

# Primary Cutaneous Lymphoma

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# Primary Cutaneous Lymphoma (PCL)

- The term **primary cutaneous lymphoma** or **PCL** is meant to separate out those patients who have skin as the only area of lymphoma at time of diagnosis [mycosis fungoides (MF) and Sezary syndrome (SS) are exceptions] from those patients who have internal lymphoma that has metastasized to the skin, so called secondary cutaneous lymphoma.
- When a patient presents with skin lesions suggestive of cutaneous lymphoma, the first challenge is to determine the subtype of lymphoma and whether it is primary or secondary
- PCLs are further divided into cutaneous T cell lymphoma (CTCL) or cutaneous B cell lymphoma (CBCL) depending on the type of lymphocyte the lymphoma starts in, pathologic features, genetic or molecular features, and the presence of certain proteins on the surface of the cells

# WHO Classification of Primary Cutaneous T-cell and NK Lymphomas

Mycosis fungoides

MF variants and subtypes

Folliculotropic MF

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

Primary cutaneous aggressive

epidermotropic CD8+ T-cell

lymphoma (provisional)

Primary cutaneous  $\gamma/\delta$  T-cell lymphoma

Primary cutaneous CD4+ small-

medium sized pleomorphic T-cell

lymphoproliferative disorder

Primary cutaneous acral CD8+ T-cell  
lymphoma

Primary cutaneous PTCL, NOS

# WHO Classification of Primary Cutaneous B-cell Lymphomas

- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Primary cutaneous follicle center cell lymphoma
- Diffuse large B-cell lymphoma, NOS
  - Primary cutaneous diffuse large B-cell lymphoma, leg type
  - Primary cutaneous diffuse large B-cell lymphoma, others
- Intravascular large B-cell lymphoma

# Primary Cutaneous Lymphoma (PCL)

- The annual incidence of PCLs in the US is 10-10.7 per million person years or about 3000 new cases per year.\*
- CTCL is more common than CBCL, making up about 70% of the cases of PCL per year
  - Mycosis fungoides (MF) is the main subtype of PCL, making up 53-73% of all cases of CTCL.
- Many subtypes of CTCL and CBCL are very rare and the actual incidence of these is unknown

*\*Olsen EA editor. Cutaneous Lymphoma. Dermatologic Clinics, October 2015.*

# Diagnosis of PCL

- Biopsy of skin lesion(s): most indurated, off topical steroids or other medications that could affect pathologic results, and sample taken of each different type of lesion
- History of type of lesions, duration and relationship to any medications
- Complete physical exam
- Blood work—both general as well as specific lymphoma-directed
- Imaging: CT scan(s), PET/CT and/or MRI
- Biopsies of lymph node, internal organ, bone marrow may be indicated depending on subtype

# Staging of PCL

- Staging takes into account all potential organs that a particular lymphoma may involve
- MF and SS may involve the blood which the other PCLs do not. MF and SS also have nuances related to lymph node involvement on biopsy that other types of PCL do not. For this reason, there is a separate staging system for MF and SS based on TNMB vs the other types of PCL, either CTCL or CBCL, which is based on TNM only.
- Staging is important for setting expectations for prognosis and selecting treatment.

# TNMB Classification of MF/SS

- T: skin. Clinical diagnosis
  - T1: <10% patches or plaques
  - T2:  $\geq$ 10% patches or plaques
  - T3: at least one tumor
  - T4: erythrodermic
- N: lymph node. Based on pathologic findings on biopsy
  - N0: normal node
  - N1-2: dermatopathic changes
  - N3: frank lymphoma
- M: viscera. Based on imaging +/- biopsy
  - M0: not involved
  - M1: at least one organ involved
- B: Blood. Based on Sezary cell prep or flow cytometry
  - B0: no involvement
  - B1: Low tumor burden.
  - B2: >1000/uL abnormal lymphocytes with clone



## Staging of MF/SS\*

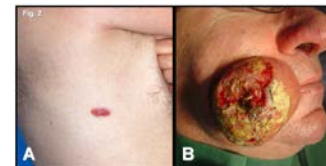
STAGE	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1,2	0-2	0	0,1
IIB	3	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA <sub>1</sub>	1-4	0-2	0	2
IVA <sub>2</sub>	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

**Blue area = designation as “early disease”. Those in yellow are changes in classification published in 2007: first change since 1979.**

\*Olsen E, et al. *Blood* 2007;110:1713-1722.

