NCCN Guidelines Version 1.2016
Primary Cutaneous B-Cell Lymphomas[a]

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Discussion

DIAGNOSIS

ESSENTIAL:

- **Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.**
- **Histopathology review of adequate biopsy (punch, incisional, excisional).**
- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2, BCL6, IRF4/MUM1**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **IHC panel: Ki-67, CD43, CD21, CD23**
  - **Cyclin D1, kappa/lambda**
  - **Assessment of IgM and IgD expression (to further help in distinguishing PC-DLBCL, leg type from PCFCL)**
- **Cytogenetics or FISH: t(14;18)**
- **If adequate biopsy material available, flow cytometry or PCR can be useful in determining B-cell clonality.**

WORKUP

ESSENTIAL:[d]

- **History and physical exam, including complete skin exam**
- **CBC, differential, comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[e] if rituximab considered**
- **Contrast-enhanced chest/abdominal/pelvic CT and/or PET-CT scan**
- **Bone marrow biopsy, if PC-DLBCL, Leg type**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:

- **Bone marrow biopsy**
  - **Consider if PCFCL**
  - **Optional if PCMZL**
- **Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis**
- **SPEP/quantitative immunoglobulins for PCMZL**

See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Follicle Center Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type (CUTB-3)

PCMZL: Primary Cutaneous Marginal Zone Lymphoma
PCFCL: Primary Cutaneous Follicle Center Lymphoma
PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type

NOTE: A germinal (or follicle) center phenotype and large cells in a skin lesion is *not* equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

[a] For non-cutaneous, see Nongastric MALT Lymphoma (NGMLT-1).

[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: PC-DLBCL: CD20+ BCL2+ CD10- BCL6+/- IRF4/MUM1+/- ; PCFCL: CD20+ BCL2- CD10-/+ BCL6+ IRF4/MUM1-; PCMZL: CD20+ BCL2+/- CD10- BCL6- IRF4/MUM1+/- cytoplasmic kappa+ or lambda+ in about 40%.

[d] Rule out drug-induced cutaneous lymphoid hyperplasia.

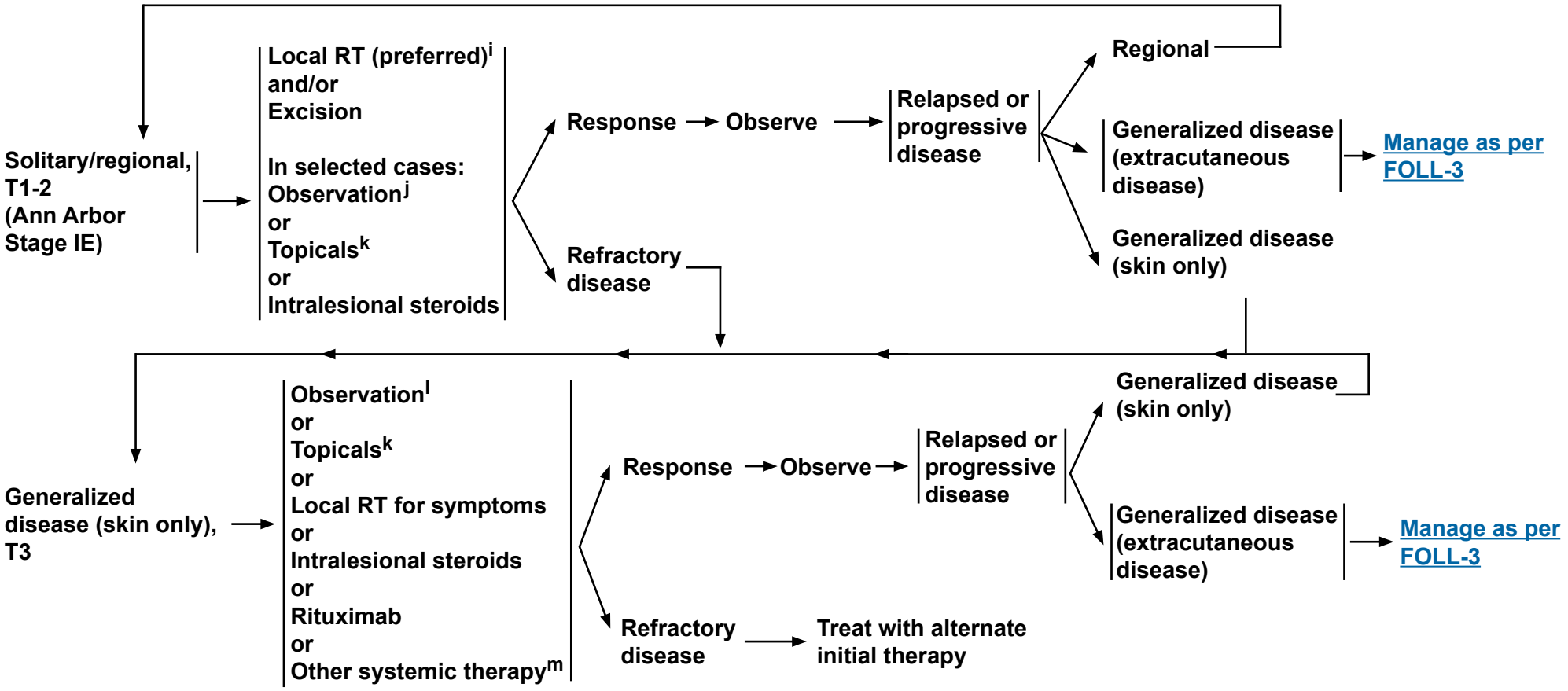
[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[f]

