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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Primary Cutaneous B-cell Lymphomas**

Version 2.2018 — January 10, 2018

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## Primary Cutaneous B-Cell Lymphomas

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

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# NCCN Guidelines Version 2.2018 Table of Contents

## Primary Cutaneous B-Cell Lymphomas

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

### [NCCN Primary Cutaneous B-Cell Lymphoma Panel Members](#) [Summary of the Guidelines Updates](#)

- [Diagnosis and Workup \(CUTB-1\)](#)
- [Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma \(CUTB-2\)](#)
- [Initial Therapy for Primary Cutaneous Follicle Center Lymphoma \(CUTB-2\)](#)
- [TNM Classification of Cutaneous Lymphoma other than MF/SS \(CUTB-A\)](#)
- [Treatment References \(CUTB-B\)](#)
- [Principles of Radiation Therapy \(CUTB-C\)](#)

### [Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(See NCCN Guidelines for B-Cell Lymphomas\)](#)

### [For Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type \(See NCCN Guidelines for B-Cell Lymphomas - DLBCL\)](#)

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

### [Classification and Staging \(ST-1\)](#)

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# NCCN Guidelines Version 2.2018 Updates

## Primary Cutaneous B-Cell Lymphomas

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

Updates in Version 2.2018 of the NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas from Version 1.2018 include:

### MS-1

- The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2018 of the NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas from Version 2.2017 include:

### CUTB-1

- **Diagnosis**
  - ▶ Useful, 2nd bullet was revised, "Cytogenetics or FISH: t(14;18) *is systemic FL is suspected.*"
- **Workup**
  - ▶ Essential, 4th bullet was revised, "Hepatitis B testing if rituximab considered"
  - ▶ Useful,
    - ◇ 1st bullet was revised by removing the two sub-bullets, "consider if PCFCL" and "consider if PCMZL" and adding footnote e, "Often reserved for patient with unexplained cytopenias or if there is clinical suspicion of other subtypes."
    - ◇ 4th bullet, "HIV testing" was added.
- Footnote was removed, "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%."

### CUTB-2

- Local RT dosing was moved to the Principles of Radiation Therapy.
- For Extracutaneous Disease, the links to the management were updated (Also for CUTB-3)
  - ▶ For PCFCL, manage as Follicular Lymphoma in the NCCN Guidelines for B-Cell Lymphomas (see FOLL-4).
  - ▶ For PCMZL, manage as Nodal Marginal Zone Lymphoma in the NCCN Guidelines for B-Cell Lymphomas (see NODE-2)

### CUTB-3

- Footnote m was added, "Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan."

### CUTB-C

- A Principles of Radiation Therapy was added.



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas<sup>a</sup>

### DIAGNOSIS

#### ESSENTIAL:

- Histopathology 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.
- Adequate biopsy (punch, incisional, excisional) of clinical lesions.
- Adequate immunophenotyping to establish diagnosis<sup>b</sup>
  - ▶ IHC panel: CD20, CD3, CD5, CD10, BCL2, BCL6, IRF4/MUM1

#### USEFUL IN CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - ▶ IHC panel may include: 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 systemic FL is suspected
- If adequate biopsy material available, flow cytometry or PCR can be useful in determining B-cell clonality.

**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.

<sup>a</sup>For non-cutaneous, see Nongastric MALT Lymphoma in [B-cell Lymphomas Guidelines](#).

<sup>b</sup>See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms ([See B-cell Lymphomas Guidelines](#)).

<sup>c</sup>Rule out drug-induced cutaneous lymphoid hyperplasia.

### WORKUP

#### ESSENTIAL:<sup>c</sup>

- History and physical exam, including complete skin exam
- CBC with differential
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing<sup>d</sup>
- Chest/abdominal/pelvic CT with contrast and/or PET/CT scan
- Bone marrow biopsy, if PC-DLBCL, Leg type
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

#### USEFUL IN SELECTED CASES:

- Bone marrow biopsy<sup>e</sup>
- Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL
- HIV testing

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  
 ([See NCCN Guidelines for B-Cell Lymphomas - DLBCL](#))

[See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma \(CUTB-2\)](#)

[See Initial Therapy for Primary Cutaneous Follicle Center Lymphoma \(CUTB-2\)](#)

[Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type \(See NCCN Guidelines for B-Cell Lymphomas - DLBCL\)](#)

<sup>d</sup>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.

<sup>e</sup>Often reserved for patient with unexplained cytopenias or if there is clinical suspicion of other subtypes.

