

BRIEF REPORT

Real-World Pattern-of-Care Analysis of Primary Cutaneous Lymphomas Radiation Therapy Among European Organisation for Research and Treatment of Cancer Members



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Purpose: We aim to determine the current treatment patterns and recommendations among physicians for cutaneous lymphomas and to identify the types of skin lymphomas for which existing radiation regimens need improvement.

Methods and Materials: A questionnaire from the European Organisation for Research and Treatment of Cancer was distributed to all members of the Cutaneous Lymphoma Tumour Group and Radiation Oncology Scientific Council. This online survey included 13 questions regarding treatment practices for patients with cutaneous lymphoma. The survey was conducted from August 21 to December 18, 2023. Frequency distributions and subgroup comparisons were calculated and analyzed.

Results: We collected 51 completed questionnaires from investigators from 19 countries specializing in cutaneous lymphoma treatment. Radiation doses varied significantly (range, 4–60 Gy). Based on the histologic entity, up to one-third of the investigators delivered hypofractionated regimens (range, 14%–35%). Reduced-dose radiation therapy (RT) was considered by 27% to 63% of investigators. Meanwhile, 18 (35%) investigators considered adapting the radiation dose to the response to immunotherapy when treating primary cutaneous diffuse large B cell lymphoma-leg type. Regarding total skin electron beam therapy, 91% of centers delivered reduced-dose regimens, and 18% of investigators applied ultrahypofractionated protocols.

Conclusions: RT in patients with cutaneous lymphoma is highly heterogeneous among the European Organisation for Research and Treatment of Cancer centers. The development of evidence-based recommendations for RT dose, fractionation, and technique for cutaneous lymphomas is required for optimization and standardization of treatment. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Introduction

Primary cutaneous lymphoma is a diverse subset of non-Hodgkin lymphomas with an incidence of around 1 case per 100,000 person-years.^{1,2} Nearly 2/3 of patients have T cell lymphoma, while 1/3 of cases are diagnosed with B cell lymphoma.³ The treatment approach for unilesional and early-stage primary cutaneous lymphoma is usually associated with long-term disease control. However, patients with advanced-stage mycosis fungoides (MF) and Sezary syndrome are generally palliative except on some rare occasions following bone marrow transplantation.⁴ Radiation therapy (RT) is an effective therapy for the various entities of cutaneous lymphomas.⁴ Recently, low-dose and hypofractionated RT regimens have gained more interest in reducing clinical toxicities as well as cost and time aspects.^{5–10} Local RT is very beneficial in patients with localized skin manifestations. Patients with MF and Sezary syndrome usually suffer from diffuse skin manifestations affecting > 10% of body surface area, and they usually require total skin electron

beam therapy (TSEBT) instead of multiple local RT fields. Because of disease rarity, radiation doses have been analyzed retrospectively, resulting in a wide range of dose recommendations in international consensus-based guidelines without proper standardization, while the discussion between high and low-dose schedules is still ongoing.^{4,5,11,12} So far, the only prospective data available in the literature address advanced-stage MF patients receiving TSEBT.^{6,13–16} This analysis aimed to ascertain the current real-world pattern-of-care and recommendations among investigators specializing in cutaneous lymphoma treatment.

Methods and Materials

We distributed a questionnaire to all members of the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Tumour Group and Radiation Oncology Scientific Council. The online questionnaire included 13 questions regarding the treatment of patients

with cutaneous lymphoma. The first part comprised 5 questions regarding the investigator's data. The second part included 5 questions on RT indications and radiation doses and 3 questions regarding interest in gaining the required experience to conduct TSEBT. The questionnaire was made accessible through the Wufoo.com website. The survey was conducted from August 21, 2023, to December 18, 2023. Responses were recorded, stored, and analyzed anonymously. This analysis utilizes online questionnaire data without human subjects' data, and ethics approval is not required.

We defined the reduced-dose local RT as RT to a total dose of ≤ 24 Gy for primary cutaneous T cell lymphoma and indolent primary cutaneous B cell lymphoma. TSEBT reduced-dose regimens ranged between total doses of 8 and 12 Gy. In the diffuse large B cell lymphoma-leg type (DLBCL-LT), reduced-dose regimens represent a total radiation dose of ≤ 30 Gy following immunochemotherapy and 40 Gy in the case of RT alone. Radiation treatment with a daily fraction > 2 Gy has been defined as a hypofractionated regimen. Frequency distributions and subgroup comparisons were calculated and described.

Results

A total of 189 inquiries were sent. Fifty-one (27%) completed questionnaires were collected from investigators from 19 countries (Table 1). Thirty-two (63%) responders were radiation oncologists, and 19 (37%) were dermatologists. Most responses were received from university hospitals ($n = 43$, 84%), and only 8 (16%) came from nonuniversity hospitals. The median number of patients treated annually was 20 (range, 1-352). Responders from university hospitals reported relatively higher median case numbers ($n = 30$) than those from nonuniversity hospitals ($n = 12$).

