Original research article

Literature review of clinical results of total skin electron irradiation (TSEBT) of mycosis fungoides in adults

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ABSTRACT

Background: Mycosis fungoides (MF) is an extranodal, indolent non-Hodgkin lymphoma of T cell origin. Even with the establishment of MF staging, the initial treatment strategy often remains unclear.

Aim: The aim of this study was to review the clinical results of total skin electron beam therapy (TSEBT) for MF in adults published in English language scientific journals searched in Pubmed/Medline database until December 2012.

Results: MF is very sensitive to radiation therapy (RT) delivered either by photons or by electrons. In limited patches and/or plaques local electron beam irradiation results in good outcomes besides the fact of not being superior to other modalities. For extensive patches and/or plaques data suggest that TSEBT shows superior response rates. The cutaneous disease presentation is favorably managed with radiotherapy due to its ability to treat the full thickness of deeply infiltrated skin. For generalized erythroderma presentation, TSEBT seems to be an appropriate initial therapy. For advanced disease, palliation, or recurrence after the first radiotherapy treatment course, TSEBT may still be beneficial, with acceptable toxicity. Recommended dose is 30–36 Gy delivered in 6–10 weeks.

Conclusion: TSEBT can be used to treat any stage of MF. It also presents good tumor response with symptoms of relief and a palliative effect on MF, either after previous irradiation or failure of other treatment strategies.

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1. **Background**

Mycosis fungoides (MF) is an extranodal, low grade, indolent non-Hodgkin lymphoma of T cell caused by skin homing CD4+ cells [1–3].

It develops primarily in the skin, however, can involve lymph nodes, blood and visceral organs [1]. It is a rare disease that mainly affects adult over the age of 40 years with an incidence of 9.6 cases per million, compromising 3000 of Americans each year [4].

The diagnosis work-up is centered on a complete history and physical examination, which includes examination of the entire skin and lymph nodes, incisional or excisional skin biopsies [5].

The most important prognostic factor is the disease stage (Appendix – Tables 1 and 2) [6–8], mainly in what refers to extent and type of involvement of the skin and the presence or absence of extracutaneous disease.

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Even with the establishment of MF staging, the initial treatment strategy often remains unclear, given the limited high quality published data and heterogeneity of the disease presentation.

2. **Aim**

The aim of this study was to review the clinical results of total skin electron beam therapy (TSEBT) for MF in adults.

3. **Materials and methods**

An electronic literature search was carried out using the Pubmed/Medline search engine with no language or year restriction, until December 2012. The search strategy was: (Mycosis Fungoides OR Lymphoma OR Non-Hodgkin OR Lymphoma, T-Cell OR Lymphoma, T-Cell, Cutaneous) AND (Radiotherapy OR TSEBT OR EBT OR TSI OR Total Skin electron beam therapy OR Electron beam therapy OR Total skin irradiation). Only English language publications that presented clinical results were selected to carry out this review.

4. **Results**

Radiation therapy (RT) is considered to be one of the most effective single treatment modality for MF [9], which is very sensitive to radiation delivered either by photons or electrons. Due to the acute and late toxicity of the use of X-rays for MF treatment, the replacement of photons by electron beam therapy has been shown to be more appropriate [9]. Electrons based therapy has the capability of delivering the radiation dose up to the superficial layers of the skin while avoiding deeper tissues, thus being less toxic [10].

4.1. **TSEBT dose**

At present, there are no randomized trials comparing low and high dose TSEBT. Experiences [11–15] up to now demonstrate that curative management of MF needs total doses of at least 20 Gy and maybe up to 30 Gy or more. Based on these records, the European Organization for the Research and Treatment of Cancer (EORTC) consensus recommended a total dose of 31–36 Gy delivered in 6–10 weeks. Fractions of 1.0–1.5 Gy every other day are more tolerable and the dose is calculated at 4 mm depth from the skin surface with low energy electrons (4–5.5 MeV) [11].

4.2. **Early stage disease: T1N0MO (IA); T1N1MO (IIA); T2N0MO (IB) and T2N1MO (IIA)**

Initial treatment for patients with T1 disease is based in skin directed therapies that include topical treatment (chemotherapy, corticosteroids), phototherapy, local radiation (X-ray or electron beam) and TSEBT [12]. All of them result in complete response rates of at least 80% [13–16].

