Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

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

Fabio Ynoe de Moraes[a], *Heloisa de Andrade Carvalho*[a,b], *Samir Abdallah Hanna*[a], *João Luis Fernandes da Silva*[a], *Gustavo Nader Marta*[a,c,*]

[a] *Department of Radiation Oncology, Hospital Sírio-Libânes, São Paulo, SP, Brazil*
[b] *Radiotherapy – Department of Radiology and Oncology, Radiology Institute – InRad, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil*
[c] *Department of Radiation Oncology, Instituto do Câncer do Estado de São Paulo – ICESP, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 20 May 2013
Received in revised form
11 July 2013
Accepted 22 August 2013

Keywords:
Mycosis fungoides
Radiotherapy
Total skin irradiation
Electron beam therapy

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.

* *Corresponding author at*: Department of Radiation Oncology, Hospital Sírio-Libânes, Rua Dona Adma Jafet 91, Sao Paulo-SP 01308-050, Brazil. Tel.: +55 11 31550558; fax: +55 11 31550983.
E-mail addresses: fymoraes@gmail.com (F.Y.d. Moraes), heloisa-carvalho@uol.com.br (H.d.A. Carvalho), samir.hanna@hsl.org.br (S.A. Hanna), jluis@hsl.org.br (J.L.F.d. Silva), gnmarta@uol.com.br (G.N. Marta).

1507-1367/$ – see front matter.
http://dx.doi.org/10.1016/j.rpor.2013.08.003

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.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rpor.2013.08.003.

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: T1N0M0 (IA); T1N1M0 (IIA); T2N0M0 (IB) and T2N1M0 (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 mechlorethamine 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 mechlorethamine [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 therapy 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 psoralen 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 (HN2), and 54 patients with T2 and 12 with T3 disease that received HN2 alone. Adjuvant HN2 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 + HN2 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 HN2 plus localized RT (44–54% versus 8%) [11,26].

The prospective French study [28] had 30% (20 patients) stage C cases (IIB, IIIA, IIIB, 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 (48.6% 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 HN2 yielded significantly higher complete response in T3 patients when compared with no HN2 (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 HN2 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 HN2 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 HN2. Other adjuvant treatments that could be used are photopheresis, bexarotene, interferon-α, and denileukin diftitox [35,36]. However, the role of adjuvant therapy in overall survival is still uncertain [13,29,37].

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

STUDY	N	METHODS	CR	DFS/PFS	OS	SKIN TOXICITY
Jones et al. (1995)[a] [10]	143	TSEBT	>90%	15-y: CSS 96%	15-y: 76%	
Quiros et al. (1997) [25]	114	TSEBT 36 Gy +PUVA	1 month: 97%(T1) 87%(T2)	5-y: 53% PUVA 85%vs Non PUVA 50% ($p = 0.02$)	5-y: 85%	Dry skin/erythema
Shouman et al. (2003) [23]	40	TSEBT 35 Gy	4–5 weeks: 87% 48 months: 27%	2-y: 66%		Acute: G II 0% Late: skin atrophy 87%
Ysebaert et al. (2004) [22]	57	TSEBT 30 Gy	T1 88%	1-y: 54,4% skin failure	5-y: 90%	Grade 1–2: 75.5%
			T2 85%		10-y: 65%	Grade 3: 24.5% Mild edema: 10%

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.
[a] Only T1N0.

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 diftitox [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 2 – Summarized clinical data for advanced stage mycosis fungoides.

Study	Population	Methods	CR	DFS/PFS	OS	Toxicity
Harrison et al. (1997) [56]	102 patients T2/T3/T4	TSEBT 5–36 Gy	T2 96% T3 96%	>30 Gy T2 8.5 y T3 2.9 y	>30 Gy T2 13.2 y T3 4.8 y	
Chinn et al. (1999) [26]	148 patients T2/T3	TSEBT (30–36 Gy) −/+ HN2	TSEBT + HN2: 76%	5-y 40% (T2) 5-y 15–20% (T3)	5y:77%/44% (T2/T3) 10-y 41%/28% (T2/T3)	Dry skin/erythema 14% skin cancer
Navi et al. (2011) [34]	180 patients T2/T3	TSEBT (30–36 Gy) −/+ HN2	T2:77% T3: 36%	T2: 8.5 y T3: 2.9 y	5-y: 63% 10-y 44%	Moderate radiation induced dermatitis
Kirova et al. (1999) [24]	66 patients T3/T4	TSEBT 30 Gy	65%	5-y: 30% 10-y 18%	5 y: 93–44%	Acute: erythema
Lindahl et al. (2011) [53]	35 patients T3	TSEBT 30 Gy	78.6%	0.5 y 92,3% 1-y 75.2% 2-y 62.7%		
Funk et al. (2008) [43]	18 patients IIIb-IV	TSEBT 25 Gy	50%	1-y 24%	1-y 48%	Moderate acute sides effects

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

[1]. Jaffe ES, Harris NL, Stein H, et al. *World health organization classification of tumours pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press; 2001.

