Cutaneous Lymphomas

9

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Abstract

Primary cutaneous lymphoma (PCL) is the second most common type of extranodal lymphoma. PCL has different clinical behavior and prognosis than those of extranodal lymphomas arising from other sites, and requires a different pretreatment evaluation system and treatment strategy. All patients with PCL should be reviewed by a multidisciplinary team to decide an appropriate treatment strategy. PCL has three major disease entities including T-cell and natural-killer (NK)-cell lymphoma, B-cell lymphoma, and precursor hematological neoplasm. Mycosis fungoides is the most common type of cutaneous T-cell lymphoma, and its clinical behavior is indolent with slow progression. The treatment strategies of mycosis fungoides are based on a "Stage-based" approach, and "Expectant policy" is a reasonable treatment option for early stage disease. Total skin electron beam therapy (TSEBT) and adjuvant therapy may be applied for the patients with stage IB-IIB. The European Organization for Research and Treatment of Cancer proposed the technical guidelines of TSEBT. The standards of care for PCLs, other than mycosis fungoides and Sézary syndrome, have not been established because of their infrequency. The treatment strategies for each PCL subtype should be decided according to disease subtype, stage, clinical features, and patient's condition.

Keywords

Primary cutaneous lymphoma • Mycosis fungoides • Sézary syndrome • Total skin electron beam therapy • Radiotherapy

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9.1 Introduction

Primary cutaneous lymphoma is the second most common type of extranodal lymphoma, with an estimated annual incidence of one per million [1–5]. The term "primary cutaneous lymphoma" refers to hematological neoplasms which are present in the skin with no evidence of extracutaneous disease at the time of diagnosis [4]. Primary cutaneous lymphoma has a significantly different clinical behavior and prognosis from those of other extranodal lymphomas arising from other sites, and requires a different treatment strategy. Primary cutaneous lymphoma includes heterogeneous disease entities, and requires each optimal treatment strategy. There were formerly some differences between the European Organization for Research and Treatment of Cancer (EORTC) classification systems for primary cutaneous lymphomas and the World Health Organization (WHO) classification, and various debate and confusion on terminology and disease entities had existed [6, 7]. These differences were resolved by representatives of both classification systems in the consensus meetings, and WHO-EORTC classification for cutaneous lymphomas has been established (Table 9.1) [4]. In the last decade, the international consensus of staging classification for cutaneous lymphoma, clinical endpoints and response criteria, and technical guidelines of total skin electron beam therapy (TSEBT) have been reported [4, 8–15]. And local therapies including topical therapy and phototherapy and novel systemic therapies including immuno-chemotherapy have been investigated [9, 10, 12, 16, 17]. In this chapter, the current standards of care and adequate radiotherapy techniques for primary cutaneous lymphomas are mainly described.

Table 9.1 WHO-EORTC* classification of cutaneous lymphomas with primary cutaneous manifestations [4]

Cutaneous T-cell and natural-killer (NK)-cell lymphomas
Mycosis fungoides
Mycosis fungoides variants and subtypes
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous gamma/delta T-cell lymphoma (provisional)

Table 9.1 (continued)

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

**WHO* World Health Organization, *EORTC* European Organization for Research and Treatment of Cancer

9.2 Pathology

The diagnosis and classification of primary cutaneous lymphomas should always be based on a combination of clinical features, histological findings, and immunephenotypical data [8, 16, 18]. Repeated skin biopsies are often required to achieve a confidential diagnosis [15]. It is always best to biopsy the most indurated area of skin. There are three main disease entities of primary cutaneous lymphomas including cutaneous T-cell and natural-killer (NK)-cell lymphoma, B-cell lymphoma, and precursor hematological neoplasm according to WHO-EORTC classification [4].

9.2.1 Mycosis Fungoides and Sézary Syndrome

The atypical cells are small- to medium-sized and mostly confined to the epidermis. They characteristically colonize the basal layer of the epidermis. They express CD3, CD4, CD45RO, CD8, and memory T-cell phenotype, but frequently lose the expression of CD8 and other pan T-cell antigens [4, 19]. The International Society for Cutaneous Lymphomas (ISCL) recommended the criteria for diagnosis of Sézary syndrome including the following factors: erythroderma defined as erythema covering at least 80% skin surface area, demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods, an absolute Sézary cell count of at least 1000 cells/mm^3, a CD4/CD8 ratio more than 10 (due to the clonal expansion of CD4+ T-cells), and loss of any or all of the T-cell antigens [4, 19, 20].