Currently, no randomized trial is available to support superiority of radiation-based therapy over other topical strategies. Albeit, some institutional experience suggests suitable outcomes when TSEBT is used. The Hamilton experience [10] which included 143 stage IA patients treated with TSEBT showed a complete response of at least 90% associated with a cause specific survival of 96% and a overall survival of 76% at 15 years of follow up. Results from 32 patients from that study treated with TSEBT plus psoralen plus ultraviolet A significantly (p = 0.03) improved the progression free survival rates at 5 years of follow-up.

Furthermore, the retrospective Stanford series [17] evaluated the long-term results of patients with stage IA MF managed with TSEBT and analyzed the factors related to disease progression and the effect of initial therapy on survival and freedom from relapse. In that series, complete response rate of at least 90% was observed with TSEBT. Patients who received TSEBT (n = 34) had a more favorable freedom-from-relapse outcome than those treated with topical mechloethamine hydrochloride (nitrogen mustard) (n = 73; p < 0.05). No significant difference was seen in the long-term survival between the two groups.

Due to the lack of benefit in overall survival and the side effects of TSEBT the standard care for patients with IA MF remains controversial. The use of TSEBT should be indicated more strongly as a primary therapy to recurrent/refractory or extensive lesions; the lesions disappear by two to three weeks after treatment [12,18].

Assessing the group of patients IB and IIA treatment with skin directed therapies, used alone or in combination is a standard. The options include: topical chemotherapy, topical corticosteroids, TSEBT and phototherapy. Nevertheless these treatment options have not been prospectively compared.

Regarding TSEBT for T2 patients the complete response rate, overall survival and progression free survival range from 76 to 90%, 75–99%, and 12–44%, respectively, at 2.5–15 years of follow-up [11]. These results are excellent when compared with a complete response rate of 34% for topical mechloethamine [19]. Rotational TSEBT was also evaluated.
with good complete response rate and a 5-year overall survival, favoring T2 stage patients [20,21].

A French series presented the treatment results of 57 patients out of 141 referred to radiotherapy [22]. Of those, 24 were staged as T1 and 33 as T2 patients. A total of 25 received topical treatment before irradiation (TSEBT: 30 Gy over 4 weeks with 6 MeV). Complete response was obtained in 85% of patients with T2 lesions. Thirty-one patients (54.4%) experienced a skin failure (23 with T2 disease) within 1 year. For the whole group, 5-year disease free survival was 50%. The 5/10/15-year overall survival rates were 90%/65%/42%, respectively. The study also reported the following significant favorable prognostic factors for overall survival: T1 (p = 0.03), complete response after first TSEBT (p = 0.04), and age younger than 60 (p < 0.001) in univariate analysis. Younger age persisted as a significant prognostic factor on multivariate analysis (p = 0.001).

Shouman et al. [23] analyzed a total of 40 patients with the diagnosis of T1/T2 MF from 1997 to 2002. All patients were treated with TSEBT (total dose of 35 Gy over 10 weeks). A complete response rate of 87.5% and a 2-year overall disease free survival of 66% were observed. TSEBT was generally well tolerated.

A prospective series published by Kirova et al. [24] analyzed 66 consecutive patients with MF treated from 1978 to 1996. All patients received topical and/or systemic therapy, and 30 Gy TSEBT delivered in 12 fractions was indicated for persistent or recurrent disease. About one third (36%) of the patients were stage A (T1N0 or T2), 33% stage B (T2 with more than 50% of skin disease), most of them being male (59%). For stage A, the survival rate at 5-year was 93% and the complete response rate, 100%. For stage B the 5-year survival rate was 79% and the complete response rate, 44%. At the final analysis all patients were able to finish the whole course of TSEBT with moderate side effects.

Combined treatment appears to be also safe and more efficient for this group of patients. Quiros et al. [25], from Yale University, in a retrospective study, reported the results from 114 T1/T2 patients treated with TSEBT and adjuvant oral psoralsen plus ultraviolet light (PUVA). They observed a 5-year overall survival of 100% in the group that received PUVA versus 82% for the non-PUVA group (p < 0.10). The 5-year disease free survival for the entire cohort was 53%. Those who received PUVA had a higher 5-year disease free survival (85% versus 50%, p < 0.02), demonstrating that PUVA is an effective adjuvant therapy with acceptable toxicity. Similar results had already been shown by the Canadian study [11].