Treatment patterns

The total radiation doses varied significantly (Fig. 1). For indolent primary cutaneous T cell lymphomas and B cell

Table 1 Respondents and institutions characteristics

Characteristic	N (%)
Type of facility	
University hospital	43 (84)
Nonuniversity hospital	8 (16)
Specialty	
Radiation oncology	32 (63)
Dermatology	19 (37)
Number of patients treated per annum (median, range)	20 (1-352)
$\geq 1-10$	15 (29)
$> 10-20$	11 (22)
$> 20-100$	13 (26)
> 100	12 (23)
Country	
Germany	11 (21)
France	5 (10)
Switzerland	5 (10)
Belgium	4 (8)
Spain	4 (8)
Italy	4 (8)
Egypt	3 (6)
Austria	2 (4)
United Kingdom	2 (4)
Ireland	2 (4)
Others	9 (17)

Abbreviation: N = number of investigators.

lymphomas, doses ranged from 4 to 46 Gy, while those for primary cutaneous DLBCL-LT ranged from 12 to 60 Gy. Regarding lymphoma type, the recommended RT doses were similar for nonuniversity-based and university-based investigators. Patients with localized MF, primary cutaneous anaplastic large cell lymphoma, indolent cutaneous cell

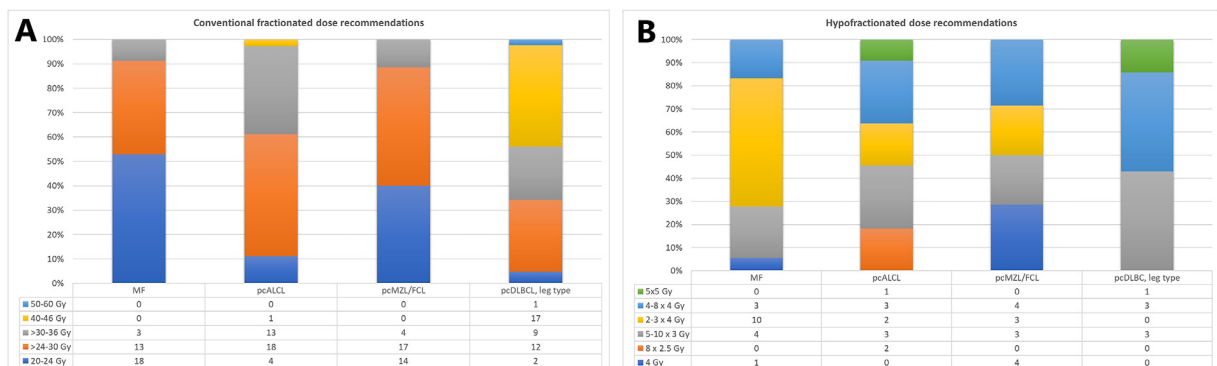


Fig. 1. Stacked bar charts with the x-axis representing disease type and the y-axis showing the proportion of recommended radiation doses. (A) Conventional fractionated regimens (B) Hypofractionated regimens.

Table 2 Proportions of radiation centers applying reduced-radiation doses and hypofractionated regimens according to the histologic entity (n = 51)

RT regimen	MF			pcALCL			MZL/FCL			DLBCL-leg type		
	Local RT			TSEBT (N = 22)								
	n (%)	Median total dose (range) Gy	n (%)	Median total dose (range) Gy	n (%)	Median total dose (range) Gy	n (%)	Median total dose (range) Gy	n (%)	Median total dose (range) Gy	n (%)	Median total dose (range) Gy
Whole cohort	51 (100)	24 (4-40)	22 (43)	12 (8-36)	51 (100)	30 (4-46)	51 (100)	30 (4-40)	51 (100)	35 (12-60)		
Reduced-dose	32 (63)	24 (4-24)	20 (91)	12 (8-12)	14 (27)	20 (4-24)	28 (55)	24 (4-24)	24 (47)	30 (12-30)		
Hypofractionated	18 (35)	12 (4-30) in 3-4 Gy fractions	4 (18)	8 (8-12) in 4 Gy fractions	11 (22)	18 (4-30) in 2.5-4 Gy fractions	14 (27)	14 (4-24) in 3-4 Gy fractions	7 (14)	25 (15-36) in 3-5 Gy fractions		

Abbreviations: DLBCL = diffuse large B cell lymphoma; FCL = follicular cutaneous lymphoma; MF = mycosis fungoides; MZL = marginal zone lymphoma; pcALCL = primary cutaneous anaplastic large cell lymphoma; RT = radiation therapy; TSEBT = total skin electron beam therapy.