# Staging of Cutaneous Lymphomas Other than MF/SS

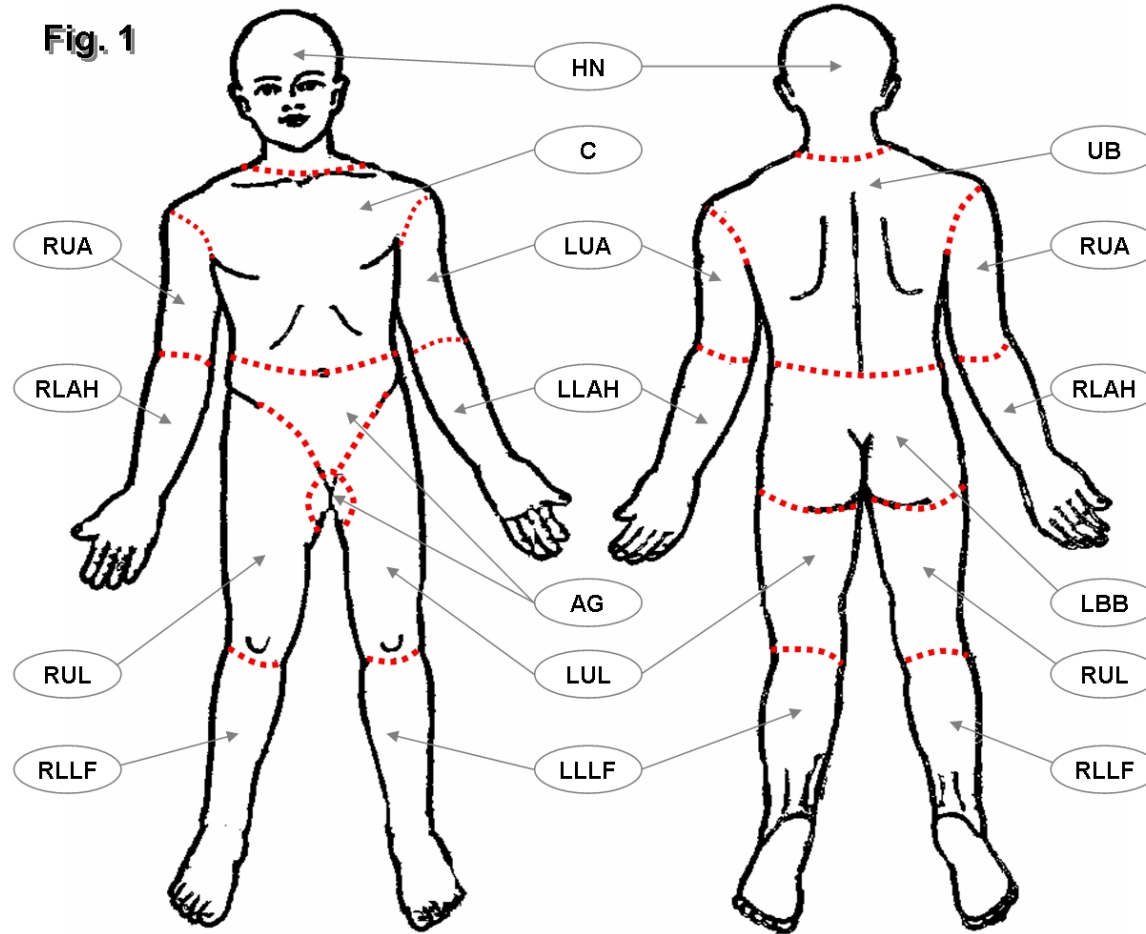
Classification		Description	
Skin (T)	T1	Solitary skin involvement	
		T1a	Solitary lesion <5 cm in diameter
		T1b	Solitary lesion $\geq$ 5 cm in diameter
	T2	Regional skin involvement : multiple lesions limited to 1 body region or 2 contiguous body regions	
		T2a	Disease encompasses a <15 cm diameter area
		T2b	Disease encompasses a $\geq$ 15 -<30 cm diameter area
		T2c	Disease encompasses a $\geq$ 30 cm diameter area
	T3	Generalized skin involvement	
		T3a	Multiple lesions involving 2 noncontiguous body regions
		T3b	Multiple lesions involving $\geq$ 3 body regions



**Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, Dummer R, and Hoppe RT for the ISCL and the EORTC. Blood 110: 479-484, 2007.**