A retrospective analysis from Stanford University [26] presented the results of 148 patients: 55 patients with T2 and 27 with T3 disease that received TSEBT with or without topical nitrogen mustard (HNZ), and 54 patients with T2 and 12 with T3 disease that received HNZ alone. Adjuvant HNZ improved the 10-year relapse free survival rate: 40% versus 10% for TSEBT alone. There was also an improvement in the complete response rates for the TSEBT + HNZ group (76% versus 39%; p = 0.03) in patients with T2 disease. However, no significant differences in survival were observed for different management programs for T2 or T3 disease.

Some phase II studies indicate favorable increases in complete response rates and freedom from relapse when adding interferon-α to PUVA in the management of T2 patients [27–29].

Clinical results and toxicity of TSEBT for early stage are summarized in Table 1.

4.3. Advanced Stage disease: T3N0-1M0 (IIB); T4N0-1M0 (III); IV and palliation

Patients with advanced disease require a more aggressive therapeutic modality. Treatment options vary depending on the characteristics of the lesions and previous treatments [30]. Nonetheless, a randomized trial demonstrated that there is no advantage of early aggressive therapy (with chemotherapy) versus conservative sequential therapy [31].

Skin tumors are favorably managed with radiotherapy due to its ability to treat the full thickness of deeply infiltrated skin. Most T3 patients present with extensive, symptomatic tumors, and the majority will die from complications of the disease [32,33].

This group frequently benefits from TSEBT as first line. The outcomes regarding complete response rates are superior when compared with topical HNZ2 plus localized RT (44–54% versus 8%) [11,26].

The prospective French study [28] had 30% (20 patients) stage C cases (IIB, IIIA, IIB, IVA and IVB). All patients achieved an important symptoms relief after TSEBT. The 5-year survival rate was 44% and the complete response rate, 39%. There were 47% partial responses.

The Danish study [15] which compared low versus high dose TSEBT also presented results of T3 patients (46.6% of the studied patients) treated with 30 Gy TSEBT. Complete response of 78.6%, partial response of 21.4% and a 37.5% rate of disease progression were observed. Freedom-from-progression rates after 0.5-, 1- and 2-years were 92.3%, 75.2% and 62.7%, respectively, in patients with T3 disease.

Adjuvant therapy must, however, be considered for patients who achieve a complete response after TSEBT. The Stanford University retrospective [30] series demonstrated that the use of TSEBT plus topical HNZ2 yielded significantly higher complete response in T3 patients when compared with no HNZ (4% versus 8%, p < 0.05 for T3, respectively). They also stated that TSEBT is an effective treatment for T3 disease and emphasize that the adjuvant treatment may improve the duration of response, resulting in a 5-year relapse free survival rate of 55% versus 30% with TSEBT alone. A small subset of patients with limited T3 disease may also need to be treated with HNZ and local RT for the tumors.

In another retrospective series from Navi et al. [34], 180 patients with T2/T3 MF disease were analyzed. They presented a complete response rate, progression free survival and 5-year overall survival of 36%, 29% and 44% for T3 patients, respectively. Patients were treated with TSEBT (30-36 Gy) with or without HNZ and, as side effect, moderate radiation induced dermatitis was observed. The authors concluded that 30 Gy was highly effective and that there was no clinical advantage of HNZ. Other adjuvant treatments that could be used are photopheresis, bexarotene, interferon-α, and denileukin difitox [35,36]. However, the role of adjuvant therapy in overall survival is still uncertain [13,29,37].
Most patients with stage IIB MF will develop recurrence after complete response to initial treatment. Relapsed patients may be saved by systemic treatments such as retinoids, histone deacetylase, interferon alfa, and denileukin difitox [30, 38, 39]. Local persistent tumors could respond to additional doses of local RT (boost) [17].

Due to its ability to produce a rapid and sustained response, TSEBT seems to be an appropriate initial therapy for T4 patients. Jones et al. [40] presented retrospective data from 28 stage III patients (T4 N0-1 M0), 13 with stage IVA (T4 N2-3 M0), 4 with stage IVB (T4 N0-3 M1) disease, and 21 with blood involvement. The median radiation TSEBT dose was 32 Gy. The 5-year progression-free survival was 69% for patients with T4N0M0 MF disease. Toxicities of radiotherapy were acceptable.

