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Radiotherapy in cutaneous lymphomas: Recommendations from the EORTC cutaneous lymphoma tumour group

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ABSTRACT

The number of primary cutaneous lymphoma patients receiving low-dose radiotherapy is increasing, though controlled clinical trials defining the standard radiation dose for each specific entity have not yet been completed. Radiation oncologists are left with making highly individualized decisions that would be better enriched by additional clinical evidence. In this expert opinion, we aim to provide a clear recommendation to improve the current practice of radiation oncology. In addition, existing literature has been reviewed to develop recommendations for all types of primary cutaneous lymphoma. A prospective trial is urgently needed to identify the factors influencing patient outcomes following different radiation doses.

1. Introduction

Primary cutaneous lymphomas are a heterogeneous group of non-Hodgkin lymphomas with increasing incidence [1]. In more than two-thirds of cases, primary lymphomas in the skin arise from T lymphocytes, while less than one-third develop from B lymphocytes [2]. The specific type of primary cutaneous lymphoma can be ascertained by histological, immunohistochemical, molecular, and in some cases flow cytometric studies [2]. Cutaneous lymphomas occur primarily in middle-aged or older adults [3].

Although most patients with cutaneous T-cell lymphoma present clinically with multiple localised lesions, a minority of patients progress to advanced stages [1,3,4]. Patients often experience symptoms that impair their quality of life and place considerable demands on medical care [5–11]. Radiotherapy (RT) for cutaneous lymphoma is probably withheld from a proportion of patients due to scarce published evidence, sometimes also limited availability, and lack of awareness of the treating physicians. However, RT is an effective therapeutic option for many different types of primary cutaneous lymphoma with excellent tolerability [12–14]. The treatment approach for patients with early stages is usually skin-directed and associated with long-term remissions, bringing the disease under control although relapses are fairly common. This contrasts with advanced mycosis fungoides (MF) and Sézary syndrome (SS) whereby most patients die of their cutaneous lymphoma. Treatment options for advanced patients are generally palliative except for some patients treated with stem cell transplantation [10]. Recent quality of life (QoL) research has shown that RT ameliorates symptoms and different subscales of health-related QoL in patients with cutaneous lymphoma [15,16]. The duration of clinical benefit following RT is usually prolonged, but may be influenced by: disease stage; delivered RT dose; and induction, combination, and maintenance systemic treatments [17–19]. On the other side, oligolesional primary cutaneous anaplastic large cell lymphoma (pcALCL) and indolent cutaneous B-cell lymphomas have a very favorable prognosis and local RT leads to improved QoL, and long-term remissions [20–24]. Primary cutaneous diffuse large B-cell lymphoma (DLBCL), leg type, has a worse prognosis and the addition of local RT can improve survival compared to systemic agents alone [25].

In this expert opinion, we aim to highlight the role of reduced-dose RT and present promising radiation dose recommendations for different types of cutaneous lymphoma.

2. As low as reasonably achievable radiation dose

RT regimens used across Europe are highly heterogeneous with a wide range of doses and fractionations employed. Over the last century, conventionally fractionated RT with 30 to 40 Gy has been considered curative and was the standard of care for cutaneous lymphoma patients until approximately 20 years ago. Recently, the use of lower doses has been increasingly applied based on the accumulation of safety and efficacy data of local RT from retrospective case series in the literature. Limited data from prospective registries investigating the total skin electron beam treatment (TSEBT) in advanced-stage MF have been recently published. Evidence gathered from randomized clinical trials comparing various radiation doses remains scarce. The advantages of low-dose regimens include their low toxicity profile and the option of repetition of the treatment sessions while maintaining a high efficacy due to the characteristic high radiosensitivity of cutaneous lymphoma skin lesions. From a patient's and healthcare perspective, low-dose RT is more convenient and requires fewer hospital visits, which may reduce time demands and costs.

3. Radiobiological effects of low-dose RT and mode of action

Low-dose RT has a direct cytotoxic effect in addition to the antitumour efficacy by preferring proinflammatory M1-like macrophage polarization and enriching natural killer cell infiltration [26]. Moreover, low doses reprogram the tumor microenvironment (TME) and enhance the trafficking and role of immune cells in skin manifestations [26]. RT-induced double-stranded DNA breaks lead to micronuclear cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP-AMP) synthase expression and interferon release [27,28]. RT doses above 12–18 Gy upregulate DNA nuclease three-prime repair exonuclease 1 (TREX1). Accordingly, TREX1 degrades cytoplasmic double- and single-stranded DNA, voiding the RT-induced antitumour immune reaction [28–30].