9.2.2 CD30-Positive Lymphoproliferative Disorders

Primary cutaneous anaplastic large-cell lymphoma shows dense nodular dermal infiltration of large pleomorphic, anaplastic, or immunoblastic cells. Immunephenotypically, CD30, CD4, and CD8 are expressed in most patients with various loss of pan T-cell

antigens [9, 21]. The pathological features of lymphomatoid papulosis are various and four pathological subtypes are delineated [9]. Immunephenotypically, CD30-positive tumor cells express CD4 in most patients, and CD8 and CD56 are expressed in some patients.

9.2.3 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type is nearly always associated with Epstein–Barr virus, and it has small-, medium-, or large-cells with NK/T-cell, or more rarely a cytotoxic T-cell phenotype. The neoplastic cells express CD2, CD56, cytoplasmic CD3Ɛ, and cytotoxic proteins, but lose the expression of CD3 [4].

9.2.4 Primary Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma becomes nodular to diffuse infiltrates while sparing the epidermis. The infiltrates are composed of small lymphocytes, marginal zone B-cells, lymphoplasmacytoid cells, and plasma cells admixed with small numbers of centroblast-like cells or immunoblast-like cells, and many reactive T-cells [4]. The marginal zone B-cells express CD20, CD79a, and bcl-2, but lose the expression of CD5, CD10, and bcl-6. Primary cutaneous follicle center lymphoma consists of centrocytes, relatively few centroblasts, and many reactive T-cells [4]. CD20, CD79a, and bcl-6 are expressed, and staining for CD5 and CD43 is negative.

9.3 Lymphoma Subtype for Radiation Therapy

9.3.1 Mycosis Fungoides and Variant Subtypes, and Sézary Syndrome

Mycosis fungoides is the most common type of cutaneous T-cell lymphomas and accounts for 50% of them [4]. The clinical behavior is indolent with slow progression [17]. The median time from symptoms' onset to diagnosis is approximately 4 years, but exceeds four decades in some patients [14, 19]. The median age at diagnosis is the mid-50s, and men are affected twice as often as women [17, 19]. Folliculotropic mycosis fungoides is a variant type characterized by the presence of folliculotropic infiltrates. Most patients show mucinous degeneration of the hair follicles, and secondary bacterial infections are frequently observed. Pagetoid reticulosis is a variant type characterized by the presence of localized patches or plaques with an intraepidermal proliferation of T-cell neoplasms [4]. Sézary syndrome is defined as a leukemic condition of cutaneous T-cell lymphoma associated with erythroderma, and accounts for 5% of cutaneous T-cell lymphoma [19, 22]. It has an aggressive clinical behavior, and the treatment goals are long-term disease control and prompt symptom relief.

9.3.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

Primary cutaneous CD30-positive lymphoproliferative disorders are the second most common conditions of cutaneous T-cell lymphomas, and include primary cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis [9]. They have an excellent prognosis, and half of them show spontaneous regression. The patients with lymphomatoid papulosis have a risk of second cutaneous or nodal lymphoid malignancies, including mycosis fungoides, cutaneous and nodal anaplastic large-cell lymphomas, and Hodgkin lymphoma [23].

9.3.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma with alpha/beta T-cell phenotype and no evidence of hemophagocytic syndrome has an excellent prognosis [8]. A hemophagocytic syndrome is associated with extremely aggressive clinical behavior, and the patients with hemophagocytic syndrome should be treated with intensive treatment [8].

9.3.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type has an aggressive clinical behavior and poor survival rate [8]. Although intensive multi-agent chemotherapy might be applied, it often indicates resistance to chemotherapy. High-dose radiotherapy to the primary site might be required for good tumor control.

9.3.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Primary cutaneous peripheral T-cell lymphoma, unspecified has three provisional subtypes, and they have generally aggressive clinical behavior and poor survival rate [8]. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma and cutaneous gamma/delta T-cell lymphoma are progressive diseases, and require intensive treatment [1]. On the other hand, primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma is an exception, and a solitary lesion has an excellent outcome after local radiotherapy or surgical excision [1].

9.3.6 Primary Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma have indolent behavior with an excellent treatment outcome [4]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an unfavorable prognosis, and requires intensive treatment.

9.4 Pretreatment Evaluation and Staging

Staging procedures including complete physical examination, complete blood count, differential white blood cell count, serum biochemistry, and appropriate imaging techniques should be performed for all patients, and bone marrow aspiration and biopsy might be required for the selected patients with advanced disease [8, 10, 16]. Standardized photographs are recommended to document the appearance of skin lesions at the time of baseline and at the time of disease progression [10]. Imaging with computed tomography (CT) is routinely undertaken for patients with mycosis fungoides T3-4 disease to assess visceral and nodal involvement, but is less valuable for patients with T1-2 disease [15, 17]. Positron emission tomography (PET) can increase the sensitivity of detection of involved lymph nodes and is useful to evaluate treatment response in patients with advanced mycosis fungoides [17].