**Note:** All recommendations are category 2A unless otherwise indicated.

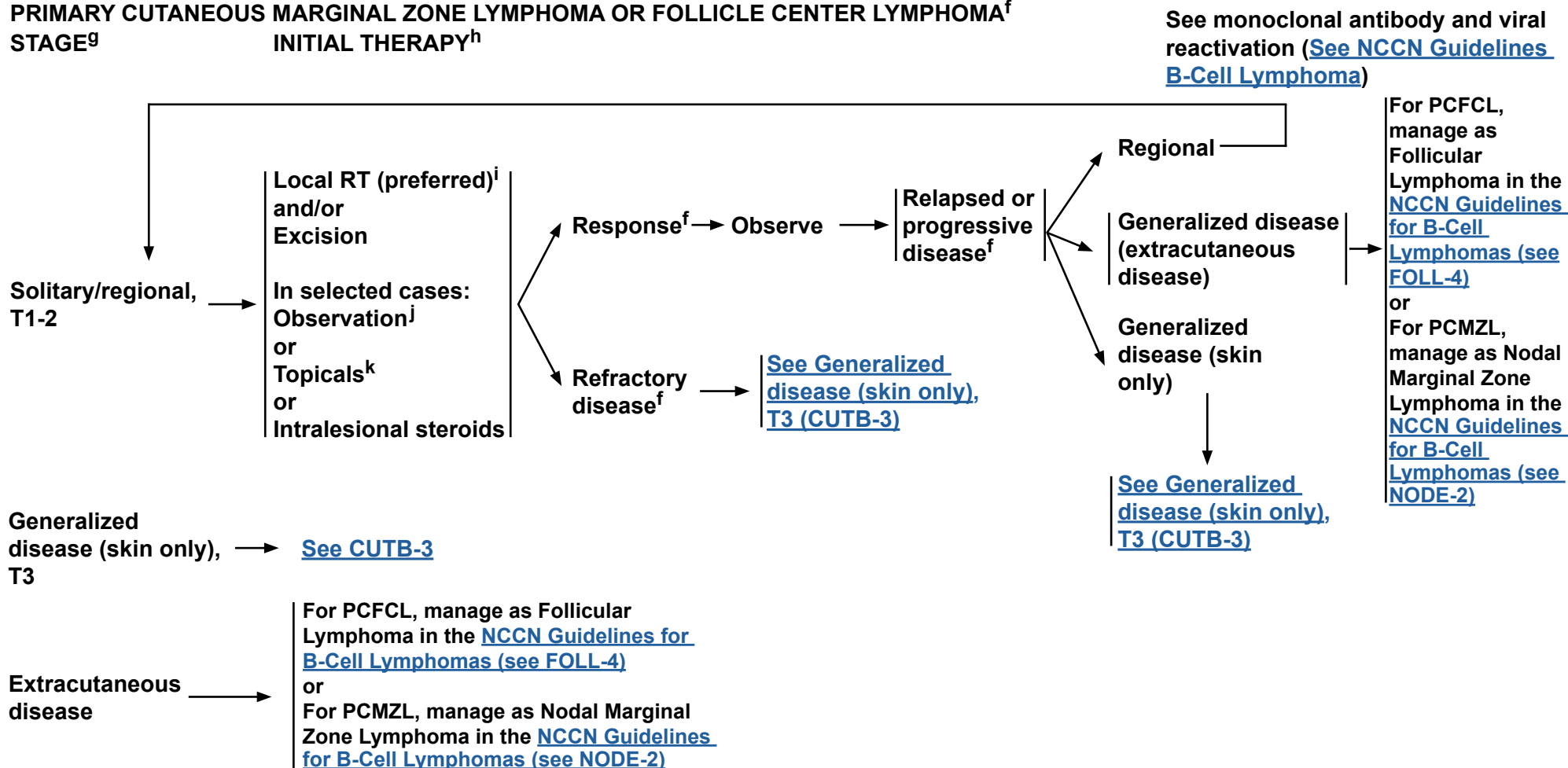
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## Primary Cutaneous B-Cell Lymphomas

### PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA<sup>f</sup> STAGE<sup>g</sup> INITIAL THERAPY<sup>h</sup>



<sup>f</sup>Additional imaging studies during the course of treatment are not needed. PET/CT (strongly preferred) or C/A/P CT with contrast at the end of treatment to assess response. It can be repeated if there is clinical suspicion of progressive disease.

<sup>g</sup>[See TNM Classification of Cutaneous Lymphoma other than MF/SS \(CUTB-A\).](#)

<sup>h</sup>[See Treatment References \(CUTB-B\).](#)

<sup>i</sup>Local RT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. [See Principles of Radiation Therapy \(CUTB-C\).](#)

<sup>j</sup>When RT or surgical treatment is neither feasible nor desired.

<sup>k</sup>There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene.

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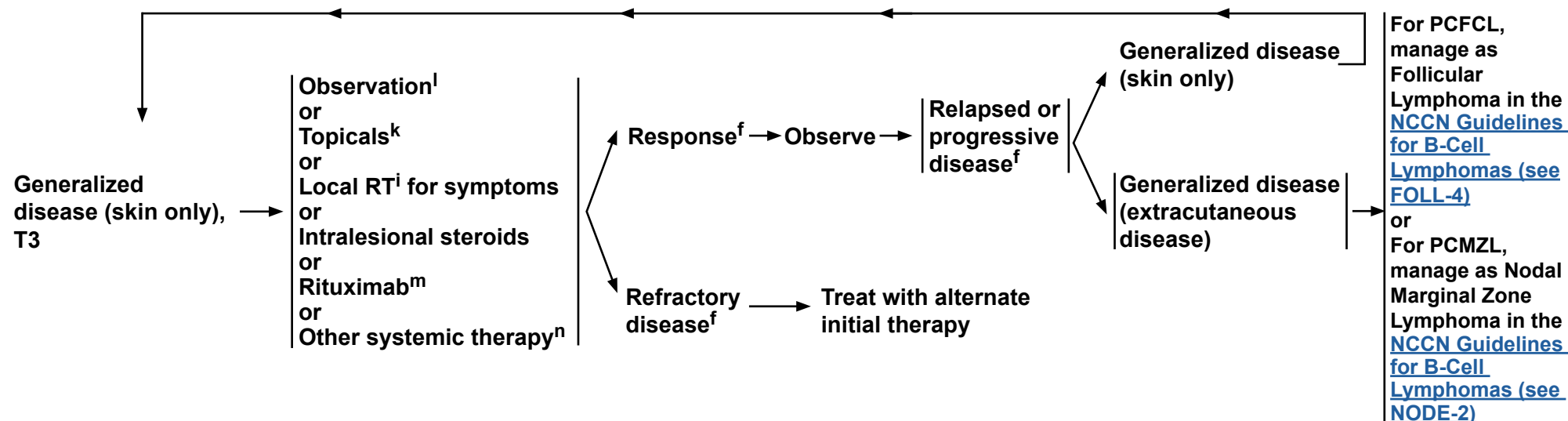


# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

### PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA<sup>f</sup> STAGE<sup>g</sup> INITIAL THERAPY<sup>h</sup>

See monoclonal antibody and viral reactivation ([See NCCN Guidelines B-Cell Lymphoma](#))



<sup>f</sup>Additional imaging studies during the course of treatment are not needed. PET/CT (strongly preferred) or C/A/P CT with contrast at the end of treatment to assess response. It can be repeated if there is clinical suspicion of progressive disease.

<sup>g</sup>See [TNM Classification of Cutaneous Lymphoma other than MF/SS \(CUTB-A\)](#).

<sup>h</sup>See [Treatment References \(CUTB-B\)](#).

<sup>i</sup>Local RT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See [Principles of Radiation Therapy \(CUTB-C\)](#).

<sup>k</sup>There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene.

<sup>l</sup>Considered appropriate in asymptomatic patients.

<sup>m</sup>Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

<sup>n</sup>In rare circumstances for very extensive or refractory disease, other combination chemotherapy regimens listed in [NCCN Guidelines for B-Cell Lymphomas, FOLL-B](#) are used.

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# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

### TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS<sup>a,b</sup>

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

<sup>a</sup>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.

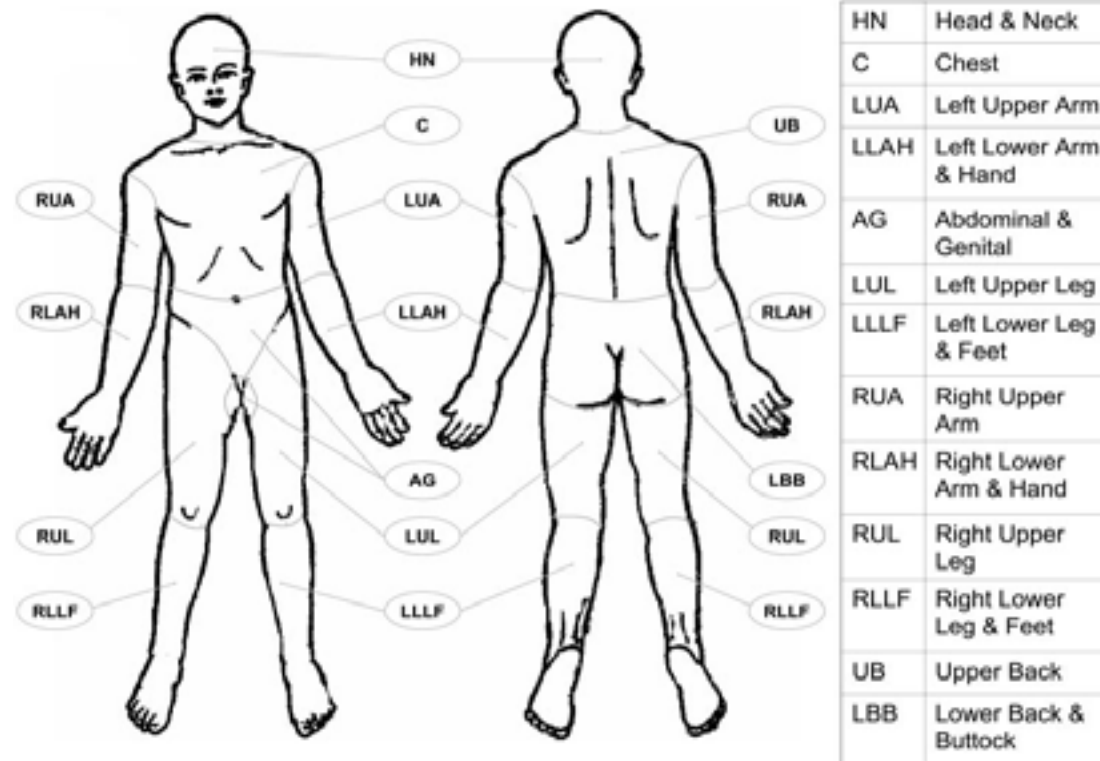
<sup>b</sup>For definition of body regions, [see Body Regions for the Designation of T \(Skin Involvement\) Category \(CUTB-A 2 of 2\)](#).