Moreover, RT can upregulate the expressions of various molecules, ligands, death receptors, neoantigens, danger signals, exosomes, danger signals, chemokines, and proinflammatory cytokines such as IFN-γ in the TME [31–33]. RT can also stimulate activated CD8 + T cell proliferation [34,35]. In selected cases, there is evidence suggesting that low-dose RT combined with conventional-dose RT and immunotherapy generates systemic antitumor responses and downregulates transforming growth factor-β, a cytokine that boosts tumor development and progression. Enhanced natural killer cell activation and infiltration within the TME and granzyme B production increase M1 and decrease M2 macrophage populations. In addition, low-dose RT activates nodal CD4 + and CD8 + T cells [26].

The role of low-dose RT proved very interesting when combined with immunotherapy to induce a systemic response. Antitumour immunotherapy with adoptive cytotoxic T lymphocytes is involved solely when preceded by RT to the primary lesions [36,37]. Thereafter, CD4 + and CD8 + cell attraction occurred in both irradiated and non-irradiated sites [38]. Ongoing clinical studies to assess safety and efficacy include a phase 2 trial of mogamulizumab (anti-CCR4 Ab) with low-dose TSEBT (ClinicalTrials.gov ID: NCT04128072); and a phase 1 trial of brentuximab combined with low-dose TSEBT (ClinicalTrials.gov ID: NCT02822586). Another phase 2 trial of low-dose TSEBT combined with

12 Gy ± mechlorethamine gel as maintenance treatment was reported recently with encouraging results [39].

4. Current treatment modalities for cutaneous T-cell lymphoma

Recently published European Organization for Research and Treatment of Cancer (EORTC) consensus recommendations inform on the treatment selection based on the patient's clinical condition and tumour stage [10]. Numerous skin-directed and systemic treatments have been developed. Recently, low-dose RT regimens used alone or in combination with additional therapies have gained growing interest. However, no randomized trials support the selection of radiation-based therapies over other modalities [40]. The most common types of radiation used are electrons, photons, kilovoltage X-ray, and brachytherapy. RT's local and systemic effects make it an essential modality. Rare types of aggressive primary CTCL such as subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma/delta T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, and primary cutaneous natural killer cells (NK)/T-cell lymphoma present with characteristic clinical and immunophenotypic features with a limited role of low-dose radiation [2]. In this section, we will review the RT role for MF, SS, pcALCL, primary cutaneous CD4 + small/medium T-cell lymphoproliferative disorder, and primary cutaneous B-cell lymphomas (Fig. 1).

4.1. Mycosis fungoides

Superficial RT is a highly effective treatment for plaques and tumours of MF. Treatment may be used as monotherapy in patients with limited disease, as adjuvant therapy in those with lesions not responding to their current therapy or as palliation for symptomatic lesions.

Treatment is usually 8–12 Gy in two or three fractions [41,42]. A high response rate was observed following low-dose RT, with a 1-year local control rate of $\geq$ 92 %. However, 4 Gy RT (in one or two fractions) exhibited an inferior local control rate [41,42]. For patients with more than 10 % BSA involvement, low-dose TSEBT regimens have earned increasing interest again to reduce toxicity and to provide the prospect of repetition in patients with relapse (Table 1). Low-dose TSEBT (8 - 12 Gy) is typically used to palliate skin lesions in advanced disease and higher RT doses (up to 24 Gy) can be used to induce remission before autologous stem cell transplantion [19,43–47]. Patients with large lesions or insufficient response to low-dose RT can receive 24 Gy [14]. Furthermore, low-dose TSEBT could be a better choice for patients who are not already heavily pretreated with several lines of therapy. However, patients who have already undergone several lines of systemic therapy and have fewer further options could benefit from a higher dose of TSEBT. Multimodal therapeutic approaches that add systemic treatments to TSEBT may be beneficial [39–41].

Treatment experience for MF variants and subtypes is limited [61,62]. One retrospective study of 203 cases included in the Dutch Cutaneous Lymphoma Registry indicated that in folliculotropic MF, RT is more effective than other modalities [61]. Similarly, low-dose TSEBT can be useful in large-cell transformed MF [43,63].