ISCL and EORTC revised the staging system and classification for mycosis fungoides and Sézary syndrome in 2007 [16]. The ISCL and EORTC staging system should be applied specifically to mycosis fungoides and Sézary syndrome (Table 9.2). T1 category for mycosis fungoides is defined as limited patches, papules, and/or plaques covering 10% or less skin surface area, T2 as patches, papules, and/or plaques covering 10% or more skin surface area, T3 as one or more tumors which are 1 cm diameter or larger, and T4 as condition of erythema covering 80% or more skin surface area [16]. N classification is diagnosed for abnormal peripheral lymph nodes, M classification for visceral involvement, and B rating for abnormal tumor cells in the peripheral blood. Total body skin scoring should be performed for evaluation of initial skin lesions and assessment of response [10]. The most widely used methods for skin scoring are the Severity Weighted Assessment Tool (SWAT) and modified-SWAT [22, 24]. ISCL and EORTC proposed a separate TNM classification for the primary cutaneous T-cell lymphomas other than mycosis fungoides and Sézary syndrome [11].

Table 9.2 The International Society for Cutaneous Lymphomas (ISCL) and EORTC revision to the staging of mycosis fungoides and Sézary syndrome [16]

Clinical stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
III	4	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

9.5 Prognostic Factors

For patients with mycosis fungoides and Sézary syndrome, four risk factors, including stage IV, age over 60 years, large-cell transformation, and elevated serum lactate dehydrogenase level, are independent prognostic factors for poor survival [3, 13]. Combining these four factors in a prognostic index model can identify the three different risk groups, and the 5-year overall survival rates of the low-risk group (zero to one factor) is 68%, that of the intermediate-risk group (two factors) is 44%, and that of the high-risk group (three to four factors) is 28%. Other poor prognostic factors include folliculotropic type, elevated soluble interleukin-2 receptor level, and T-cell clonality in the skin and peripheral blood [22, 23, 25]. Advanced stage, elevated beta-2 microglobulin, and elevated lactate dehydrogenase level are associated with the risk of large-cell transformation [1, 22].

Poor prognostic factors of cutaneous B-cell lymphoma include unfavorable histology (diffuse large cell type or immunoblastic large cell type) and unfavorable skin sites (trunk, legs, disseminated) [26, 27]. Poor prognostic factors of indolent cutaneous B-cell lymphoma consist of elevated serum lactate dehydrogenase level, morphology of the lesion (non-nodular lesion), and multiple lesions (>1) [28].

9.6 Treatment Strategy

Reliable histological diagnosis and complete pretreatment staging evaluation are essential, and all patients should be reviewed by a multidisciplinary team to decide an appropriate treatment strategy [15].

9.6.1 Mycosis Fungoides

Most mycosis fungoides are low-grade malignancies with long survival time, but the patients with advanced diseases and aggressive variant subtypes show poor prognosis [3, 22]. The treatment strategies of mycosis fungoides are based on a “Stage-based” approach [3]. Patients with limited patches or plaques (stage IA; T1N0M0B0-1) have a normal life expectancy, and “Expectant policy” is a legitimate treatment option [1, 14, 15]. Over-aggressive therapy with multiagent chemotherapy and/or high-dose radiotherapy should be avoided [1]. For the patients with stage IA, skin-directed therapy including topical corticosteroids, topical chemotherapy, topical retinoid, phototherapy (psoralen-ultraviolet A light therapy [PUVA]), and local radiotherapy are recommended [1, 14, 15]. If a skin-directed therapy fails to obtain an adequate response, a rotation to other skin-directed therapies should be attempted before aggressive systemic therapies or TSEBT. The patients with stage IB (T2N0M0B0-1) and IIA

(T1-2N1-2M0B0-1), the folliculotropic variant, and large-cell transformation require more aggressive treatment, but skin-direct therapies including topical corticosteroids, topical chemotherapy, phototherapy, and local radiotherapy should be administrated rather than systemic therapies [1, 14, 15]. For patients with rapidly progressive generalized or thickened plaque lesions, TSEBT might be considered as the initial therapy rather than skin-directed therapy alone. TSEBT followed by adjuvant therapy including skin-directed therapy and extracorporeal photopheresis (ECP) produces a significant benefit of relapse-free survival, but not overall survival [1, 12, 18, 23]. For the patients with stage IIB (T3N0-2M0B0-1) and stage III (T4N0-2M0B0-1), PUVA plus alpha-interferon, TSEBT plus local radiotherapy, and retinoid plus alpha-interferon are recommended [1, 14].