# NON-MF/NON-SS CUTANEOUS LYMPHOMAS

Fig. 1



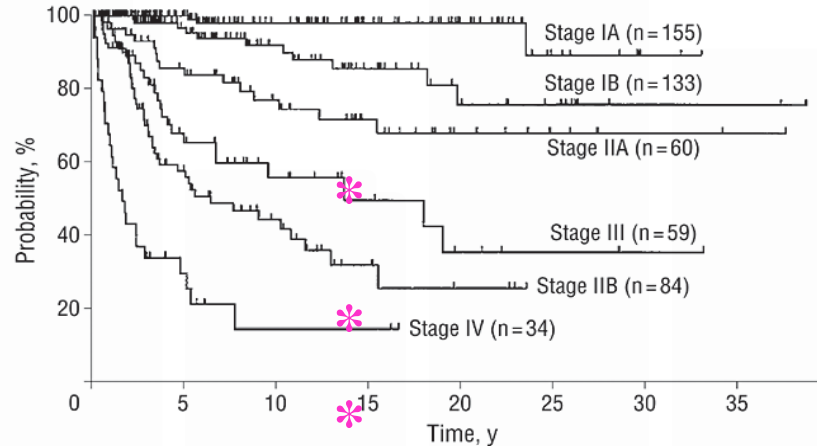
HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLL	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

# ISCL/EORTC TNM Classification of Cutaneous Lymphomas Other than MF/SS

Classification		Description
Lymph nodes (N)	N0	No clinical or pathologic lymph node involvement
	N1	Involvement of one peripheral lymph node region that drains an area of current or prior skin involvement
	N2	Involvement of $\geq 2$ peripheral lymph node regions or involvement of any lymph node region that does not drain in an area of current or prior skin involvement
	N3	Involvement of central lymph nodes
Viscera (M)	M0	No evidence of extracutaneous non-lymph node disease
	M1	Evidence of extracutaneous non-lymph node disease

**Kim YH et al. Blood 110: 479-484, 2007**

**Actuarial disease-specific survival of 525 patients with mycosis fungoides and Sezary syndrome according to their clinical stage at diagnosis (stages IA-IV)**



Kim, Y. H. et al. Arch Dermatol 2003;139:857-866.

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Published survival curves are discouraging. But need to keep in mind that these survival curves above included patients enrolled from 1958-1999 including years when treatments were quite different than today. The 15 year follow-up point noted above occurred prior to introduction interferon in 1986 by Hoffman LaRoche and ECPP in 1987 and all agents specifically approved for MF since. Treatments utilized prior to 1980s included primarily radiation, chemotherapy, topical nitrogen mustard (Hasserick 1959) and PUVA (Gilchrest 1976). Survival today is much different and documentation of this is needed.

# Treatment of PCL 2018

- Multiple skin-directed treatments, interferon, retinoids, monoclonal antibodies, checkpoint inhibitors, CAR T-cell therapy, standard and novel chemotherapies, bone marrow transplant
- Treatment preferences are unique for each subtype lymphoma
- Stage-based treatment but menu of therapies, no step-based guidelines
- Goals for therapy are remission or control of disease and prolongation of life: there is no cure for any of these PCLs at this time

# Treatment of PCL 2018

- Immunomodulators and skin directed therapy (and combinations) are often best treatments for the more indolent types of PCL as these can be used long term without significant negative side effects.
- Targeted monoclonal antibodies and chemotherapy are available for the more aggressive forms of PCL: side effects generally limit long term use
- Dermatologists and oncologists may approach therapies differently.

# Efficacy Rating of Treatments for PCL

- MF/SS currently have separate response criteria from other PCLs
- All define response in skin, nodes, viscera (and blood in MF/SS) and use combination of all to give global response score
- Response rate:
  - CR: 100% clearance of baseline disease. Important as this is the only response that implies a remission and would potentially allow stopping treatment
  - PR: 50% clearance of baseline disease. This response usually leads to adding additional therapy to try to induce a CR
  - OR: CR and PR combined
  - PD: usually defined as either greater than 25% increase disease from baseline or an additional negative factor that changes prognosis (new tumor in patch/plaque disease for example)
- Response duration: date when criteria for CR or PR met until date first lost
- Progression free survival: date of initiation of treatment to PD or death



## PUVA IN THE TREATMENT OF IA-IIA MF\*

Aside from radiation, most effective topical treatment. In peril from most sites now changing to using NBUVB instead.