<sup>c</sup>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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**NCCN Guidelines Version 2.2018**  
**Primary Cutaneous B-Cell Lymphomas**[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)**BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY<sup>a,d,e</sup>**

<sup>a</sup>This work was originally published in Blood. Kim YH, Willemze R, Pimpinelli 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.

<sup>d</sup>Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.

<sup>e</sup>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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## Primary Cutaneous B-Cell Lymphomas

### TREATMENT REFERENCES

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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**

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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.

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#### **Palliative low-dose RT**

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#### **Chemoimmunotherapy**

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# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

### PRINCIPLES OF RADIATION THERAPY

#### PCMZL and PCFCL

- Optimal initial management for solitary/regional PCMZL and PCFCL is with external beam RT, 24-30 Gy.
- For relapsed/refractory disease, 4 Gy external beam RT may be adequate
- Surface margins beyond area of clinically evident disease will vary depending on lesion size and body site and must take into account dosimetry of the beam being used. Surface margins of 1.0-1.5 cm are generally adequate.
- Margins in depth should include the volume at risk for involvement.
- Generally, treatment with 6-9 MeV electrons (with surface bolus) provides an adequate depth of treatment. Alternatively, low energy x-rays (~100 Kv) may be used.

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# NCCN Guidelines Version 2.2018 Staging Primary Cutaneous B-Cell Lymphomas

## Classification

**Table 1**

### WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2018)

#### Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable\**
  - ▶ *Splenic diffuse red pulp small B-cell lymphoma\**
  - ▶ *Hairy cell leukemia-variant\**
- Lymphoplasmacytic lymphoma
  - ▶ Waldenström's macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Monoclonal immunoglobulin deposition diseases
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - ▶ *Pediatric nodal marginal zone lymphoma\**
- Follicular lymphoma
  - ▶ In situ follicular neoplasia
  - ▶ Duodenal-type follicular lymphoma
- Pediatric-type follicular lymphoma
- *Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - ▶ In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - ▶ Germinal center B-cell type
  - ▶ Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL, NOS
- *EBV-positive mucocutaneous ulcer\**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8-positive DLBCL, NOS\**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration\**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

\*Provisional entities are listed in italics.

[Continued on next page](#)



# NCCN Guidelines Version 2.2018 Staging Primary Cutaneous B-Cell Lymphomas

## Classification

### Table 1 continued

#### WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2018)

##### Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells\**
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoma of childhood
- Hydroa vacciniforme-like lymphoproliferative disorder
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma\*
- *Indolent T-cell lymphoproliferative disorder of the GI tract\**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - ▶ Lymphomatoid papulosis
  - ▶ Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma\**
- *Primary cutaneous acral CD8-positive T-cell lymphoma\**
- *Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder\**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma\**
- *Nodal peripheral T-cell lymphoma with TFH phenotype\**
- Anaplastic large-cell lymphoma, ALK positive
- Anaplastic large-cell lymphoma, ALK negative
- *Breast implant-associated anaplastic large-cell lymphoma\**

##### Hodgkin Lymphoma

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - ▶ Nodular sclerosis classical Hodgkin lymphoma
  - ▶ Lymphocyte-rich classical Hodgkin lymphoma
  - ▶ Mixed cellularity classical Hodgkin lymphoma
  - ▶ Lymphocyte-depleted classical Hodgkin lymphoma

##### Posttransplant Lymphoproliferative Disorders (PTLD)

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis-like PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

##### Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

\*Provisional entities are listed in italics.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2018 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2018;127:2375-2390.



# NCCN Guidelines Version 2.2018 Staging Primary Cutaneous B-Cell Lymphomas

## Staging

### Lugano Modification of Ann Arbor Staging System\* (for primary nodal lymphomas)

<u>Stage</u>	<u>Involvement</u>	<u>Extranodal (E) status</u>
<b>Limited Stage I</b>	<b>One node or a group of adjacent nodes</b>	<b>Single extranodal lesions without nodal involvement</b>
<b>Stage II</b>	<b>Two or more nodal groups on the same side of the diaphragm</b>	<b>Stage I or II by nodal extent with limited contiguous extranodal involvement</b>
<b>Stage II bulky**</b>	<b>II as above with “bulky” disease</b>	<b>Not applicable</b>
<b>Advanced Stage III</b>	<b>Nodes on both sides of the diaphragm</b>  <b>Nodes above the diaphragm with spleen involvement</b>	<b>Not applicable</b>
<b>Stage IV</b>	<b>Additional non-contiguous extralymphatic involvement</b>	<b>Not applicable</b>

\*Extent of disease is determined by PET/CT for avid lymphomas, and CT for non-avid histologies

Note: Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue

\*\*Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging.

Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved. Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.



## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise indicated.**

## Table of Contents

<b>Overview .....</b>	<b>MS-2</b>
<b>Literature Search Criteria and Guidelines Update Methodology .....</b>	<b>MS-2</b>
<b>Diagnosis.....</b>	<b>MS-3</b>
<b>Workup.....</b>	<b>MS-4</b>
<b>Treatment Options.....</b>	<b>MS-5</b>
<b>Primary Cutaneous Marginal Zone Lymphoma and Primary Cutaneous Follicle Center Cell Lymphoma.....</b>	<b>MS-6</b>
Initial Treatment.....	MS-6
Treatment for Relapsed or Refractory Disease.....	MS-7
<b>Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type .....</b>	<b>MS-7</b>
<b>References.....</b>	<b>MS-9</b>



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

### Overview

Primary cutaneous B-cell lymphomas (PCBCLs) are a group of B-cell lymphomas originating in and usually confined to the skin. PCBCLs represent approximately 20% of all extranodal non-Hodgkin's lymphomas (NHLs). In the United States, the SEER data from the NCI indicated that the incidence of cutaneous T-cell lymphomas accounted for 71%, whereas PCBCLs accounted for 29% from 2001 to 2005.<sup>1</sup> The WHO-EORTC classification for cutaneous lymphomas distinguishes 3 main types of PCBCLs:<sup>2</sup>

- Primary cutaneous marginal zone lymphoma (PCMZL);
- Primary cutaneous follicle-center lymphoma (PCFCL); and
- Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type)

In addition to the aforementioned subtypes, PCDLBCL, not otherwise specified (PCDLBCL-NOS) with clinicopathologic features intermediate between PCFCL and PCDLBCL, leg type has also been described.<sup>3</sup>

PCFCL and PCMZL are generally indolent or slow growing. PCFCL is more prevalent in the scalp and the forehead, whereas the trunk and extremities are the most common sites for PCMZL. PCDLBCL, leg type is usually aggressive, associated with a generally poorer prognosis (mainly due to the higher frequency of extracutaneous relapses), and most commonly arises on the leg although it can arise at other sites.<sup>4,5</sup> In an Italian series of 467 patients with PCBCL, PCFCL, PCMZL, and PCDLBCL, leg type were reported in 57%, 31%, and 11% of patients, respectively.<sup>4</sup> Extracutaneous involvement eventually developed in 6% of patients with PCMZL, 11% with PCFCL, and 17% with PCDLBCL, leg type. The 5-year overall survival (OS) rate was significantly higher for patients with PCMZL and PCFCL than for patients with PCDLBCL, leg

type (97%, 96%, and 73%, respectively;  $P < .0001$ ).<sup>4</sup> In patients with PCMZL and PCFCL, the disease-free survival (DFS) and OS rates were significantly higher for patients with single lesions compared with those with regional or disseminated lesions (5-year DFS, 62% vs. 44%; 5-year OS, 97% vs. 85%), whereas the difference in outcomes between single and regional or disseminated lesions was not significant in patients with PCDLBCL, leg type (5-year DFS rate 55% vs. 44%; 5-year OS rate 79% vs. 67% for single and regional or disseminated lesions, respectively).<sup>4</sup> In an analysis of 300 patients with PCBCL from the Dutch Cutaneous Lymphoma Registry, PCFCL, PCMZL, and PCDLBCL comprised 57%, 24%, and 19% of cases, respectively.<sup>5</sup> The incidence of extracutaneous relapse was 47% among patients with PCDLBCL, leg type compared to 11% and 9%, respectively, for patients with PCFCL and PCMZL. The 5-year disease-specific survival rates in this series were 95%, 98%, and 50%, respectively.

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Primary Cutaneous B-Cell Lymphomas, a literature search was performed to obtain key literature published between May 2016 and October 2017, using the following search terms: cutaneous diffuse large B-cell lymphoma, cutaneous follicle center lymphoma, and cutaneous marginal zone lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>6</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

The PubMed search resulted in 28 citations and their potential relevance was examined. The data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

### Diagnosis

The diagnosis of PCBCLs is established by adequate biopsy of skin lesions. Incisional, excisional, or punch biopsy is preferred to shave biopsy, as PCBCLs have primarily dermal infiltrates, often deep, which are less well-sampled and can be missed by a shave biopsy. Review of the slides by a pathologist with expertise in the diagnosis of PCBCL is recommended. Adequate immunophenotyping of the biopsy sample is essential for the diagnosis of the exact subtype of PCBCL. In addition, immunophenotyping is also useful to rule out cutaneous lymphoid hyperplasia (also known as pseudolymphoma or lymphocytoma cutis)<sup>7-9</sup> and in the differential diagnosis of intravascular large B-cell lymphoma, which often manifests in skin and is associated with a poor prognosis.<sup>10</sup>

Gene expression profiling studies have shown that PCFCL has a germinal center B-cell (GCB) phenotype and PCDLBCL, leg type has an activated B-cell (ABC) phenotype.<sup>11,12</sup> In nodal DLBCL, the GCB phenotype is associated with a better prognosis than the ABC phenotype. Thus, a germinal (or follicle) center phenotype and large cells in a skin lesion is not equivalent to DLBCL but is consistent with PCFCL with a GCB phenotype.