Repeated TSEBT is an optional salvaged treatment for the selected patients with relapsed diseases after standard-dose TSEBT [29, 30]. The following eligibility criteria for second-course TSEBT are the initial response to TSEBT, a long disease-free interval from the initial therapy, exhaustion of other treatment approaches, and diffuse skin involvement [31].

9.6.2 Sézary Syndrome

Several retrospective studies reported that combination therapy with TSEBT and ECP and/or multi-agent chemotherapy produced favorable treatment outcomes [8, 17, 18]. European Society for Medical Oncology guidelines recommended ECP and/or other systemic approaches for Sézary syndrome [3, 8]. Many systemic therapeutic regimens, including cytotoxic drugs and novel molecular target therapies, have been investigated [3].

9.6.3 Cutaneous CD30-Positive Lymphoproliferative Disorders

EORTC, ISCL, and United States Cutaneous Lymphoma Consortium (USCLC) reported consensus statements for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders [9]. Surgical excision and radiotherapy are most common and best documented therapies for solitary or localized cutaneous anaplastic large-cell lymphoma [2, 9]. Spontaneous regression of cutaneous lesion has been observed in about 40% of patients with cutaneous anaplastic large-cell lymphoma, and patients should be informed that the outcome after spontaneous regression of initial relapse tumors is excellent [15]. Chemotherapy may be used in patients with multifocal lesions and relapsed diseases. Topical steroids, phototherapy, and low-dose methotrexate are most common treatments for lymphomatoid papulosis [8, 9, 15]. For large lymphomatoid papulosis lesion, which persists for months, surgical excision or local radiotherapy might be recommended as an alternative approach to a wait for spontaneous regression [21, 23].

9.6.4 Subcutaneous Panniculitis-Like T-Cell Lymphoma

A solitary lesion of subcutaneous panniculitis-like T-cell lymphoma with no evidence of hemophagocytic syndrome might be treated with local radiotherapy alone [8]. A lesion with hemophagocytic syndrome has an aggressive clinical behavior, and it should be treated with intensive multi-agent chemotherapy. High-risk patients with hemophagocytic syndrome have generally been treated with anthracycline-based chemotherapy and radiotherapy [4, 15].

9.6.5 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type has a chemotherapy-resistant behavior, and high-dose local radiotherapy is the first choice for the localized lesion [8]. The patients with advanced disease might be treated with multi-agent chemotherapy including platinum-based regimens with or without local radiotherapy; however, the treatment outcome is disappointing [4, 15, 32].

9.6.6 Cutaneous B-Cell Lymphoma

The ISCL and EORTC reported the consensus statements for the management of the three subtypes of cutaneous B-cell lymphoma [8]. Primary cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma are indolent types. Local radiotherapy or surgical excision might be chosen as the first-line therapy for the patients with localized and solitary lesion. Wait-and-see policy, local radiotherapy, rituximab, or single agent chemotherapy might be selected for the patients with multifocal lesions [4, 8, 33, 34]. Interferon alpha or anthracycline-based chemotherapy might be suggested as alternative therapies [4]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an aggressive behavior, and multi-agent aggressive chemotherapy and/or local radiotherapy might be performed. Rituximab and/or local radiotherapy will be suggested as alternative therapies [8].

9.7 Radiation Therapy

9.7.1 Radiotherapy Techniques of Local Radiotherapy

9.7.1.1 Planning CT

Planning CT is essential to obtain an appropriate dose distribution. The radiopacity marker is useful to grasp the tumor extension in CT images.

9.7.1.2 Gross Tumor Volume (GTV)

GTV is defined as a visible and palpable lesion. For tumor lesions, evaluation using CT and/or magnetic resonance image (MRI) is required.

9.7.1.3 Clinical Target Volume (CTV), Planning Target Volume (PTV), and Radiation Field

CTV for patients with patch and/or plaque disease should cover the epidermis and dermis [12, 23]. The thickness of the epidermis and dermis varies from a minimum of approximately 2 mm at the trunk to a maximum of approximately 4.5 mm at the hands and soles of the feet. Local radiotherapy for cutaneous lymphoma is based on involved-site radiotherapy (ISRT) [35]. No prophylactic regional node irradiation is required for the majority of primary cutaneous lymphoma. PTV could be considered according to the fixation, reproducibility, and physiological motion. The lateral field margin of local radiotherapy of curative intent can be limited 2–3 cm beyond GTV [3, 23, 34]. For the palliative radiotherapy, the visible lesion with a margin of 1–2 cm of surrounding healthy-looking skin might be covered [34, 36].