4.2. Sézary syndrome

TSEBT for Sézary syndrome remains controversial and rarely achieves long-term remissions [13,64]. In a disease defined by blood involvement, TSEBT also exerts a systemic impact by reducing circulating Sézary cell counts [55,65]. For selected patients with SS, integrated immunomodulatory agents, targeted therapies, and TSEBT followed by stem cell transplantation represent an encouraging option [46,47,66]. Potential outcomes of TSEBT in combination with current immunotherapies include rapid improvement of skin symptoms and QoL within four to eight weeks of RT initiation [15,67]. TSEBT has been described to reduce not only cutaneous tumour burden but also lymphadenopathy if begun before or simultaneous to systemic treatment [65,68]. In refractory SS cases, RT can reprogram the TME by upregulating the expression of targeted receptors (e.g., CCR4) [69]. In addition, TSEBT may be applied in cases suffering from severe immune-related

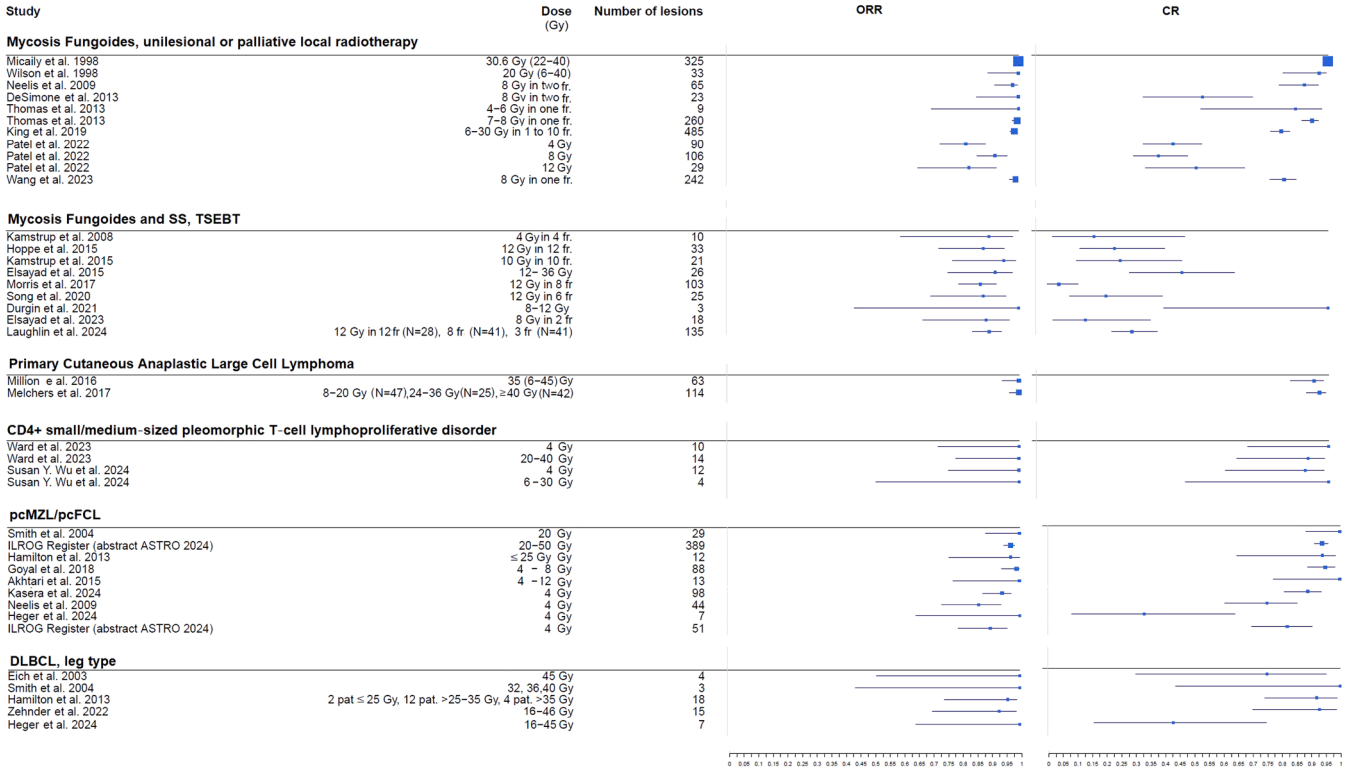

Fig. 1. Forrest plots that summarize treatment effects in each type.

Table 1
Efficacy and toxicity rates of modern-dose radiotherapy regimens for patients with primary cutaneous T-cell lymphomas.