Maingon et al. [41], in a retrospective study of advanced MF, described the results of TSEBT combined with photon beam irradiation in 45 patients. The overall response rate was 81% for T3 patients, 61% for T4, 79% for N1 and 70% for N3. The 5-year actuarial overall survival was 37% for T3 and 44% for T4 (p = 0.84). Indeed, they demonstrated that patients with advanced disease might be treated with the addition of photon beams to TSEBT, with good results.

Although, for patients with blood involvement, there is no evidence that TSEBT can result in a significant malignant cells decrease in the circulation blood, potentially altering the natural history of the disease in patients B1 or B2 [42]. TSEBT is an optional approach but it should be used carefully because severe skin toxicity is normally observed (desquamation with total doses as low as 4 Gy) [34].

In palliative perspective in which there is extensive skin and extra-cutaneous disease or recurrence after the first radiotherapy treatment course, TSEBT is still an option presenting benefits with acceptable toxicity.

Funk et al. [43] analyzed the palliation effect of TSEBT in 18 patients with cutaneous T-cell non-Hodgkin’s lymphoma in advanced stages (IIB – IV) (72% MF) refractory to prior treatments. The median total dose was 25 Gy, and the median follow-up was 11 months. Fifty percent of patients achieved a complete response, and 39%, partial response. At 1 year, the progression-free survival was 24% and the overall survival was 48%. All patients had moderate acute side effects. An update of this study with 25 patients concluded that TSEBT is an efficient and well-tolerated considerable treatment option [44]. Some case report [45] for stage IV symptomatic MF showed a complete response of 100% at an 18 month-follow up with low dose TSEBT. An institutional series [46] of 49 (which included IV stage MF) patients treated with TSEBT showed 38.8% and 45% rate of skin relapse and 10 years skin relapse free survival, respectively.

A Yale University study [47] with the purpose to evaluate the efficacy and toxicity of additional TSEBT for recurrent lesions analyzed a total of 14 patients treated with at least two courses of TSEBT, with five of those patients receiving a third course with a median follow up of 36 months. The mean doses for the first, second and third courses of TSEBT were 36 Gy, 18 Gy and 12 Gy respectively. Thirteen patients (93%) achieved a complete response after the initial course. After the second course, 12 patients (86%) had a complete response; of the five patients who underwent a third course, three (60%) achieved a complete response. The median disease-free interval after the first course of therapy for those with a complete response was 20 months and 11.5 months after the second course. Median survival after the second course was 15 months. The treatment was well tolerated beside the fact that all patients presented skin side effects.

Becker et al. [48] from Stanford University published results from a retrospective analysis of 15 patients with MF that relapsed. All received two courses of high-dose electron beam therapy to the skin and adjuvant therapies between the first and second courses. The mean dose for the total skin treatment was 32.6 Gy for the first course and 23.4 Gy for the second course. Eleven of the 15 patients had a complete response after the first course, with a mean duration of 11.6 months. The second course of therapy resulted in six complete and nine partial responses. Late toxicity observed was restricted to skin dryness, telangiectasias, pigmentation changes and alopecia. Thus, for MF patients delivering two courses of total skin electron beam therapy is technically feasible, tolerable, and efficacious. The criteria used to screen patients included initial good response to total skin electron treatment, long disease-free interval, exhaustion of other therapeutic modalities, and generalized skin involvement at relapse.

Clinical results and toxicity of TSEBT for advanced stage are summarized in Table 2.

### Table 1 – Summarized clinical data for early stage (T1/T2N0) mycosis fungoides.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>METHODS</th>
<th>CR</th>
<th>DFS/PFS</th>
<th>OS</th>
<th>SKIN TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. (1995) [10]</td>
<td>143</td>
<td>TSEBT</td>
<td>&gt;90%</td>
<td>15-y: CSS 96%</td>
<td>15-y: 76%</td>
<td>Dry skin/erythema</td>
</tr>
<tr>
<td>Quiros et al. (1997) [25]</td>
<td>114</td>
<td>TSEBT 36 Gy + PUVA</td>
<td>1 month: 97%(T1)</td>
<td>5-y: 53%</td>
<td>5-y: 85%</td>
<td></td>
</tr>
<tr>
<td>Shouman et al. (2003) [23]</td>
<td>40</td>
<td>TSEBT 35 Gy</td>
<td>4-5 weeks: 87%</td>
<td>2-y: 66%</td>
<td></td>
<td>Acute: G II 0%</td>
</tr>
<tr>
<td>Ysebaert et al. (2004) [22]</td>
<td>57</td>
<td>TSEBT 30 Gy</td>
<td>T1 88%</td>
<td>1-y: 54.4% skin failure</td>
<td>5-y: 90%</td>
<td>Late: skin atrophy 87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2 85%</td>
<td></td>
<td>10-y: 65%</td>
<td>Grade 1–2: 75.5%</td>
</tr>
</tbody>
</table>

N: number of patients; CR: complete response; DFS: disease free survival; PFS: progression free survival; OS overall survival; TSEBT: total skin electron beam therapy; PUVA: adjuvant oral psoralen plus ultraviolet light; CSS cause specific survival.