9.7.2 Dose of Local Radiotherapy

Appropriate electron beam energy should be selected for the thickness of the patch and plaque lesions, and photon beams might be considered for tumor lesions. A 0.5–1 cm tissue equivalent plastic plate (bolus) is used daily to prescribe 80–90% iso-dose line to cover each lesion [3].

9.7.2.1 Mycosis Fungoides

Dose-response relationship has been obtained, and the optimal radiation dose of curative intent for mycosis fungoides is higher than 30 Gy in 1.2–2 Gy per fraction [1, 3, 37]. The standard-dose radiotherapy 31–36 Gy have a trend toward a higher overall response rate and longer event-free survival rates comparing with lower-dose regimens [1, 38]. And also radiotherapy is useful for palliative therapy. Although the clinical response after 4 Gy in two fractions is unacceptable and the remission time is very short for the symptomatic mycosis fungoides, symptom relief after 8 Gy in two fractions is favorable with a complete response rate over 90% [29, 34, 36]. A single fraction of 7–8 Gy produces excellent palliative effects with complete response rate of 94%, and the mean time for relapse is around 9 months [39].

9.7.2.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

EORTC, ISCL, and USCLC recommended that local radiotherapy of 40 Gy in 20 fractions was applied as first-line monotherapy for primary cutaneous anaplastic large cell lymphoma [9, 21]. On the other hand, the National Comprehensive Cancer Network (NCCN) recommended a total dose of 30–36 Gy for primary cutaneous anaplastic large cell lymphoma [35].

9.7.2.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

Although there is little information on the appropriate radiation dose for subcutaneous panniculitis-like T-cell lymphoma, the International Lymphoma Radiation Oncology Group (ILROG) recommended high-dose radiotherapy more than 40 Gy [34].

9.7.2.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

The NCCN recommended a radiation dose of 45–60 Gy when combined therapy including chemotherapy and radiotherapy might be applied [35]. ILROG recommended that 50 Gy to the initial lesion followed by boost irradiation of 5–10 Gy to residual lesion might be applied [34].

9.7.2.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

The NCCN recommended that a radiation dose of 30–36 Gy might be used for consolidation radiotherapy, and 40–50 Gy might be used for the patients who do not achieve a complete response [35]. The ILROG recommended a radiation dose of 24–30 Gy for the primary cutaneous gamma/delta T-cell lymphoma [34].

9.7.2.6 Cutaneous B-Cell Lymphoma

A total dose of 24–30.6 Gy for cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma has been recommended [33–35]. Symptomatic relief after a low-dose palliative radiotherapy of 4 Gy in two fractions is comfortable for the patients with these indolent lymphomas [34–36]. For the patients with primary cutaneous diffuse large B-cell lymphoma, leg type, total dose of 30–40 Gy is applied for consolidation after chemotherapy, and the patients with partial response after chemotherapy require 40–50 Gy [34, 35].

9.7.3 Radiotherapy Techniques of Total Skin Electron Beam Therapy (TSERT)

The EORTC proposed the technical consensus guidelines of TSEBT for mycosis fungoides [12]. And some other technical reports and review articles are available to optimize the clinical practice in each institute [3, 29, 40–43].

9.7.3.1 Target Volume of TSEBT

CTV for patients with patch and plaque lesions should include epidermis, adnexal structures, and the dermis [12, 23]. For the patients with tumor lesions with thickness of more than 5 mm and infiltrative lesions, CT and MRI are useful to evaluate the depth of lesions.

9.7.3.2 Treatment Schedule and Dose of TSEBT

EORTC recommended a total dose of 31–36 Gy prescribed to the skin surface to produce a dose of at least 26 Gy at a depth of 4 mm in trunk skin along the central axis [12]. Twenty percent iso-dose line should be within 20 mm from the skin surface to minimize dose to underlying structures. Two Gy will be given to the entire skin surface over the course of a 2-day treatment cycle [23]. This treatment cycle repeats for 4 days per week for a total of 8–9 weeks with a 1-week break, and a total dose of 32–36 Gy is given to the skin surface over 9–10 weeks. A small fraction size of less than 1.2 Gy per day does not compromise effectiveness, but a large fraction size more than 2 Gy leads to late adverse effects [12]. Total radiation dose less than

30 Gy have a trend to lower overall response rate and shorter event-free survival [38]. Although the short-course TSEBT of 30 Gy in 20 fractions over 5 weeks produces acceptable toxicities and reliable effects, the short-course regimen is under investigation [43]. Low-dose TSEBT regimens (e.g., 10 Gy in 1 Gy over 12 days) are well-tolerated and achieve short-term palliation [25, 38].