[2]. Hinds GA, Heald P. Cutaneous. T-cell lymphoma in skin of color. *J Am Acad Dermatol* 2009;**60**:359–75.

[3]. Sander CA, Flaig MJ, Jaffe ES. Cutaneous manifestations of lymphoma. A clinical guide based on WHO classification. *Clin Lymphoma* 2001;**2**:86–100.

[4]. Bradford PT, Devesa SS, Anderson WF, et al. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood* 2009;**113**: 5064–73.

[5]. Marta GN, Gouvêa CB, Ferreira SB, et al. Mycosis fungoides: case report treated with radiotherapy. *An Bras Dermatol* 2011;**86**:561–4.

[6]. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the international Society of cutaneous Lymphomas (ISCL) and the cutaneous lymphomas task force of the European Organization of research and treatment of cancer (EORTC). *Blood* 2007;**110**: 1713–22.

[7]. Edge SB, Byrd DR, Compton CC, et al. *AJCC cancer staging handbook*. 7th ed. New York: Springer; 2010.

[8]. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011;**29**:2598–607.

[9]. Hoppe RT. Mycosis fungoides radiation therapy. *Dermatol Ther* 2003;**16**:347–54.

[10]. Jones GW, Hoppe RT, Glatstein E. Electron beam treatment for cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am* 1995;**9**:1057–76.

[11]. Jones GW, Kacinski BM, Wilson LD, et al. Total skin electron radiation in the management of mycosis fungoides: Consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. *J Am Acad Dermatol* 2002;**47**:364–70.

[12]. Marta GN, Hanna SA, da Silva JLF. Radiotherapy Approach in the treatment of mycosis fungoides: principles and recommendations. *J Cell Sci Ther* 2012;**3**:1–4.

[13]. Jones G, Wilson LD, Fox-Goguen L. Total skin electron beam radiotherapy for patients who have mycosis fungoides. *Hematol Oncol Clin North Am* 2003;**17**:1421–34.