Study type	Number of patients/lesions	RT dose (range)	ORR (CR), %	Tox. Grade 3/4, %	Outcome	Ref.
Primary cutaneous T-cell lymphoma						
Mycosis Fungoides, unilesional or palliative local radiotherapy						
Retrospective	325	30.6 Gy (22 −40)	100 (100) TTR ≤ 8 months	No	1 % local relapses	Micaily et al. [48]
Retrospective	21/33	20 Gy (6 −40)	100 (97)	No	15 % local relapses (<20 vs. ≥20 Gy n.s.)	Wilson et al. [49]
Retrospective	31/88	4 - 8 Gy in two fr.	NA (30) 98 (92)	No	8 % local relapses after 8 Gy	Neelis et al. [42]
Retrospective	10/23	8 Gy in two fr.	100 (57)	No	No local relapses	DeSimone and Guenova et al. [50]
Retrospective	58/270	7 −8 Gy in one fr. (in 260 lesions)	96 (94)	No	1.5 % local relapse rate	Thomas et al. [51]
Retrospective	41/225	4, 8, and 12 Gy (in two to six fr.)	87 (47) n.s. between doses Median TTR 8 weeks	27 % following 12 Gy versus 0 % after 4 −8Gy	Local relapse 77 %, 91 %, and 96 % (P = .034)	Patel et al. [41]
Retrospective	46/242	8 Gy in one fraction	99 (85)	No	No local relapses **Less financial tox.**	Wang et al. [52]
Mycosis Fungoides and SS, TSEBT						
Prospective	10 MF	4 Gy in 4 fr.	90 (20)	No	Median time to progression: 3.5 mo	Kamstrup et al. [53]
Prospective	33 MF	12 Gy in 12 fr.	88 (27) Median TTR 8 weeks (3 −12)	6 %	Median DOCB: 18 mo	Hoppe et al. [43]
Prospective	19 MF 2 SS	10 Gy in 10 fr.	95 (29)	No	Median DOR: 6 mo	Kamstrup et al. [44]
Retrospective	26 MF 10 SS 9 non-MF/SS	12- 36 Gy	92 (50) 70 (50) 89 (78)	0 % following 12 Gy with lower acute tox. Grade 2	Median time to progression: 5 mo (<30 vs. ≥30 Gy n.s.) **Less time tox.**	Elsayad et al. [17]
Prospective	103 MF	12 Gy in 8 fr.	87 (18)	8 %	Median time to progression: 7 mo Median DOR: 12 mo	Morris et al. [54]
Prospective	25 MF patients	12 Gy in 6 fr.	88 (24) TTR 8 weeks (4 −16)	No	Median DOR: 17 mo **QoL data available**	Song et al. [16]
Retrospective	3 SS	8 −12 Gy	100 (100)	No	DOR range: 24 −30 mo	Durgin et al. [55]
Prospective	15 MF 3 SS	8 Gy in 2 fr.	89 (17)	6 %	TTNT 12 mo **QoL data available**	Elsayad et al. [56]
Retrospective	83 MF 16 SS	12 Gy in 12 fr. (N = 28) 12 Gy in 8 fr. (N = 41) 12 Gy in 3 fr. (N = 41)	90 (33 %) Median TTR 6 weeks	No	Median time to progression 3.5 months (0 −24)	Laughlin et al. [57]
Primary Cutaneous Anaplastic Large Cell Lymphoma						
Retrospective	56/63	35 (6 −45)	100 (95) (RT dose n.s.)	NA	2 % local relapses (RT dose n.s.)	Million e al. [22]
Retrospective	69/114	8 −20 Gy (N = 47) 24 −36 Gy (N = 25) ≥ 40 Gy (N = 42)	100 (97) (RT dose n.s.)	NA	No local relapses	Melchers et al. [58]
CD4 + small/medium-sized pleomorphic T-cell lymphoproliferative disorder						
Retrospective	24	4 Gy in 2 fr. (N = 10) 20 −40 Gy (N = 14)	100 (100) 100 (93)	0 % 7 %	No local relapses (more relapses after surgery)	Ward et al. [59]
Retrospective	16	4 Gy in 1–2 fr. (N = 12) 6 −30 Gy (N = 4)	100 (92) 100 (100)	0 %	No local relapses	Wu et al. [60]

FU: follow-up, Gy: Gray, DFS: disease-free survival, TTR: time to response, n.s.; non-significant, MF: mycosis fungoides, fr.: fraction, SS: Sézary syndrome, Tox.: toxicity, DOCB: duration of clinical benefit, Mo.: months, DOR: duration of response, NA: not available, QoL: quality of life.

toxicities during therapy-free intervals or before systemic treatment to prevent skin flares or worsening of cutaneous symptoms [70–72].