9.7.3.3 TSEBT Delivery Techniques

Three TSEBT delivery techniques, which include large electron field techniques, rotation techniques, and patient's shift during irradiation, correspond with the EORTC recommendations [3, 40]. The dual-large field electron beam techniques have been applied in many institutes, and the radial dose homogeneity can be obtained even in a medium sized radiotherapy room with a source-to-surface distance of approximately 4 m [3, 12, 23]. Dose inhomogeneity in the air at the source-to-surface distance should be less than 10% within vertical and lateral dimensions [12]. Short treatment distance may require the use of beam-scattering devices, but these devices increase photon contamination. The total dose to bone marrow from photon contamination should be less than 0.7 Gy [12]. The beam-scattering devices using lucite plate attenuate the electron energy from the nominal 6 MeV to approximately 4 MeV at the treatment source-to-surface distance [42]. The beam-scattering devices are placed as close as possible to the patient surface in order to degrade and further scatter the electrons [3]. Electron beam energy should be decided after the actual measurement using phantom and radiographic film [42]. A combination of low-energy electron beams and more penetrating high-energy beams will be required to achieve appropriate dose coverage [12]. The heterogeneity of the dose within the main target can be minimized by using supplemental regional patch irradiations to the low-dose areas to compensate. The dose rates range from 0.2 Gy per minute to 1 Gy per minute depending on the source-to-surface distance [40]. The treatment time affects an appropriate patient positioning during irradiation [40]. Support devices might be useful to keep the patient in the same position during irradiation.

Patients should be positioned to maximize unfolding of skin to improve dose homogeneity [12]. Keeping the correct orientation toward the beam, setting the joints in the limbs at appropriately large angles, and slightly bending the trunk and hips to expose folds in the lower trunk are essential. In total, there are six treatment positions, namely antero-posterior, right anterior oblique, left posterior oblique, postero-anterior, left anterior oblique, and right posterior oblique positions [12, 23, 34]. Each treatment position is treated with both upper and lower fields to improve dose homogeneity in the vertical dimension of dual-large field electron beams. Routine measurements of the heterogeneity of TSEBT are essential to monitor the low-dose and high-dose areas [12]. The soles of feet, vertex of head, perineum, trunk wrinkles, medial thighs, and infra-mammary regions are low-dose areas which require supplemental regional patch irradiation. Conversely, the hands, dorsal sites of the feet, and dorsal penis may be overdosed and require shielding to limit the dose to less than 36 Gy [23].

9.7.3.4 Supplemental Regional Patch Irradiation

The perineum, vertex of head, and the soles of the feet are low-dose areas, and supplemental regional patch irradiation is required. Other potentially low-dose areas or "Shadowed areas" include upper medial thighs, buttocks-thighs, inframammary folds, trunk wrinkles, and the flatter regions of the face and trunk [23, 34, 40]. Careful unfolding of skin with the use of tape, netting, bras, expanded polystyrene wedges, and extreme positioning can minimize patch irradiation for low-dose areas. The supplemental regional patch irradiation is transmitted through tissue equivalent bolus. At the Yale-New Haven Hospital, the supplemental regional patch irradiation to the perineum of 1 Gy per day is applied during the first 9 and last 9 treatment days, and that to the soles of feet of 1 Gy per day is applied during the first 7 and last 7 treatment days [23, 42].

9.7.3.5 Boost Irradiation for Tumor Lesions

Tumor lesions with a thickness of more than 5 mm require the supplemental boost irradiation to cover the target with an appropriate dose. Fields require a minimal margin, and higher-energy electron beams are used [23]. The supplemental dose should be less than 20 Gy, administered in 10–15 fractions. The early use of supplemental boost irradiation for tumor lesions will lead to appropriate dose distribution of TSEBT. For the patients with symptomatic lesions, boost irradiation before TSEBT might be useful for symptom relief, and a local radiation field of 4–6 Gy is given 1–2 weeks before the start of TSEBT [12].

9.7.3.6 Shielding

The high-dose area around the risk organs should be shielded to avoid severe adverse events. The eye globe should not receive more than 15% of the prescribed dose [12]. At the Yale-New Haven Hospital, the external eye shields are applied at the first 11 cycles, and the internal eye shields are applied at the last 7 cycles [23, 42]. The lip shield is applied at the first 1–4 cycles. The hand and fingernails shields are required to avoid the high-dose which leads to a decline in quality of life. The lead mitts for hands are used every other cycle (cycles 1, 3, 5, 7, and 9). The dorsal sites of the feet require shields during cycles 1–3, 5, 7, 9, 11, 13, 15, 17, and 18. The dorsal penis shields are used with perineum boost irradiation only. In some patients, ears and ankles are overdosed and require shielding [23].