PCFCL is consistently BCL6-positive, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern and the detection of *BCL2* rearrangement is associated with extracutaneous spread.<sup>13,14</sup> PCMZLs are always negative for BCL6 and CD10, but are often BCL2-positive.<sup>15</sup> PCDLBCL, leg type tumors are of ABC origin with expression of CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.<sup>5,16,17</sup>

While the diagnosis of PCMZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish between PCFCL and PCDLBCL, leg type, partly because the cell size (large vs. small) is not a defining feature as it is in nodal B-cell lymphomas. PCFCL and PCDLBCL are CD20- and BCL6-positive. BCL2 is usually negative in PCFCL but highly expressed in PCDLBCL, leg type.<sup>14</sup> In addition, PCFCL is usually IRF4/MUM1-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive and shows strong expression of FOXP1.<sup>17</sup>

The initial IHC panel should include CD20, CD3, CD5, CD10, BCL2, BCL6, and IRF4/MUM1. Under certain circumstances, evaluation of additional immunohistochemical markers such as Ki-67, CD43, CD21, CD23, cyclin D1, and kappa/lambda may be useful to further establish the lymphoma subtype. Additionally, assessment of surface IgM and IgD expression may also be helpful in distinguishing PCDLBCL, leg type from PCFCL.<sup>18</sup>

A high prevalence of *MYD88* L265P mutation (occurring in about 60% of patients) has been reported in patients with PCDLBCL, leg type and is associated with inferior clinical outcomes.<sup>19</sup> In a retrospective analysis of 61 patients diagnosed with PCDLBCL, leg type, *MYD88* L265P mutation was associated with shorter disease-specific survival and was also an independent adverse prognostic factor for OS. The 3- and



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

5-year disease-specific survival rates for those with *MYD88* L265P mutation were 65.7% and 60.2%, respectively, compared to 85% and 72%, respectively, for patients with the wild-type allele.<sup>19</sup> In a more recent report that evaluated the prevalence of *MYD88* L265P mutation in patients with PCFCL (21 patients) and PCDLBCL (25 patients), leg type identified in the French Cutaneous Lymphoma Study Group Database, *MYD88* L265P mutation was detected in 76% of the patients with PCDLBCL, leg type and was absent in all of the patients with PCFCL.<sup>20</sup> These findings suggest that determination of *MYD88* L265P mutation status could be helpful to further distinguish PCDLBCL, leg type from PCFCL.

Mantle cell lymphoma (MCL) is not a primary cutaneous lymphoma and finding it in the skin requires a careful search for extracutaneous disease. Clinical presentation on the leg and blastoid cytology along with high proliferative index and expression of BCL2, IRF4/MUM1, and IgM would often represent MCL with skin involvement.<sup>21</sup> The use of cyclin D1 may be useful to differentiate PCMZL (negative for CD5 and cyclin D1) from MCL (positive for CD5 and cyclin D1).

The t(14;18) translocation only rarely occurs in CBCLs. Therefore, the detection of a t(14;18) translocation in CBCL suggests the presence of systemic follicular lymphoma (FL).<sup>22</sup> Cytogenetics or FISH to detect t(14;18) may be useful if systemic FL is suspected. The feasibility of flow cytometric immunophenotyping of skin biopsies for the assessment of B-cell clonality has been reported, although it has not been widely used.<sup>9</sup> If adequate biopsy material is available, molecular analysis or flow cytometry could be useful in determining B-cell clonality.

### Workup

The initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease. The absence of

extracutaneous disease at diagnosis is part of the definition of primary CBCL. The workup includes a complete physical examination, a comprehensive skin examination, and CT and/or PET/CT of the chest, abdomen, and pelvis.<sup>23</sup> PET/CT may have higher sensitivity in the detection of both local and distant metastases than CT.<sup>24</sup> However, this is not validated and the higher rates of false-positive findings can create confusion.

Bone marrow biopsy is essential for PCDLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment; its role is unclear for PCFCL and PCMZL. Recent studies have indicated that bone marrow biopsy is an essential or more often a valuable component of staging in PCFCL first presenting in the skin, whereas it appears to have a more limited value in PCMZL presenting in the skin, and may be considered only in selected patients.<sup>23,25</sup> The International Society for Cutaneous Lymphomas (ISCL) and the EORTC Task Force recommend that bone marrow biopsy be obtained for cutaneous lymphomas with intermediate to aggressive behaviors and should be considered for cutaneous lymphomas with indolent behavior and when there is any evidence of extracutaneous disease, as indicated by other staging assessments (eg, radiographic evidence or serologic clues such as elevated monoclonal or polyclonal immunoglobulins).<sup>23</sup> Senff et al evaluated 275 patients with histologic features consistent with marginal zone lymphoma (MZL; n = 82) or follicle center lymphoma (FCL; n = 193) first presenting in the skin.<sup>25</sup> Bone marrow involvement was seen in about 11% of patients in the FCL group compared with 2% in the MZL group. FCL patients with skin lesions and a positive bone marrow had a significantly worse prognosis compared with those with PCFCL; the 5-year OS rate was 44% and 84%, respectively.<sup>25</sup> The guidelines recommend considering bone marrow biopsy for patients with unexplained cytopenias or if there is a clinical suspicion of other





# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

subtypes. Peripheral blood flow cytometry will be useful in selected cases, if complete blood cell (CBC) count demonstrates lymphocytosis.