4.3. Primary cutaneous anaplastic large cell lymphoma

pcALCL present as unilesional, grouped, or, rarely, multifocal lesions. Genetic rearrangements are detected in some cases, with no significant predictive value [2]. Unilesional or multiple localised lesions may be treated with RT [62]. RT is very effective and results in few relapses at doses of 20 Gy and even [22,58,73,74]. Patients with nodal or visceral manifestations or cases of diffuse skin lesions require systemic therapies with or without RT [62]. Palliative RT with 2×4 Gy might promptly alleviate cutaneous symptoms and limit the number of hospital visits [58].

4.4. Primary cutaneous CD4 + small/medium T-cell lymphoproliferative disorder

Patients usually experience a unilesional plaque or tumour on the head and neck region or upper half of the body [2]. If the treatment is required, low-dose RT with 4 Gy in two fractions was established to be effective and tolerable, with a 100 % remission rate and no local relapses [59,60].

5. Primary cutaneous B-cell lymphomas

Primary cutaneous marginal zone lymphoma (pcMZL) and primary cutaneous follicle centre lymphoma (pcFCL) are the most common types of primary cutaneous B-cell lymphomas and are usually associated with an excellent prognosis. Doses of 4 Gy can be curative in many cases of pcFCL and pcMZL (Table 2). Lesions larger than 5 cm in diameter that are treated with 4 Gy have been shown to have worse outcomes [23]. A small retrospective studies indicated comparable response rates and rates of in-field recurrence between ultra-low dose and higher-dose RT schedules [75-77]. On the other hand, a recent retrospective study with a long follow-up period found that ultra-low dose RT with 4 Gy had inferior response rates and higher rate of in-field relapse compared to higher doses [78]. As a result, it may be beneficial to explore a response-adapted approach with RT dose escalation to a cumulative dose of 24 Gy in case of residual disease or local failure after 4 Gy [78, 79].

Primary cutaneous DLBCL, leg type is relatively rare and carries a worse prognosis. The treatment algorithm for the primary cutaneous DLBCL-leg type is adopted from the nodal type. Usually, it mandates anti-CD20 immunotherapy-integrated regimens (i.e., rituximab-based), age-adapted chemotherapy, and a consolidation RT in localised cases. However, many elderly patients with comorbidities may not tolerate conventional chemoimmunotherapy and are treated with local radiation alone [25,85]. In a small retrospective study, Zehnder et al. [85] showed identical effectiveness of RT when compared to immunochemotherapy alone in selected cases. At the same time, Kraft et al. [25] confirmed an additional benefit of local RT following systemic therapies in a small case series. Following systemic therapies, radiation doses may be reduced to 30 Gy with equivalent effectiveness [86]. Lately, systemic DLBCL cases responding to systemic treatments were treated with consolidative RT with 20 Gy with relatively lower toxicities [87].

Table 2
Efficacy and toxicity rates of modern-dose radiotherapy regimens for patients with primary cutaneous B-cell lymphomas and unilesional or multiple localised lesions.