9.8 Outcomes

9.8.1 Mycosis Fungoides and Sézary Syndrome

The 10-year overall survival rate of patients with limited plaque disease is 80%, that of patients with generalized plaques is 45%, and that of patients with tumor is 25% [1, 4, 17, 31]. After the local radiotherapy for the solitary lesion, the 10-year relapse-free rates are approximately 50–70% [23, 29, 44]. After TSEBT

for extensive patch and plaque lesions (stage IB; T2N0M0B0-1), the 10-year relapse-free survival rates are only 10–20% [23, 29]. The patients with visceral involvement have poor prognosis, and the median survival is less than 2 years [1]. Most patients with Sézary syndrome dies of opportunistic infections which are due to immunosuppression [4, 38].

In 2011, the consensus statement of response criteria in mycosis fungoides and Sézary syndrome was reported by ISCL, USCLC, and EORTC [10]. For the solitary lesion of mycosis fungoides, the mean overall duration of response to local radiotherapy of 30.6–36 Gy in 17–20 fractions ranges from 24 to 42 months [44]. The rates of in-field relapses range from 0 to 25%, and that of outside relapses of radiation field range from 0 to 33%. Complete response rates after TSEBT are approximately 90% for patients with patch and plaque lesions and approximately 70% for patients with erythroderma (T4N0-2M0B0-1, stage III) [14, 23]. However, more than half of them demonstrated skin relapse within one year after treatment [38].

Multiple-course TSEBT will be an optional treatment for selected patients [29, 31]. The salvage TSEBT of 23.5 Gy after the initial TSEBT produces complete response in 40% of patients and partial response in 60% of patients [31]. The patients with partial response develop the systemic disease, and the interval from the second course of TSEBT to death ranges from 2 to 66 months. Low-dose TSEBT of 12 Gy in 12 fractions over 3 weeks produces reliable and rapid reduction of disease burden, but the median duration of clinical benefits is 17 months [30]. For the symptomatic mycosis fungoides, the clinical response after palliative local radiotherapy of 4 Gy in two fractions is only 30%. The clinical response after 8 Gy in two fractions is more than 90% [36]. The size and thickness of the lesions don't affect the clinical response rates.

9.8.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

The 5- and 10-year overall survival rates of patients with primary cutaneous anaplastic large cell lymphoma are 83% and 78%, respectively [21]. After local radiotherapy for patients with solitary lesion of primary cutaneous anaplastic large cell lymphoma, the 5- and 10-year disease-specific survival rates are 95% and 90%, respectively [4, 23]. Although local radiotherapy or surgical excision is applied for localized lesion as first-line monotherapy, relapse after local therapy occurs in approximately 40% of patients [9]. Local relapses in the skin are not associated with worsened prognosis. On the other hand, spontaneous regression of tumor has been observed in about 40% of patients. Lymphomatoid papulosis has an excellent prognosis with a 5-year overall survival rate of 98–100% [4, 23]. Only 4% of patients with lymphomatoid papulosis develop a systemic disease, and only 2% of patients died of systemic disease with a median follow-up period of 6 years [4, 21].

9.8.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

The 5-year overall survival rate of subcutaneous panniculitis-like T-cell lymphoma may be more than 80% [4]. The 5-year overall survival rate of patients with and without hemophagocytic syndrome are 46% and 91%, respectively [8].

9.8.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

The extranodal NK/T-cell lymphoma, nasal type has an aggressive behavior. A median survival of patients with cutaneous lesion alone is 27 months, and that of patients with cutaneous and extracutaneous lesions is only 5 months [4].

9.8.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

The prognosis of primary cutaneous peripheral T-cell lymphoma, unspecified is disappointing with 5-year overall survival rate of 16% [4]. A median survival time is 32 months in patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional entity) [4]. It trends to disseminate to other visceral sites including lung, testis, and central nervous system. Most patients with cutaneous gamma/delta T-cell lymphoma (provisional entity) have aggressive disease resistance to multi-agent chemotherapy and radiotherapy, and the median survival time is only 15 months [4]. Patients with primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional entity) have a relatively favorable prognosis with 5-year overall survival rate of 75% [4].

9.8.6 Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma has risk of relapse compared with gastric marginal zone B-cell lymphoma [33]. After local radiotherapy, half of the patients with cutaneous marginal zone B-cell lymphoma developed relapse in other skin sites, which are outside of the radiation field [33]. Although the 10-year progression-free survival rate is approximately 50%, the 5-year overall survival rate is almost 100% because of effective salvage therapy and indolent nature [4]. Cutaneous relapses after radiotherapy occur in 20% of patients with primary cutaneous follicle center lymphoma; however, the 5-year overall survival rate is more than 95% [4]. According to the prognostic index of indolent cutaneous B-cell lymphoma including elevated serum lactate dehydrogenase, morphology, and number of lesions, the low-risk group without risk factors has a 5-year progression-free survival rate of 91%, the intermediate-risk group with one risk factor has that of 64%, and the high-risk group with two or three risk factors has that of 48%,

respectively [27, 28]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an unfavorable prognosis, and the 5-year overall survival rate after systemic chemotherapy and/or local radiotherapy is approximately 26–55% [4, 27, 45].