STAGE[g] | **INITIAL THERAPY[h]**

See monoclonal antibody and viral reactivation (NHODG-B)



Extracutaneous disease → Manage as per FOLL-3

[f]Unless clinically indicated, additional imaging studies during the course of treatment are not needed.
[g]See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[h]See Treatment References (CUTB-B).

[i]Local RT is the preferred initial treatment, but not necessarily the preferred treatment for relapse.
[j]When RT or surgical treatment is neither feasible nor desired.
[k]There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene.
[l]Considered appropriate in asymptomatic patients.
[m]In rare circumstances for very extensive or refractory disease, other combination chemotherapy regimens listed in FOLL-B are used.

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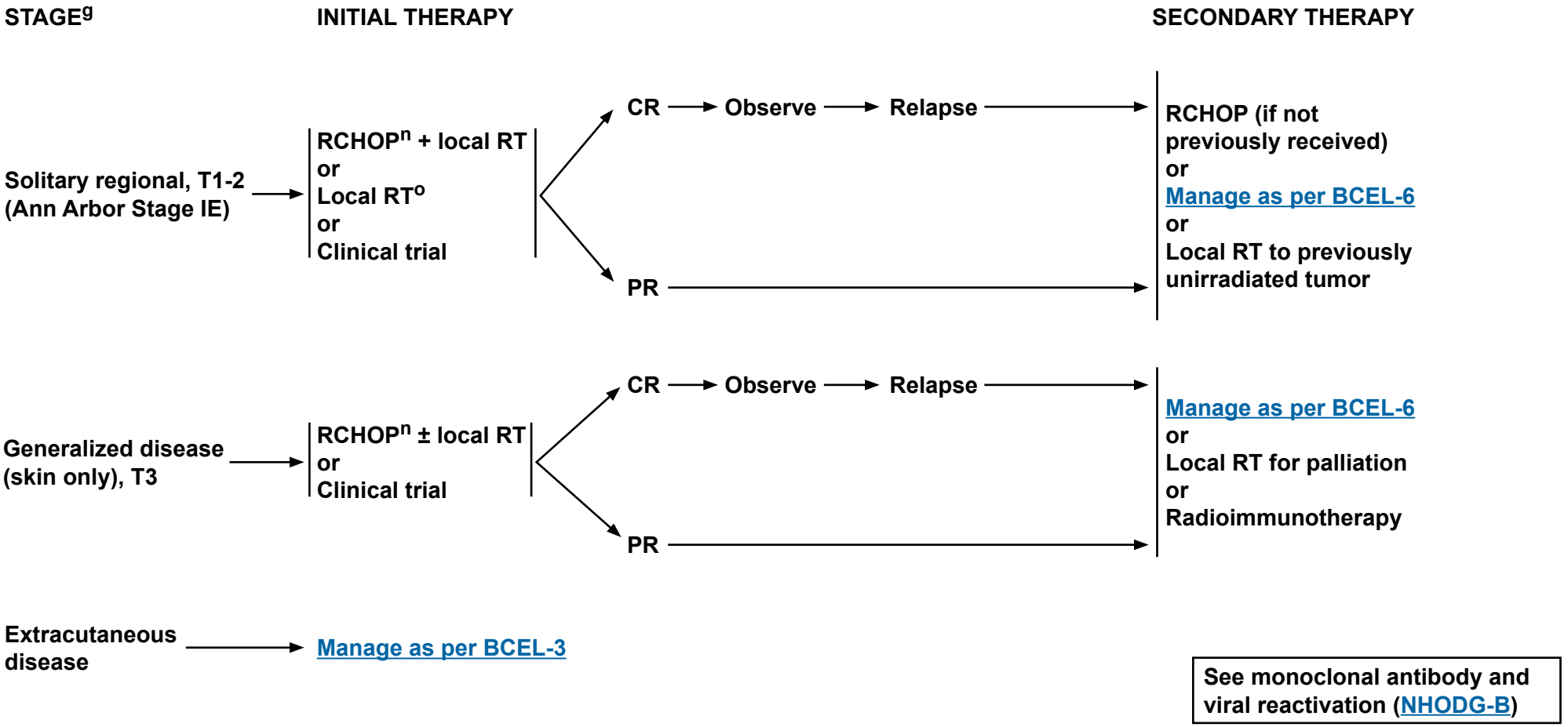
PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE



See monoclonal antibody and viral reactivation (NHODG-B)

[g]See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[n]For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.
[o]For patients not able to tolerate chemotherapy.

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TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS[a,b]

T	
T1	**Solitary skin involvement** **T1a: a solitary lesion <5 cm diameter** **T1b: a solitary >5 cm diameter**
T2	**Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions[b]** **T2a: all-disease-encompassing in a <15-cm-diameter circular area** **T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area** **T2c: all-disease-encompassing in a >30-cm-diameter circular area**
T3	**Generalized skin involvement** **T3a: multiple lesions involving 2 noncontiguous body regions[b]** **T3b: multiple lesions involving ≥3 body regions[b]**
N	
N0	**No clinical or pathologic lymph node involvement**
N1	**Involvement of 1 peripheral lymph node region[c] that drains an area of current or prior skin involvement**
N2	**Involvement of 2 or more peripheral lymph node regions[c] or involvement of any lymph node region that does not drain an area of current or prior skin involvement**
N3	**Involvement of central lymph nodes**
M	
M0	**No evidence of extracutaneous non-lymph node disease**
M1	**Extracutaneous non-lymph node disease present**

[a]This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) Blood 2007;110:479-484. © The American Society of Hematology.

[b]For definition of body regions, see Body Regions for the Designation of T (Skin Involvement) Category (CUTB-A 2 of 2).

[c]Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, and iliac.

