ISSN: 2469-5750

Sager et al. J Dermatol Res Ther 2017, 3:045
DOI: 10.23937/2469-5750/1510045
Volume 3 | Issue 1
Open Access

Journal of
Dermatology Research and Therapy

REVIEW ARTICLE

Radiotherapy for Mycosis Fungoides: Review of the Literature

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Abstract

Apart from systemic or nodal lymphomas, cutaneous lymphomas present a heterogeneous group of relatively infrequent non-Hodgkin lymphomas with distinct clinical characteristics. Among cutaneous lymphomas, primary cutaneous T cell lymphomas account for the majority of cases with Mycosis Fungoides (MF) being the most prevalent subtype. Skin-directed treatment constitutes the principal mode of management for early stage MF, and systemic therapies or combination of modalities are typically employed in more advanced stages. Radiation therapy including Total Skin Electron Beam Therapy (TSEBT) is a viable skin-directed tratment modality in the management of patients suffering from MF. Radiotherapy may be used alone or as part of multidisciplinary management with excellent complete response rates. Total skin irradiation is a sophisticated procedure which may be performed using different techniques such as rotational techniques, large electron field techniques, and translational techniques. Prospective randomized comparisons of different therapeutic options in the management of different stages of MF are lacking partly due to its rarity. Nevertheless, radiotherapy may be particularly effective in eradication of cutaneous tumors or thick plaques with its deep penetration capability. While radiation therapy offers the potential for cure in selected patients with unilesional disease, it may also be used for improving local control and palliating symptoms in advanced stages of MF. Radiotherapy doses of ≥ 30 Gy have been used for a long time period considering a dose-response relationship, however, there is a trend towards the use of lower doses recently since many patients may eventually need reirradiation in the course of their disease. MF is considered to be highly radiosensitive, and encouraging treatment results have been achieved with even low doses of radiation. Herein, we present a concise review of the literature regarding the use of radiotherapy in MF management.

Keywords

Mycosis fungoides, Radiotherapy, Total skin electron beam therapy (TSEBT)

Introduction

Apart from systemic or nodal lymphomas, cutaneous lymphomas present a heterogeneous group of relatively infrequent non-Hodgkin lymphomas with distinct clinical characteristics. Among cutaneous lymphomas, primary cutaneous T cell lymphomas account for the majority of cases with Mycosis Fungoides (MF) being the most prevalent subtype [1-14]. With infiltration of the skin by skin-homing CD4-positive helper T cells, cutaneous lesions are typical. However, it may take several years to make the specific diagnosis of MF given the long natural history with preceding indolent inflammatory processes in many cases. Initial biopsies of the skin lesions may be non-diagnostic and a history of several therapies for benign skin disorders is not uncommon. Following an indolent course, progression to MF may take several years and multiple biopsies may be required to make the specific diagnosis [15-17]. Once the diagnosis is established, clinical stage and other factors affecting prognosis should be thoroughly considered in the management of patients with MF [1-12,14].

While skin-directed treatment constitutes the principal mode of management for early stage disease, systemic therapies and combination of modalities are typically employed in more advanced stages. Herein, we present a concise review of the literature regarding the use of radiotherapy in MF management.

Total Skin Electron Beam Therapy (TSEBT)

Using photons or electrons, total skin irradiation is successful in addressing diffuse cutaneous disease. Electrons are more commonly preferred given their short and well-defined ranges allowing optimization of dose delivery. Rapid dose fall-off in electron therapy

Citation: Sager O, Gamsiz H, Dincoglan F, Demiral S, Uysal B, et al. (2017) Radiotherapy for Mycosis Fungoides: Review of the Literature. J Dermatol Res Ther 3:045. doi.org/10.23937/2469-5750/1510045

Received: April 13, 2017: **Accepted:** June 10, 2017: **Published:** June 12, 2017

also spares deep normal tissues. Although history of TSEBT dates back to 1950s, its utility has been widespread after the linear accelerators [18]. The application of TSEBT warrants special expertise and infrastructure which may be mostly available in well-equipped large-scale hospitals. Reported results indicate that TSEBT is an efficacious and tolerable management modality for MF [19-30].

Total skin irradiation is a sophisticated procedure which may be performed with different techniques including rotational techniques, large electron field techniques, and translational techniques [12,31-39]. Considering that TSEBT is a technically challenging modality, patients should be referred to high-volume treatment facilities with special expertise. Achieving dose homogeneity is important. If present, boosting of underdosed areas including the perineum, top of scalp, upper medial thigh, soles of feet, ventral penis, pannicular folds in obese patients, and inframammary folds in women may be required along with appropriate shielding of eyes, ears, scalp, dorsal penis, wrists, ankles, hands and feet.

Although a conventional total dose of ≥ 30 Gy has been used with success, there is a current trend towards considering lower doses of TSEBT in the range of 10 to 12 Gy to allow for reirradiation with fewer adverse effects [3,6,19]. There are encouraging results with lower doses of TSEBT, however, prospective randomized studies are needed to further refine dose-fractionation schedules with direct comparison of different regimens [6,19-23,27].

Adverse effects of TSEBT may include skin erythema, partial alopecia, pruritus, desquamation, blisters, dyspigmentation, affected limb's edema, skin pain, fatigue, nail dystrophies, decreased perspiration, telangiectasia, cutaneous infections, xerosis, cataracts, premature aging, and infertility in some patients [40]. As a very rare instance, secondary cancers may be of concern [41-43].

