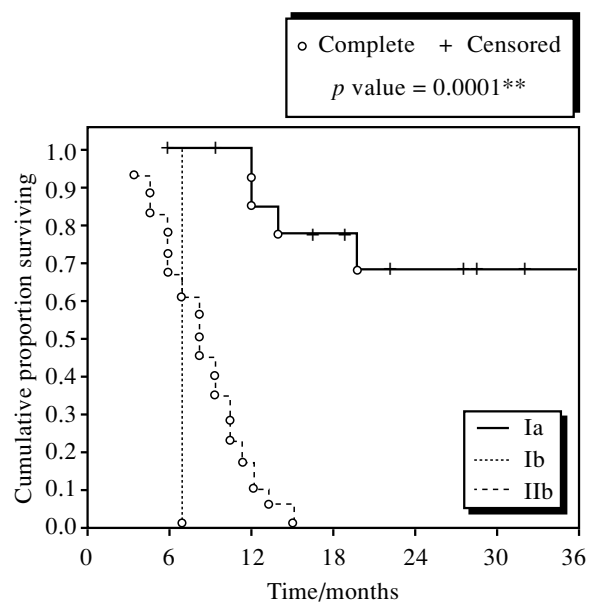


Fig. (5): DFS in relation to stage.

Table (1): TNMB classification for MF.

<i>T (skin):</i>	
T1	Limited patch/plaque (< 10% of skin surface)
T2	Generalized patch/plaque (> 10% of skin surface)
T3	Tumours
T4	Generalized erythroderma
<i>N (nodes):</i>	
N0	Lymph nodes clinically uninvolved
N1	Lymph nodes enlarged, histologically uninvolved
N2	Lymph nodes clinically uninvolved, histologically involved
N3	Lymph nodes enlarged and histologically involved
<i>M (viscera):</i>	
M0	No visceral involvement
M1	Visceral involvement
<i>B (blood):</i>	
B0	Atypical circulating cells (Sezary) not present or < 5%
B1	Atypical circulating cells (Sezary) present > 5%

Table (2): Clinical staging system for mycosis fungoides.

Clinical stages	TNM classification		
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1-2	N1	M0
IIB	T3	N0-1	M0
IIIA	T4	N0	M0
IIIB	T4	N1	M0
IVA	T1-4	N2-3	M0
IVB	T1-4	N0-3	M1

Table (3): Clinical features of the 40 patients.

Characteristics	Number of patients (%)	
Sex	Male	31 (77.5)
	Female	9 (22.5)
Performance status	0	25 (62.5)
	1	15 (37.5)
Stage	Ia (T1)	16 (40.0)
	Ib (T2)	18 (45.0)
	Iib (T3)	6 (15)
Age of patients in years (median)	< 50	18 (45)
	> 50	22 (55)
Duration of skin lesion prior to TSEB in years (median)	< 4	17 (42.5)
	≥ 4	23 (57.5)

Table (4): Prior therapy to TSEB.

Type of therapy	Number of patients (%)
No specific treatment	7 (17.5)
Chemotherapy	11 (27.5)
PUVA	10 (25)
Localized radiation therapy	3 (7.5)
Chemotherapy + PUVA	4 (10)
Chemotherapy + localized radiation therapy	5 (12.5)
Total	40 (100)

Table (5): Sites of relapse in MF group after TSEBT.

Sites of relapse	Number (%)
Upper medial aspect of thigh	9 (37.5)
Site of tumours lesions	6 (25)
Axillary region	5 (20.8)
Dorsal surface of forearm	3 (12.5)
Inframmary breast region	1 (4.2)
Total No. of patients (%)	24 (100)

Table (6): Salvage therapy of MF group after TSEBT.

Treatment	Number of patients (%)
PUVA	14 (48.2)
Radiation boost	10 (34.5)
Chemotherapy	5 (17.3)
Total	29 (100)

Table (7): Final response rate in MF group.

Final response	Number of patients (%)
CR	18 (45)
PR	15 (37.5)
PD	3 (7.5)
Lost follow up	4 (10)

Table (8): Acute and late radiation reaction of TSEB in MF patients.

Type of reaction	Grade 0	Grade I	Grade II	
Acute	Erythema	18 (45%)	22 (55%)	0 (%)
	Dry skin	13 (12%)	27 (68%)	0 (%)
	Leucopenia	34 (85%)	6 (15%)	0 (%)
Late	Ankle oedema	16 (40%)	5 (13%)	19 (48%)
	Alopecia	0 (%)	1 (2%)	39 (98%)
	Pigmentation	30 (75%)	10 (25%)	0 (%)
Skin atrophy	35 (87%)	5 (13%)	0 (%)	

DISCUSSION

The efficacy of TSEBT in MF has been demonstrated in other studies by several authors [17-22]. The aim of our study was to introduce the technique of TSEBT in the treatment of patients with MF attending at the Radiation Oncology Department, National Cancer Institute, Cairo University. Long term studies are necessary to evaluate the overall effect of the treatment modality. As regards the clinical characteristic of our patients, they were comparable to what is mentioned in the literature. MF is characterised by its long indolent clinical course over many years. In our study, the duration of skin lesions prior to TSEBT ranged from one up to ten years with a median of 4 years. This corresponded to Van Volten study [23], which reported the duration of symptoms prior to TSEBT ranging from one year up to 13 years. Also Reddy et al. [24], reported duration of disease prior to TSEBT ranging from 3 months to 480 months with a median duration of 110.8 months.