Study type	Number of patients/ lesions	RT dose	ORR (CR), %	Tox. Grade 3/4, %	Duration of responses or TTNT	Ref.
Primary cutaneous B-cell lymphoma pcMZL/pcFCL						
Retrospective	29	20 −48 Gy	100 (100)	NA	Local relapse rate 25 % 5-y RFS 62 %, local 8 %	Smith et al. [80]
Retrospective	154	NA	(82) (99)	NA	5y-DFS ≥ 94 %	Senff et al. [81]
Retrospective	18/44	4 Gy in 2 fr.	86 (75) TTR ≤ 6 weeks	No	11 % local relapse rate	Neelis et al. [42]
Retrospective	44	4 −40 Gy	100 (100) (RT dose n. s.)	No	No local relapses	Akhtari et al. [76]
Retrospective	54/88	4 −8 Gy in 2 fr. (N=51) 24 −40 Gy (N= 37)	99 (95)	No (Less acute & chronic tox. Grade 1 −2)	Local relapse rates: 20 % vs. 8 % (RT dose n.s.)	Goyal et al. [82]
Retrospective	103/124	≤ 25 Gy (N = 12) > 25 −35 Gy (N = 67) > 35 Gy (N = 7)	97 (94)	NA	Local relapse rate: 2 % (RT dose n. s.) RT improve time to progression (P = .02)	Hamilton et al. [83]
Retrospective	43/98	2×2 Gy	94 (89)	No	Local relapse rate: 6 %	Kasera et al. [77]
Prospective observational	40	36 Gy (range, 4 −50)	95 (72)	No	Local relapse rate: 13 %. **QoL data available**	Heger and Elsayad et al. [24]
Retrospective ILROG-register	440	4 Gy in 2 fr. (N = 51) 8 −50 Gy (N = 389)	90 (82) 97 (94)	No	Local relapse rate: 28 % vs. 5 % (p < 0.001)	Oertel et al.[78]
DLBCL, leg type						
Retrospective	4	45 Gy/1.8 Gy (N = 2) 45 Gy/3 Gy (N = 2)	100 (75)	No grade 3/4 tox.	No local relapses	Eich et al. [84]
Retrospective	3	36 Gy (32 −40)	100 (100)	NA	Local relapse rate: 33 %	Smith et al. [80]
Retrospective	18	≤ 25 Gy (N = 2) > 25 −35 Gy (N = 12) > 35 Gy (N = 4)	96 (92)	NA	Local relapse rate: 4 % (RT dose was n.s.)	Hamilton et al. [83]
Retrospective	15	16 Gy/4Gy (N = 3) 32 Gy/4 Gy (N = 4) 36 −46/2 Gy (N = 3) 24/4 Gy (N = 2) 40/4 Gy (N = 2) 25/5 Gy (N = 1)	93 (93)	NA	No local relapses	Zehnder and Guenova et al. [85]
Prospective observational	7	36 Gy (range, 16 −45)	100 (43)	14 %	Local relapse rate: 14 % **QoL data available**	Heger and Elsayad et al. [24]

pcMZL: Primary cutaneous marginal zone lymphoma, pcFCL: primary cutaneous follicle centre lymphoma, RFS: relapse-free survival, FU: follow-up, Gy: Gray, DFS: disease-free survival, TTR: time to response, n.s.; non-significant, DLBCL: diffuse large B cell lymphoma, Tox.: toxicity, DOCB: duration of clinical benefit, Mo.: months, DOR: duration of response, NA: not available, R-CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), and vincristine sulfate, prednisone, QoL: quality of life.

Hypofractionated regimens with a weekly dose of 4 Gy until response or up to 40 Gy yield comparable efficacy [85]. Furthermore, immunotherapy is also associated with clinical efficacy in relapsed and refractory cutaneous DLBCL patients [25]. Prospective interdisciplinary trials on this rare type of lymphoma are warranted.

5.1. Recommendation

Based on the abovementioned data, reduced-dose RT represents a very effective treatment for the more indolent cutaneous lymphomas (i.e., MF, pcALCL, CD4 + small/medium-sized T-cell lymphoproliferative disorder, pcMZL, and pcFCL). Although the evidence supporting RT is still low due to the lack of prospective randomized trials. On the other hand, for patients with advanced MF, SS, and DLBCL, leg type there is still room for improvement, and they could benefit from combined modalities, especially with modern immunomodulatory agents and immunotherapies. The authors developed a treatment algorithm to standardize the radiation dose recommendations across the EORTC centres (Figs 2A and 2B). The increasing significance of shared decision-making for patients receiving RT underscores the critical need for the eagerly anticipated ESTRO consensus guideline [88]. This guideline will define patient empowerment from a radiation oncology perspective, shaping the future of patient care in this field. In addition, health-related QoL data following modern radiation doses are warranted to enhance patient empowerment strategies [88].

6. Conclusions

Local RT at low doses is an effective therapy for many types of primary cutaneous lymphoma. It can achieve rapid relief of cutaneous lesions and symptoms with low toxicity with a low rate of local relapse. Low dose TSEBT similarly can lead to good response rates however relapse is common and new approaches are required to prolong remissions. We urgently need a prospective randomized trial with translational research to pinpoint the parameters that affect the outcomes of patients with primary cutaneous lymphoma following different radiation doses.