lymphoma, and primary cutaneous DLBCL-LT were treated with reduced-dose regimens in 63%, 27%, 55%, and 47% of treatment centers, respectively (Table 2). Regarding DLBCL-LT, 18 (35%) centers treated patients according to their clinical responses to systemic agents, while those undergoing RT alone received a median dose of 40 Gy (range, 36-60). The proportion of hypofractionated regimens ranged between 14% and 35% among treating centers. Only 22 (43%) investigators had TSEBT expertise and/or access to this technique. Of these, 91% delivered reduced-dose regimens, and 18% of investigators applied hypofractionated protocols. The use of reduced-dose and hypofractionated regimens was similar between university hospital-based and nonuniversity-based responders in all types of lymphoma. Regarding TSEBT, the proportions of university and nonuniversity hospitals using this technique were similar (44% vs 37%). Nearly half of the radiation oncologists (45%, 13/29) without TSEBT expertise would like to establish the technique at their institutions. Regarding local RT dose recommendations, the International Lymphoma Radiation Oncology Group (ILROG) guidelines were followed by 73%, 56%, 73%, and 50% of investigators in patients MF, primary cutaneous anaplastic large cell lymphoma, marginal zone lymphoma/follicular cutaneous lymphoma, and DLBCL-LT, respectively. Following ILROG guidelines, all TSEBT dose recommendations ranged between 8 and 36 Gy. Dermatologists and radiation oncologists both demonstrated equal adherence to the ILROG guidelines.

Discussion

We conducted this international patterns-of-care analysis to understand the dose variation between the treating centers for patients who have primary cutaneous lymphoma among EORTC members. The analysis revealed 2 main findings: (1) significant variability in practice patterns, and (2) several researchers do not adhere to the ILROG guidelines. However, the response rate to this survey was only 27%; it represents the only available analysis of real-world multinational pattern-of-care data in the literature concerning this rare skin disease. Although the cutaneous lymphoma specialists and experts across Europe answered the survey, we observed heterogeneity between treating institutions of the radiation doses. Therefore, our analysis adequately represents the large proportion of patients treated in specialized institutions. The ILROG guidelines were followed by 50% to 73% of investigators for local RT of primary cutaneous lymphomas. Some investigators may not follow the ILROG guidelines for cutaneous lymphomas, published in 2015, because of the availability of recent data on lower doses and hypofractionation. Additionally, we believe some respondents' practices may deviate from current evidence-based approaches. On the other hand, all TSEBT dose recommendations were under ILROG guidelines. This was probably caused by accumulating evidence for lower radiation doses.^{6,13-16}

According to our abovementioned criteria, 27% to 63% of investigators treat their patients with reduced-dose regimens.

The rest of the investigators apply conventional radiation doses, and many patients are likely overtreated according to recent data.^{7,10,17-21} In particular, radiation dose > 24 Gy is still recommended by 37% to 45% of investigators in MF, marginal zone lymphoma, and follicular cutaneous lymphoma. In comparison, almost 2/3 of investigators prescribed > 24 to 46 Gy in patients with primary cutaneous anaplastic large cell lymphoma. Nearly half of the investigators apply 36 to 60 Gy in primary cutaneous DLBCL-LT. However, 35% of investigators considered adapting the radiation dose to the response to immunochemotherapy when treating primary cutaneous DLBCL-LT. Therefore, we highlighted the importance of having updated guidelines and consensus statements that reflect current data.²²

Regarding TSEBT, only 43% of investigators have this technique at their institutions. A total of 91% of centers delivered reduced-dose regimens, and 18% of investigators applied ultrahypofractionated protocols, probably because of the existence of prospective data in the literature. Only 9% of investigators still apply conventional TSEBT doses with 36 Gy in patients with diffuse MF manifestations. Nearly half of the radiation oncologists (45%) who do not have TSEBT at their institutions would like to establish the technique, which warrants the initiation of workshops and scientific activities to transfer the required experiences.

This analysis has several limitations. One major limitation is the response rate of only 27%. Additionally, the low percentage of responses from nonuniversity centers suggests that the data may not fully represent the patterns-of-care being delivered. Future research should focus on identifying the barriers to adopting low-dose regimens. Developing evidence-based recommendations for RT dose, fractionation, and technique for cutaneous lymphomas is needed to optimize and standardize radiation treatment. Multicentre prospective studies of RT doses are urgently needed.

Conclusions

RT of cutaneous lymphoma patients by EORTC centers is highly heterogeneous. Up to 2/3 of centers still use conventional-dose regimens for certain cutaneous lymphomas. However, trends are moving toward the acquisition of experience and acceptance of low-dose and hypofractionated regimens. The development of evidence-based recommendations for RT dose, fractionation, and techniques in cutaneous lymphomas is warranted.

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