### Treatment Options

RT is very effective when used as initial local therapy as well as for cutaneous relapses in most patients with indolent PCBCL.<sup>26-29</sup> In a retrospective study of 34 patients with PCBCL treated with RT, 5-year relapse-free survival (RFS) rates ranged from 62% to 73% for PCFCL and PCMZL but were only 33% for patients with PCDLBCL, leg type.<sup>27</sup> The 5-year OS rate was 100% for PCFCL and PCMZL but was 67% for PCDLBCL, leg type. Senff et al evaluated the outcome of 153 patients with PCBCL (25 with PCMZL; 101 with PCFCL; and 27 with PCDLBCL) who were initially treated with RT with a curative intent.<sup>28</sup> Overall, 45% of patients had single lesions while localized or disseminated lesions were seen in 43% and 12% of patients, respectively. Complete response (CR) was obtained in 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCDLBCL, leg type were 60%, 29%, and 64%, and the 5-year disease-specific survival rates were 95%, 97%, and 59%, respectively. The PCFCLs presenting on the legs also had a higher relapse rate (63%) and a lower 5-year disease-specific survival (44%) compared with PCFCLs occurring at other sites (25% and 99%, respectively).<sup>28</sup>

Low-dose involved-field RT (4 Gy in two fractions) is an effective treatment option for palliation of symptoms in patients with persistent (initial) lesions or recurrent symptomatic disease.<sup>30</sup> The results of a more recent retrospective study also showed that RT ≤12 Gy (4 Gy for relapsed disease) was equally effective as RT >12 Gy in patients with indolent PCBCL (42 patients; 16 patients had PCFCL).<sup>31</sup>

RT and excision were also associated with higher response rates compared to chemotherapy in patients with indolent histologies, but

were generally used for those with more limited disease; therefore, a direct comparison cannot be made.<sup>4,32-34</sup> In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with PCBCL, the CR rate and the 5- and 10-year OS rates for all patients with PCFCL and PCMZL who received first-line treatment (RT in 53%, with total dose of 35–45 Gy; chemotherapy in 25%, mainly with CHOP; surgery in 23%) were 92% to 95%, 96% to 97%, and 89% to 91%, respectively.<sup>4</sup> The relapse rate was 44% to 46.5% and extracutaneous spread was observed in 6% to 11% of patients. Relapse rate did not vary by the type of initial therapy. In patients with PCDLBCL, leg type, the CR rate and 5- and 10-year OS rates were 82%, 73%, and 47%, respectively. PCDLBCL, leg type was associated with higher relapse rates (55%) and higher incidences of extracutaneous spread (17%) — a higher relapse rate was confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy.<sup>4</sup> In a retrospective analysis of 137 patients with PC-MZL, initial treatment with surgical excision, RT, or a combination of both resulted in a CR rate of 88% (93% for patients with solitary or localized disease and 71% for those with multifocal lesions).<sup>34</sup> Although there were no significant differences in the rate of recurrences between the treatment modalities, surgery alone was associated with more recurrences at the initial site.

Chemotherapy is effective for multifocal skin lesions in patients with PCFCL or PCMZL.<sup>35-37</sup> Rituximab has been shown to be effective for indolent PCBCL with multiple lesions that cannot be managed effectively with local therapy.<sup>38-42</sup> In a retrospective analysis of 15 patients with indolent PCBCL, rituximab resulted in an overall response rate (ORR) of 87% (60% CR). The ORR was 100% for patients with PCFCL and 60% for PCMZL. With a median follow-up of 36 months, the



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

median duration of response was 24 months.<sup>41</sup> In another series of 16 patients with PCBCL, 14 patients (87.5%) achieved a CR with rituximab monotherapy; 35% of these patients with CR eventually relapsed between 6 and 37 months.<sup>42</sup>

The feasibility and efficacy of intralesional rituximab has also been demonstrated in a small series of patients with PCMZL and PCFCL.<sup>43-46</sup> In an observational multicenter study conducted by the Spanish Working Group on Cutaneous Lymphoma (17 patients with PCMZL and 18 patients with PCFCL), intralesional rituximab induced CR and partial response (PR) in 71% and 23% of patients, respectively, with a median DFS of 114 weeks.<sup>44</sup> The response rates were similar among patients with PCMZL and PCFCL. In another report that evaluated the efficacy of rituximab in treatment of patients with PCMZL and PCFCL, although intralesional rituximab resulted in response rates similar to that of intravenous rituximab, within a 12-month follow-up period, relapses were more frequent among patients treated with intralesional rituximab.<sup>43</sup>

A recent retrospective analysis showed that the type of treatment modality (skin-directed vs. definitive RT with or without systemic therapy) did not affect the time to first recurrence among patients with T1 and T2/T3 lesions (55 patients; majority of patients had indolent PCBCL; 25 patients with PCMZL and 24 patients with PCFCL).<sup>47</sup> The rates of recurrence were higher for T2/T3 lesions compared to T1 lesions (58% and 31%, respectively). The time to first recurrence for T1 lesions was 33% and 29%, respectively, for patients with PCMZL and PCFCL; however, the difference was not significant. Among patients with T2/T3 lesions, there was a non-significant trend toward higher rate of recurrence for PCMZL than PCFCL (73% and 38%, respectively).

### Primary Cutaneous Marginal Zone Lymphoma and Primary Cutaneous Follicle Center Cell Lymphoma

#### Initial Treatment

Because there are no data from randomized clinical trials, the treatment recommendations included in the NCCN Guidelines are derived from the management practices of patients with PCBCL at NCCN Member Institutions based on the limited data from retrospective analyses and studies involving a small cohort of patients.