In case of palliative radiotherapy for indolent cutaneous B-cell lymphoma, the clinical response rate after the low-dose radiotherapy of 4 Gy in two fractions is more than 80% [35, 36]. The clinical response after radiotherapy is obtained within 1 month, and its duration is approximately 6 months. The size and thickness of the lesion don't affect the response rate. The low-dose radiotherapy of 4 Gy in two fractions can be repeated as needed.

9.9 Toxicity

9.9.1 Acute Toxicities

TSEBT is well tolerated in the majority of patients. Mild or moderate general fatigue is observed in 38–98% of patients, grade 1–2 skin reaction including pruritus, hyperpigmentation, edema, and erythema in 47–95%, alopecia in 66–95%, xerosis in 58%, nail loss in 13–16%, and problems with temperature regulation in 7% [3, 18, 23, 38, 43]. The most uncomfortable adverse effects during treatment are edema of the hands and feet in 26–50% of patients, and bullae in the feet are shown in 19% of patients (Fig. 9.1) [18, 23, 43]. Skin infection is shown in 31% of patients, and cutaneous abscess is rarely observed during treatment [43]. These symptoms

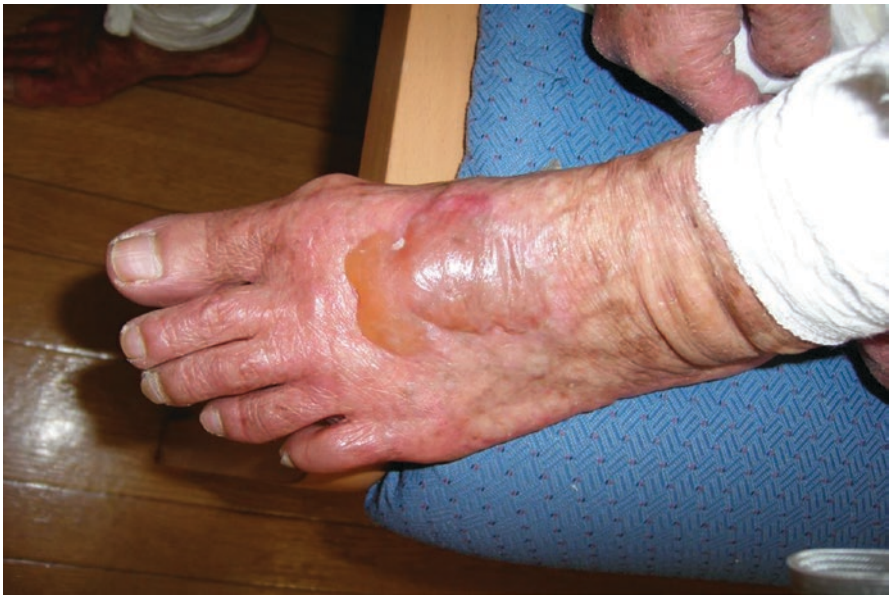

Fig. 9.1 Bullae in feet were observed during the total skin electron beam therapy

are nearly always temporary and mostly ameliorate after 2 or 3 weeks [29]. Rare acute adverse effects after TSEBT include nasal bleeding and parotiditis [23, 43].

9.9.2 Late Toxicities

Long-term adverse effects after TSEBT are typically mild, and may include permanent nail dystrophy, xerosis, telangiectasia, hyperpigmentation, hyperkeratosis, partial scalp alopecia, and fingertip dysesthesia [23, 29, 38]. Hair typically returns, but the color and texture of the hair may be different when it regrows [3, 29]. Nails might be brisk, and edema of hands and feet will be observed. Uncommon adverse effects include blisters on the fingers and feet, anhidrosis, skin infection, minor parotitis, gynecomastia, and corneal abrasion due to internal eye shield [3]. Young patients should be thoroughly counseled regarding risks of gonadal toxicity. The safety of multiple-course TSEBT has been reported. When an interval between two courses of TSEBT is sufficiently long, two courses TSEBT of total dose 56 Gy is feasible with mild toxicities including erythema, edema, alopecia, and dry skin [31]. Both local radiotherapy and TSEBT are associated with risk of development of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma within the radiation field [18, 23, 44]. Benign secondary neoplasms including diffuse lipoma and eccrine poroma have been reported [29].

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