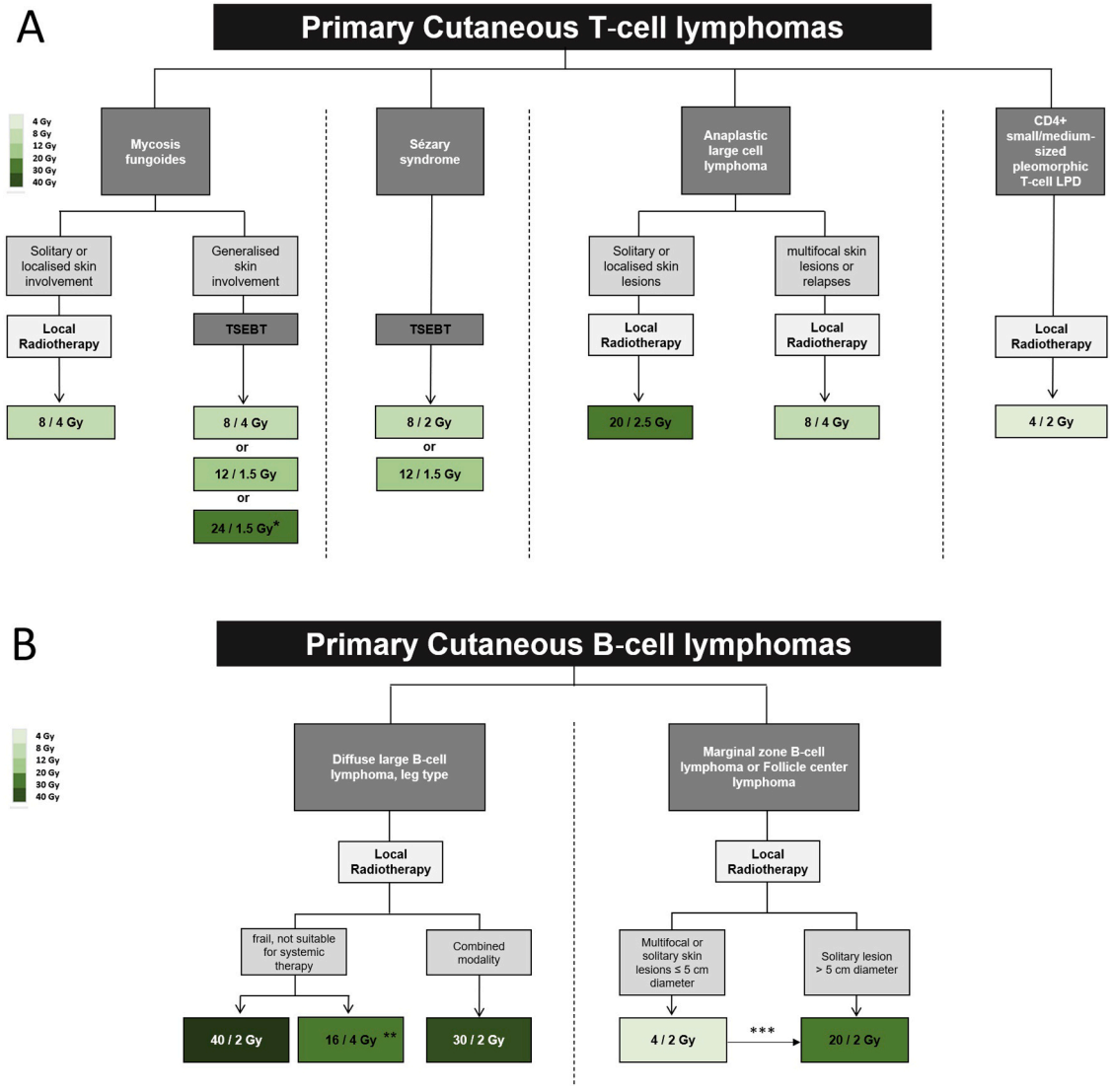

Fig. 2. Radiotherapy dose recommendations for primary cutaneous lymphomas with the total radiation dose/fraction dose.
* Before stem cell transplant
** Repeat if no complete response at 4 months
*** Residual lesions or stable disease at 4 months or progressive disease at any time

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CRediT authorship contribution statement

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Declaration of Competing Interest

Khaled Elsayad: received consulting and lecture fees from Kyowa Kirin and Gilead Sciences.

Franz Trautinger: received consulting and lecture fees from Kyowa Kirin, Recordati Rare Diseases and Takeda.

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All remaining authors have declared no conflicts of interest.

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