Local therapy (excision, RT, or topical therapy) is suitable for PCFCL and PCMZL in patients with solitary/regional lesions (T1-T2) and systemic therapy (rituximab or combination chemoimmunotherapy regimens) is often more appropriate for patients with generalized (skin only) disease.<sup>35-42</sup>

Imaging studies during the course of treatment are not needed. PET/CT (preferred) or CT with contrast may be repeated at the end of treatment for assessment of response and can be repeated if there is clinical suspicion of progressive disease. Extracutaneous disease should be managed according to FL as outlined in the NCCN Guidelines for B-cell Lymphomas.

#### **Solitary or Regional Disease (T1-T2)**

RT (24–30 Gy; alone or in combination with excision) or excision alone is recommended as the initial treatment.<sup>26-28,31,33,34,48</sup> Local RT is the preferred initial treatment. Observation is an option when RT or excision is neither desired nor feasible (eg, lesions on the scalp where hair loss is a major concern).

Topical therapy (steroids, imiquimod, or nitrogen mustard or bexarotene gel) or intralesional steroids may be considered for selected patients. Several case reports have shown the effectiveness of topical therapy





# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

(steroids, imiquimod, and nitrogen mustard or bexarotene gel) for patients with multifocal lesions.<sup>35,49-52</sup> Interlesional steroids have also been used in the management of PCFCL or PCMZL, although only limited data are available.<sup>32,53,54</sup>

Observation is recommended for patients with disease responding to initial therapy, and those with refractory disease should be managed as described for generalized disease below.

### **Generalized Disease (skin only; T3)**

Observation, topical therapy, local RT (24–30 Gy) for palliation of symptoms, and intralesional steroids or rituximab are included as treatment options. In patients with very extensive or symptomatic disease, other combination chemotherapy regimens recommended for the treatment of FL may be used.<sup>35-37</sup>

Observation is recommended for patients with disease responding to initial therapy, and those with refractory disease should be treated with an alternate initial treatment option.

### **Treatment for Relapsed or Refractory Disease**

While PCMZL and PCFCL respond to initial therapy, disease relapse is common in the majority of patients with regional or generalized disease, regardless of type of initial treatment. However, relapses are generally confined to the skin in which case survival does not appear to be affected.

Patients with regional or localized relapse should receive additional therapy (excision, intralesional steroids, local RT [4 Gy] or topical therapy using steroids, imiquimod, nitrogen mustard, or bexarotene gel), and those with generalized disease relapse confined to the skin should receive additional therapy with treatment options recommended for

generalized disease at presentation. Low-dose RT (4 Gy) may be adequate for relapsed or refractory disease.<sup>30,31</sup>

Patients with a PR or persistent progressive disease following additional treatment should be treated with the other options included in the listing of initial treatment to improve response before starting treatment for refractory disease. Patients with extracutaneous relapse or those with cutaneous relapse that is not responding to any of the initial treatment options should be managed according to the FL as outlined in the NCCN Guidelines for B-Cell Lymphomas.

### **Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type**

RT alone is less often effective in patients with PCDLBCL. While these lesions do respond to RT, remissions are often short-lived and higher rates of dissemination to extracutaneous sites occur.

The potential utility of using chemotherapy in combination with rituximab for the management of patients with PCDLBCL, leg type has been described in retrospectively analyses and case reports.<sup>55-59</sup> In a retrospective multicenter study from the French Study Group on 60 patients with PCDLBCL, leg type, patients treated with anthracycline-containing chemotherapy and rituximab had a more favorable short-term outcome, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival outcomes.<sup>55</sup> Among 12 patients treated with anthracycline-based chemotherapy with rituximab, the CR rate was 92% compared to 62% for patients who received other therapies. The 2-year OS rate for these two groups was 81% and 59%, respectively. In a more recent report from the French study group (115 patients), the 3- and 5-year survival rates were 80% and 74%, respectively, for patients who received multiagent chemotherapy with



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

rituximab compared to 48% and 38%, respectively for patients who received less-intensive therapies.<sup>58</sup> A more recent retrospective analysis involving 21 patients with PCBCL treated in a single center also reported excellent outcomes with anthracycline-based chemotherapy, including R-CHOP or R-CVP irrespective of staging and pathologic subtype.<sup>59</sup> Eighteen of 21 patients received treatment for PCBCL (12 chemotherapy alone, 3 RT alone, and 3 chemotherapy and RT) and CR was observed in 17 patients.

PCDLBCL, leg type has a poorer prognosis than other types of PCBCL and is generally treated with more aggressive chemotherapy regimens used for systemic DLBCL as outlined in the NCCN Guidelines for B-Cell Lymphomas.



# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

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# NCCN Guidelines Version 2.2018

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# NCCN Guidelines Version 2.2018

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# NCCN Guidelines Version 2.2018

## Primary Cutaneous B-Cell Lymphomas

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## NCCN Guidelines Version 2.2018 Primary Cutaneous B-Cell Lymphomas

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

56. Posada Garcia C, Florez A, Pardavila R, et al. Primary cutaneous large B-cell lymphoma, leg type, successfully treated with rituximab plus chemotherapy. *Eur J Dermatol* 2009;19:394-395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19467966>.

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