Cutaneous Lymphoma: Diagnosis, Staging and Prognosis

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Cutaneous Lymphoma Foundation

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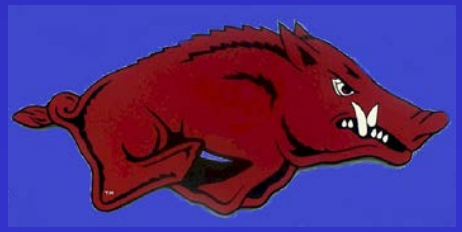
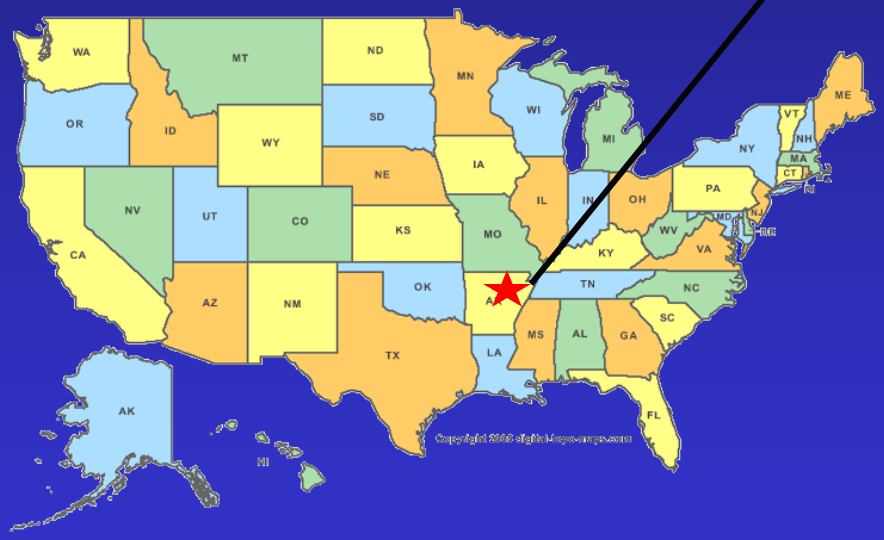
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES



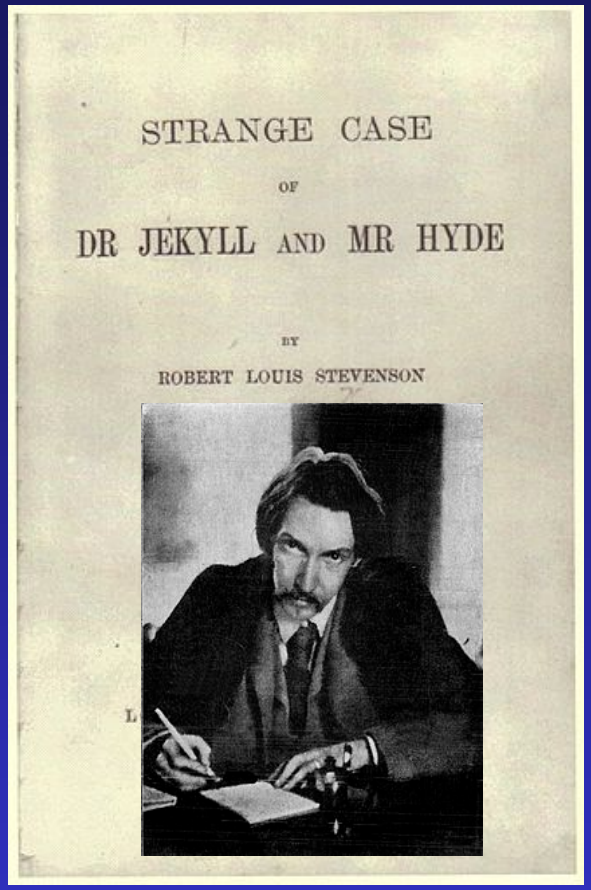
Little Rock, Arkansas



UAMS

Conflict of Interests

- Actelion – Research, advisory board
- Novartis - research
- Elorac – research
- Regeneron - Advisory