Radiotherapy Dose-Fractionation Schemes for MF Management

Radiotherapy doses of ≥ 30 Gy have been used for a long time period considering a dose-response relationship, however, there is a trend towards the use of lower doses recently since many patients may eventually need reirradiation in the course of their disease [44]. MF is considered to be highly radiosensitive, and encouraging treatment results have been achieved with even low doses of radiation [19-23].

Radiotherapy may be used in all stages of MF for different management goals including disease eradication, improvement of cosmesis and effective palliation of symptoms such as itching, scaling and discharge. Given the rarity of MF, there is paucity of randomized data on comparative assessment of different therapeutic options in the management of different stages of the disease. Nevertheless, radiotherapy may be particularly effective in eradication of cutaneous tumors or thick plaques with its deep penetration capability.

In early stage disease presenting with solitary lesion limited to a single anatomic site, radiotherapy may be used to achieve the primary goal of disease eradication along with improvement of clinical symptoms and prevention of progressive disease [45-49].

A wide range of radiotherapy doses from 6 to 40 Gy has been used in the management of unilesional MF with typical treatment margins of ≥ 2 centimeters [6,47,48]. A dose range of 20 to 30 Gy may be feasible and a recent guideline from the International Lymphoma Radiation Oncology Group recommends a dose range of 20 to 24 Gy for radiotherapy of patients with unilesional MF [5,6]. For patients with early stage MF, vigilant follow-up for a long duration may be needed for prompt detection of recurrences.

In the study by Chan, et al., daily treatment of patients using electrons with a dose of 30.6 to 36 Gy resulted in complete response and was generally well-tolerated with few side effects including erythema, dyspigmentation, desquamation, ulceration, and fatigue [45].

In the study by Piccinno, et al., localized superficial X-ray therapy was used in the management of 15 patients with minimal stage IA MF [46]. With a total median dose of 22 Gy, complete remission was 95.45% at 1 month from completion of treatment [46].

In the study by Micaily, et al., a complete response rate of 100% was achieved using a median local electron radiation dose of 30.6 Gy with resolution of all treated lesions within 1 to 2 months after radiotherapy [47]. There were no recurrent disease or systemic progression and no treatment-induced long-term toxicities. At 10 years, reported rates of overall survival and relapse-free survival were 100% and 86.2%, respectively [47].

In the study by Wilson, et al., a complete clinical remission rate of 97% and long-term disease free survival rate of 91% was achieved in patients treated with a dose of ≥ 20 Gy [48].

Total Skin Electron Beam Therapy (TSEBT) has also been used for management of early stage MF [28-30]. In the study by Ysebaert, et al. using TSEBT, overall response rate was reported to be 94.7% at 3 months after completion of TSEBT, and the authors concluded that TSEBT was highly effective in management of patients with MF [28].

In the study by Jones, et al., a complete response rate of 95% was achieved using a dose of 31 to 36 Gy for patients with stage IA MF with a progression free survival of 35% at 15 years [29].

In the study by Hoppe, et al., complete regression of all skin lesions was achieved in 86% of the patients with limited plaques and 10-year survival was 76% for this patient group [30].

Given the radiosensitivity of MF, radiotherapy plays a central role in local palliation, particularly for lesions localized in sanctuary areas. Symptomatic cutaneous lesions unresponsive to other therapeutic alternatives may be managed with radiotherapy in any stage of MF. Lesions are typically treated using treatment margins of 1 to 2 centimeters [6,47,48]. While superficial irradiation is performed using electrons and low photon beam energies, treatment of thick lesions may require orthovoltage/megavoltage beams or electrons of higher energy. For local palliation, radiotherapy including TSEBT is a viable therapeutic option [4-8,27,50,51]. Several dose-fractionation schemes have been employed in the literature. Low-dose radiotherapy of 8 to 12 Gy delivered in 2 to 4 fractions may improve symptoms and allows reirradiation when indicated [4]. Regarding patient convenience and cost-effectiveness, notable success has been achieved using single fraction doses of 7 to 8 Gy for local palliation with complete response rates of 94.4% [52]. In the study by Neelis, et al., a complete response rate of 92% was achieved using a dose of 8 Gy delivered in 2 fractions [53].

As a rare indication, palliative local irradiation at a total dose of 20 to 30 Gy given in fraction sizes of 2 to 3 Gy may also be used for MF patients suffering from symptomatic nodal or visceral disease [5].

Conclusions

MF is the most common form of primary cutaneous T cell lymphomas. Skin-directed treatments, systemic therapies and combination of modalities are used in management of MF. Due to the scarcity of prospective randomized data governing treatment decisions, diversity exists in MF management which may also be affected by institutional experience and availability of therapies. Radiation therapy including TSEBT constitutes a viable skin-directed treatment modality and may be utilized alone or as part of multidisciplinary management for patients with MF.

Radiotherapy may be used in all stages of MF for different management goals including disease eradication, improvement of cosmesis and effective palliation of symptoms such as itching, scaling and discharge. Prospective randomized comparisons of different therapeutic options in the management of different stages of MF are lacking partly due to its rarity. Nevertheless, radiotherapy may be particularly effective in eradication of cutaneous tumors or thick plaques with its deep penetration capability. While radiation therapy offers the potential for cure in selected patients with unilesional disease, it may also be used for improving local control and palliating symptoms in advanced stages of MF. Radiotherapy doses of ≥ 30 Gy have been used for a long time period considering a dose-response relationship, however, there is a trend towards the use of lower doses recently since many patients may eventually need reirradiation in the course of their disease. MF is considered to be highly radiosensitive, and encouraging treatment results have been achieved with even low doses of radiation. Precise identification of molecular features along with direct comparison of radiotherapy dose-fractionation schemes in randomized controlled trials may aid in future refining of therapeutic strategies.

Conflict of Interest

None.

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