[14]. Ramsay DL, Lish KM, Yalowitz CB, et al. Ultraviolet-B phototherapy for early-stage cutaneous T-cell lymphoma. *Arch Dermatol* 1992;**128**:931–3.
[15]. Diederen PV, van Weelden H, Sanders CJ, et al. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides. A retrospective study. *J Am Acad Dermatol* 2003;**48**:215–9.
[16]. Zackheim HS, Epstein Jr EH, Crain WR. Topical carmustine (BCNU) for cutaneous T cell lymphoma. A 15-year experience in 143 patients. *J Am Acad Dermatol* 1990;**22**:802–10.
[17]. Kim YH, Jensen RA, Watanabe GL, et al. Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. *Arch Dermatol* 1996;**132**:1309–13.
[18]. Neelis KJ, Schimmel EC, Vermeer MH, et al. Low dose palliative radiotherapy for cutaneous B and T-cell lymphomas. *Int J Radiat Oncol Biol Phys* 2009;**74**:154–8.
[19]. Kim YH, Martinez G, Varghese A, et al. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003;**139**:165–73.
[20]. Evans MDC, Hudon C, Podgorsak EB, et al. Institutional experience with a rotational total skin electron irradiation (RTSEI) technique—a three decade review (1981–2012). *Rep Pract Oncol Radiother* 2013, published online 20 June 2013 http://dx.doi.org/10.1016/j.rpor.2013.05.002
[21]. Piotrowski T, Pawlaczyk M, Fundowicz D. Total skin electron irradiation with rotarydual technique in the treatment of mycosis fungoides. Efficacy and toxicity. *Rep Pract Oncol Radiother* 2003;**8**:S536–7.
[22]. Ysebaert L, Truc G, Dalac S, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation). *Int J Radiat Oncol Biol Phys* 2004;**58**:1128–34.
[23]. Shouman T, Aguib N, El- Taher Z, et al. Total skin electron beam therapy (TSEBT) in the management of mycosis fungoides: single institutional experience. *J Egypt Natl Canc Inst* 2003;**15**:275–83.
[24]. Kirova YM, Piedbois Y, Haddad E, et al. Radiotherapy in the management of mycosis fungoides: indications, results, prognosis. Twenty years experience. *Radiother Oncol* 1999;**51**:147–51.
[25]. Quiros PA, Jones GW, Kacinski BM, et al. Total skin electron beam therapy followed by adjuvant psoralen/ultraviolet-A light in the management of patients with T1 and T2 cutaneous T-cell lymphoma (mycosis fungoides). *Int J Radiat Oncol Biol Phys* 1997;**38**:1027–35.
[26]. Chinn DM, Chow S, Kim YH, et al. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. *Int J Radiat Oncol Biol Phys* 1999;**43**:951–8.
[27]. Kuzel TM, Roenigk Jr HH, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. *J Clin Oncol* 1995;**13**:257–63.
[28]. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998;**92**:3578–81.
[29]. Chiarion-Sileni V, Bononi A, Fornasa CV, et al. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. *Cancer* 2002;**95**:569–75.
[30]. Duarte RF, Schmitz N, Servitje O, et al. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant* 2008;**41**:597–604.
[31]. Kaye FJ, Bunn Jr PA, Steinberg SM, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989;**321**:1784–90.
[32]. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010;**28**:4730–9.
[33]. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol* 2003;**139**:857–66.
[34]. Navi D, Riaz N, Levin YS, et al. The Stanford University experience with conventional-dose,total skin electron-beam therapy in the treatment of generalized patch or plaque (T2) and tumor (T3) mycosis fungoides. *Arch Dermatol* 2011;**147**:561–7.
[35]. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer* 2003;**98**:993–1001.
[36]. Wobser M, Göppner D, Lang SC, et al. Durable complete remission of therapy-refractory, tumor-stage cutaneous T-cell lymphoma under radioimmunotherapy with electron beam irradiation and denileukin diftitox. *Arch Dermatol* 2010;**146**:805–6.
[37]. Wilson LD, Licata AL, Braverman IM, et al. Systemic chemotherapy and extracorporeal photochemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy. *Int J Radiat Oncol Biol Phys* 1995;**32**:987–95.
[38]. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001;**19**:2456–71.
[39]. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2009;**27**:5410–7.
[40]. Jones GW, Rosenthal D, Wilson LD. Total skin electron radiation for patients with erythrodermic cutaneous T-cell lymphoma (mycosis fungoides and the Sezary syndrome). *Cancer* 1999;**85**:1985–95.
[41]. Maingon P, Truc G, Dalac S, et al. Radiotherapy of advanced mycosis fungoides: indications and results of total skin electron beam and photon beam irradiation. *Radiother Oncol* 2000;**54**:73–8.
[42]. Masood N, Russell KJ, Olerud JE, et al. Induction of complete remission of advanced stage mycosis fungoides by allogeneic hematopoietic stem cell transplantation. *J Am Acad Dermatol* 2002;**47**:140–5.
[43]. Funk A, Hensley F, Krempien R, et al. Palliative total skin electron beam therapy (TSEBT) for advanced cutaneous T-cell lymphoma. *Eur J Dermatol* 2008;**18**:308–12.
[44]. Hauswald H, Zwicker F, Rochet N, et al. Total skin electron beam therapy as palliative treatment for cutaneous manifestations of advanced, therapy-refractory cutaneous lymphoma and leukemia. *Radiat Oncol* 2012;**7**:118.
[45]. Lens MV, Belda MS, Lopez EA, et al. Mycosis fungoides: case report treated with low-dose palliative radiotherapy. *Rep Pract Oncol Radiother* 2013;**18**:S275–81.
[46]. Garcia RG, Suppo PP, Veragua AR. Mycosis fungoides: description of the technique and clinical results. *Rep Pract Oncol Radiother* 2013;**18**:S82–3.
[47]. Wilson LD, Quiros PA, Kolenik SA, et al. Additional courses of total skin electron beam therapy in the treatment of patients with recurrent cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996;**35**:69–73.
[48]. Becker M, Hoppe RT, Knox SJ. Multiple courses of high-dose total skin electron beam therapy in the management of mycosis fungoides. *Int J Radiat Oncol Biol Phys* 1995;**32**:1445–9.

[49]. Price NM, Electron beam therapy. Its effect on eccrine gland function in mycosis fungoides patients. *Arch Dermatol* 1979;**115**:1068–70.
[50]. Desai KR, Pezner RD, Lipsett JA, et al. Total skin electron irradiation for mycosis fungoides. Relationship between acute toxicities and measured dose at different anatomic sites. *Int J Radiat Oncol Biol Phys* 1988;**15**:641–5.
[51]. Stein ME, Anacak Y, Zaidan J, et al. Second primary tumors in mycosis fungoides patients. Experience at the Northern Israel Oncology Center (1979–2002). *J Buon* 2006;**11**:175–80.
[52]. Licata AG, Wilson LD, Braverman IM, et al. Malignant melanoma and other second cutaneous malignancies in cutaneous T-cell lymphoma. The influence of additional therapy after total skin electron beam radiation. *Arch Dermatol* 1995;**131**:432–5.
[53]. Lindahl LM, Kamstrup MR, Petersen PM, et al. Total skin electron beam therapy for cutaneous T-cell lymphoma: a nationwide cohort study from Denmark. *Acta Oncol* 2011;**50**:1199–205.
[54]. Price NM. Electron beam therapy. Its effect on eccrine gland function in mycosis fungoides patients. *Arch Dermatol* 1979;**115**:1068–70.
[55]. Desai KR, Pezner RD, Lipsett JA, et al. Total skin electron irradiation for mycosis fungoides. *Relationship between acute toxicities and measured dose at different anatomic sites Int J Radiat Oncol Biol Phys* 1988;**15**:641–5.
[56]. Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. *Int J Radiat Oncol Biol Phys* 2011;**81**:651–7.