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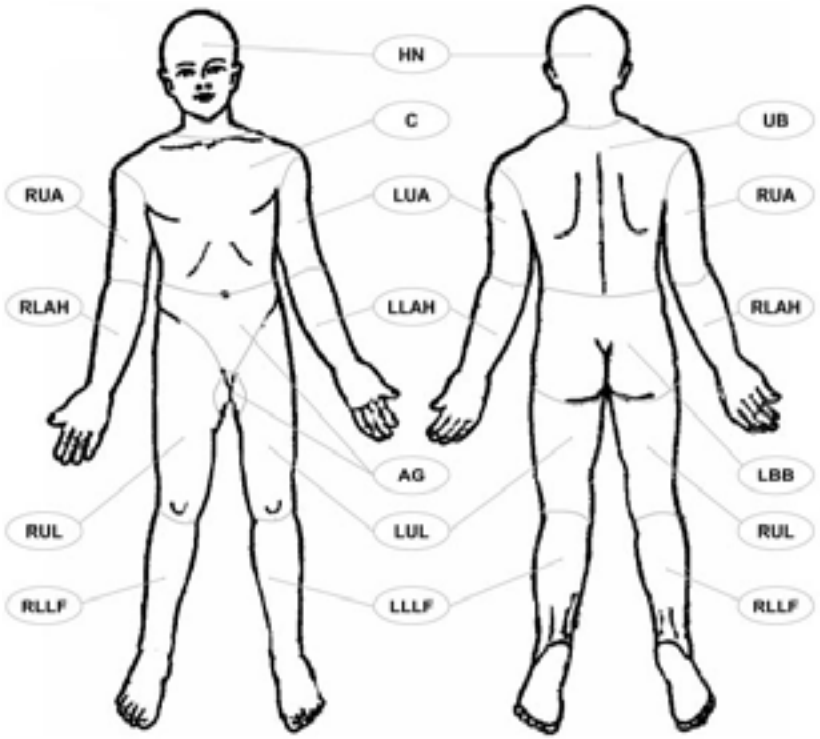
BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY[a,b,c]



HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

[a]This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) Blood 2007;110:479-484. © The American Society of Hematology.
[b]Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.
[c]Definition of body regions: Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—midaxillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum; lateral borders—mid-axillary lines. Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines. Lower back/buttocks: superior border—inferior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—midaxillary lines. Each upper arm: superior borders—glenohumeral joints (exclusive of axillae); inferior borders—ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior borders—inguinal folds, inferior gluteal folds; inferior borders—mid-patellae, midpopliteal fossae. Each lower leg/foot: superior borders—mid-patellae, mid-popliteal fossae.

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TREATMENT REFERENCES

Rituximab

Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol 2008;59:953-957.

Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer 2000;89:1835-1844.

Valencak J, Weihsengruber F, Rappersberger K, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: Response and follow-up in 16 patients. Ann Oncol 2009;20:326-330.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

Heinzerling L, Dummer R, Kempf W, Schmid MH, Burg G. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol 2000;136:374-378.

Topicals

Topical/intralesional corticosteroids

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478.

Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. Br J Dermatol 2010;163:223-225.

Topical nitrogen mustard

Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. British Journal of Dermatology 2006;154:1207-1209.

Topical bexarotene

Trent JT, Romanelli P, Kerdel FA. Topical Targretin and Intralesional Interferon Alfa for Cutaneous Lymphoma of the Scalp. Arch Dermatol 2002;138:1421-1423.

Topical imiquimod

Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393.

Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620-622.

Chemotherapy

Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: Clinical and therapeutic features in 50 cases. Arch Dermatol 2005;141:1139-1145.

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Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150.

Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219.

Rijlaarsdam JU, Toonstra J, Meijer OW, Noordijk EM, Willemze R. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: A clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 1996;14:549-555.

Vermeer MH, Geelen FA, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. Arch Dermatol 1996;132:1304-1308.

Palliative low-dose RT

Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

Chemoimmunotherapy

Grange F, Joly P, Barbe C, et al. Improvement of survival in patients with primary cutaneous diffuse large B-cell lymphoma, leg type, in France. JAMA Dermatol 2014;150:535-541.

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