Best study: 104 patients (94% white) seen 1979-1995 at Northwestern University with IA-IIA MF treated with PUVA 2-3X per week until CR (defined as clinical and histological clearing). Maintenance treatment given as decreasing frequency of treatment to once q 1-6 weeks. Querfeld C et al Arch Dermatol 2005: 141: 305

Stage	N	CR (%)	Median cumulative PUVA to CR	Disease free survival 10 yrs	Progress to higher stage
IA	57	68%	198 (29-1900) J/cm <sup>2</sup>	30%	9%
IB-IIA	47	62%	166 (45-392) J/cm <sup>2</sup>	50%	12%

# INTERFERON ALFA IN THE TREATMENT OF MF

- Most effective systemic agent for MF
- Usual dose: 3-6 MU tiw to qd subq IFN alfa 2b
  - Long term maintenance well tolerated—no cumulative effect AEs
  - Side effects: less energy, decrease in appetite, rare depression
- Efficacy: single agent response well documented. Examples of combination therapy given below. Used in combination frequently with bexarotene low dose but efficacy data lacking on this combination vs single agent therapy.

Treatment	Stage	CR	OR
IFN 3-6 MU tiw to qd	I-IV	20-40%	50-80%
IFN 3-12 MU tiw + PUVA	IA-IVA	60-75%	
IFN 9 MU tiw + MTX 10 mg/m <sup>2</sup> biw	IIB-IVB	74%	

# Systemic Single Agent Therapies for Mycosis Fungoides

<b>Treatment</b>	<b>Class</b>	<b>CR</b>	<b>OR</b>
Interferon	Antiviral, antiproliferative	20-40%	50-80%
Bexarotene*	RXR Retinoid	5%	50%
MTX low dose	Inhibits dihydrofolate reductase	Unk	33-58%
MTX high dose	Inhibits dihydrofolate reductase	64%	82%
Vorinostat	HDAC inhibitor	none	30%
Romidepsin	HDAC inhibitor	6%	34%
Brentuximab	antiCD30 +microtubule-disrupting agent	10%	50%
Pralatrexate	Inhibits dihydrofolate reductase and polyglutamylation	6%	41%
Mogamulizumab	Antibody targets CCR4		28%
Pembrolizumab	Antibody targets PD-1	4%	38%

\*At FDA approved dose of 300 mg/m<sup>2</sup>

# Difficulties in Advancing Therapy for PCLs

- Lack of data
  - Data primarily from short term industry sponsored trials and only for MF/SS and CD30+ LPD
  - Data from clinical practice and combination therapies lacking
  - No data on how choices of therapy chosen—effect of cost, access, physician preference lacking
  - No data on long term adverse effects of therapy
  - No data on effect of treatment on QoL, family, work

# USCLC Registry

- USCLC is an organization of physicians dedicated to the advancement of patient care for those with cutaneous lymphoma
- The purpose of the USCLC Registry is to establish a long term, secure and easily accessible electronic online registry platform for the collection of data on patients with cutaneous lymphoma in the United States and collaborating partner nations
- Patients will be consented to participate by their lymphoma doctor and their doctor will input the data: this is a total volunteer effort by the physician and his/her institution to pay for the time that this takes.

# Goals of USCLC Registry

- To determine the incidence and geographic locations of patients with the various subtypes of cutaneous lymphoma in the US and collaborating partner nations
- To determine and validate factors for each type of cutaneous lymphoma that may affect prognosis including those related to:
  - Demographic factors
  - Staging
  - Pathologic, molecular and genetic features of skin, lymph nodes, bone marrow, blood or internal organs
  - Radiologic characteristics including various types of imaging
  - Blood tumor burden or blood markers of significance

# Goals of USCLC Registry

- To determine the efficacy and safety of various treatments or interventions (monotherapies or in combination) for patients with each subtype of cutaneous lymphoma as determined by both physicians and patients
- To determine the cost-effectiveness of various treatments or interventions used to treat each subtype of cutaneous lymphoma

# Goals of USCLC Registry

- To enable patients with the various subtypes of cutaneous lymphoma to input data on the effect of their disease and treatment(s) on their and their families' quality of life
- To enhance the communication between patients with cutaneous lymphoma and the physicians directing their care
- To develop and validate new quality of life metrics for patients with cutaneous lymphoma
- To develop meaningful outcome measures that are of value to physician and patient alike



# Goals of USCLC Registry

- To provide a platform for clinical trials of patients with cutaneous lymphoma to facilitate collaborative research with other national and international organizations
- To develop a virtual tissue bank at each site for the purpose of studies on potential biomarkers of each subtype of cutaneous lymphoma with cross-reference to Registry data
- To educate physicians, by their participation in this registry, with best current approaches and treatments of these cutaneous lymphomas and to encourage participation in research

# Future Goals for PCL

- To advance patient care in terms of survival and quality of life for all patients with PCL
- To continue to search for a cure or, at the very least, long term remissions for affected patients
- To enhance the partnership and communication between physicians and patients regarding meaningful outcomes for PCL
- To grow the collaborative effort between USCLC, CLF and industry to meet these goals