* Only T1N0.
Table 2 – Summarized clinical data for advanced stage mycosis fungoides.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>CR</th>
<th>DFS/PFS</th>
<th>OS</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison et al. (1997)</td>
<td>102 patients</td>
<td>TSEBT 5–36 Gy</td>
<td>T2 96%</td>
<td>&gt;30 Gy</td>
<td>&gt;30 Gy</td>
<td>Dry skin/erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 96%</td>
<td>T2 8.5 y</td>
<td>T2 13.2 y</td>
<td>T3 4.8 y</td>
<td>14% skin cancer</td>
</tr>
<tr>
<td>Chinn et al. (1999)</td>
<td>148 patients</td>
<td>TSEBT (30–36 Gy) +/- HN2</td>
<td>5-y 40% (T2)</td>
<td>5y:77%/44% (T2/T3)</td>
<td>Moderate radiation induced dermatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSEBT + HN2: 76%</td>
<td>T2: 8.5 y</td>
<td>T2: 8.5 y</td>
<td>T2: 8.5 y</td>
<td>Moderate radiation induced dermatitis</td>
</tr>
<tr>
<td>Navi et al. (2011)</td>
<td>180 patients</td>
<td>TSEBT (30–36 Gy) +/- HN2</td>
<td>T2:77%</td>
<td>5-y 15–20% (T3)</td>
<td>5-y: 63%</td>
<td>Moderate radiation induced dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2/T3</td>
<td>T3: 36%</td>
<td>T3: 2.9 y</td>
<td>T3: 2.9 y</td>
<td>Moderate radiation induced dermatitis</td>
</tr>
<tr>
<td>Kirova et al. (1999)</td>
<td>66 patients</td>
<td>TSEBT 30 Gy</td>
<td>65%</td>
<td>5-y: 30%</td>
<td>10-y: 18%</td>
<td>Acute: erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 y 92.3%</td>
<td>5: 93–44%</td>
<td>T2: 8.5 y</td>
<td>Acute: erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-y 75.2%</td>
<td>T3: 2.9 y</td>
<td>T3: 2.9 y</td>
<td>Acute: erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-y 62.7%</td>
<td>T3: 2.9 y</td>
<td>T3: 2.9 y</td>
<td>Acute: erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-y 24%</td>
<td>T3: 2.9 y</td>
<td>T3: 2.9 y</td>
<td>Acute: erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-y 48%</td>
<td>T3: 2.9 y</td>
<td>T3: 2.9 y</td>
<td>Acute: erythema</td>
</tr>
</tbody>
</table>

CR: complete response; DFS: disease free survival; PFS: progression free survival; OS overall survival; TSEBT: total skin electron beam therapy; HN2: topical nitrogen mustard.

5. Conclusions

TSEBT can be used to treat the whole skin in any stage of MF. Re-irradiation also seems to be safe in persistent or recurrent disease even after other therapeutic approaches, with good response rates. TSEBT is generally well tolerated, but some side effects are present. Temporary loss of toe/finger nails, localized anhydrosis, rarely mild epistaxis, and parotiditis are some acute sides effects [18,49,50]. Persistent nail dystrophy, xerosis, telangiectasias, permanent partial alopecia, fingertip anesthesia, and possible infertility in male patients can appear as chronic effects [54,55]. Secondary cutaneous malignant diseases have been observed in patients treated with TSEBT, particularly in those exposed to multiples therapies [51,52].

The low numbers of patients in the studies and only one randomized trial found in this review reflects the scarcity of the disease. So, better evidence-based approaches will be difficult to be developed. At present, diminishing the skin side effects that are tolerable but may impair quality of life should be one of the goals for future research as new treatments associations or targeted therapies.

Conflict of interest

None to declare.

Financial disclosure

None to declare.

REFERENCES