Patients with MF can be managed initially with many modalities but TSEBT has a high chance of inducing remission and is associated with an excellent long-term results [19]. Complete response and long-term disease free intervals occurring frequently in such patients usually depends on the extent of skin involvement, characteristics of the lesions and radiation dose. Only patients with early disease may be offered a realistic chance of cure. Approximately 40% to 50% of patients with MF at stage IA remain free from relapse 7 years after receiving 40 Gy to the entire surface [20].

In our series, an initial response was seen in 35 out of 40 patients (87.5%) within 4-5 weeks after ending of TSEBT. Twenty nine patients developed cutaneous relapse (72.5%) after 4-36 months with a total follow up period up to 48 months (median 19.5 months). Similarly, Van Vloten et al. [23], reported the results of TSEBT for 40 patients with MF with an initial response in 87.5% after initial irradiation, yet more than 50% of these patients relapsed after 2-72 months within a total follow up period up to 116 months (median 57.5 months).

Various dose schemes have been tried in different centers, but it was reported clearly that lower doses than 30 Gy was associated

with lower results compared to a dose of about 3500 cGy that gave the best results in MF [9]. In our protocol we was used a dose of 3500 cGy over 10 weeks as the Stanford group which have long experience with TSEBT in MF [12].

In our series, the overall 3-years disease free survival was 66% for the whole group. Multivariate analysis showed that T-stage was the only independent prognostic factor. Patients with T1 disease achieved 93.75% complete remission whereas those with T2 disease had an over all response rate of 88.89%; (16.7% CR and 72.2 PR). In the study from Standford University [9], they reported that 86% of the patients with early stage (superficial plaque) as opposed to 44% of tumours stage patients achieved complete response. Results reported by Tadros et al. [17], also supported this view, where patients with superficial disease had 96% complete response compared with 71% for the more advanced stage group. Jones et al. [19], studied the prognosis of newly diagnosed patients with T1-4 N0-1 B0M0 MF treated with TSEBT. The CR rate was 85% for the whole group. The response according to stage was IA 89%, IB 82%, IIA 69% and IIB 62%. This series concluded that TSEBT gave good results with T1 NoBoMo disease. T3-4 disease was less likely to respond but it relapsed more quickly and implied a poor survival but radiation offered good palliation. T2 responded like T1 but relapsed like T3-4. This study also suggested that fewer than 50% of T1 No-1 patients may be cured and there was no evidence that other stages can be cured with radiation. In our study, only 31.25% (5/16) T1 patients developed cutaneous skin relapse whereas 100% of all T2 disease relapsed. Patients with T3 disease (6/40) carried the worst prognosis with evidence of disease progression in 83.33% of them. Though T3 patients were few in number, there was no evidence that their response was worse than that of T2 patients.

The inferior results of our study were mostly attributed to that 33 out of 40 patients (82.5%) were previously treated. Only 7 patients received TSEBT as first line therapy and all of them 7/7 (100%) achieved CR whereas 11/33 patients (33.33%) who had received previous therapy to TSEBT achieved CR. The results reported by Jones et al. [20], showed that TSEBT produced superior clinical results in newly diag-

nosed disease compared with results in patients whom prior therapies have failed before TSEBT was used. Out of 282 patients treated, only 197 received TSEBT as first line therapy for a new primarily diagnosed MF and 85 received TSEBT after at least one prior therapy had failed. For the 197 patients, the rates of CR for all stages ranged from 75% to 95% whereas in the remaining 85 patients who received TSEBT subsequent to failure of one to four other previous therapies for MF, the rates of CR ranged from 43% to 83%.

The system of staging currently in use has not made a distinction within the T3 category regarding the number of nodules or extent of skin involvement (ESI). The ESI has been reported as a prognostic indicator of disease free and overall survival of patients with T3 disease. Quiros et al. [25], reported that for T3 patients, all 8 patients (100%) who had < 10% skin involvement and 74% of 38 patients with > 10% skin disease achieved a CR. At 18 months, all those who had < 10% skin involvement were free from relapse while all those with more extensive disease had relapsed. Among patients with T1 and T2 disease, Hoppe and coworkers [11], reported that ESI had an impact on the DFS and OS of these patients. Those with T1 and T2 patients with limited disease demonstrated prolonged DFS and OS compared with those with more T1 and T2 disease.

In agreement with other studies [20-24], our TSEBT technique did not cause any serious adverse effects and hospitalisation was never needed for that reason. There was no instances of moist desquamation and no systemic side effects were encountered. As our follow-up period was not so long, it was difficult to comment on the incidence of second malignancy. The published reports did not mention about any incidence of second malignancy after TSEBT.

It was a common observation that many patients in CR relapsed subsequently, which raised the question of whether the addition of adjuvant therapy might prolong DFS and improve OS. Options for adjuvant therapy included several modalities especially topical nitrogen mustard (HN2) and PUVA.

Conclusion: patients with MF confined to the skin, TSEBT is a safe treatment modality

and is associated with high CR rate and long DFS compared to other known modalities. The best results can be obtained in newly diagnosed patients without previous specific treatment and T1 disease.

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