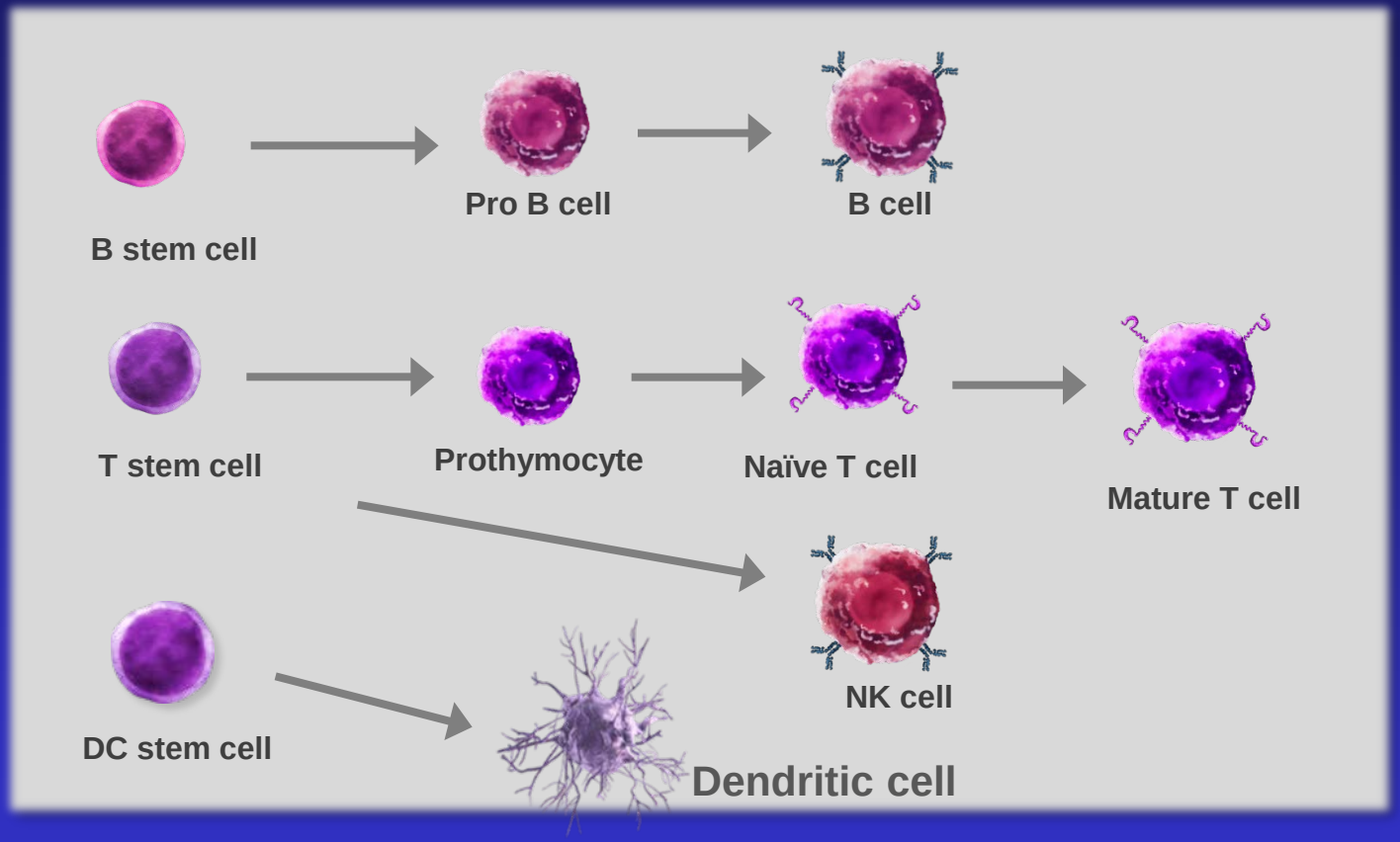


Cutaneous T cell lymphoma, indolent but can be a aggressive cancer. Much like Dr. Jeckyll and Mr. Hyde We need to better understand the cancer to find the right “potion” to treat CTCL (Mr Hyde).

Cutaneous Lymphoma

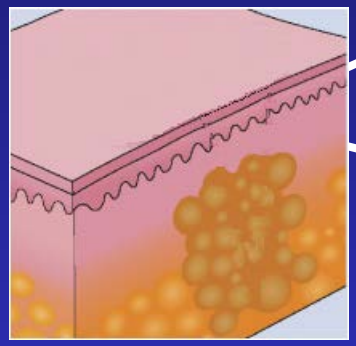
- Overview
- Clinical Presentation
- Diagnosis
- Staging
- Prognosis

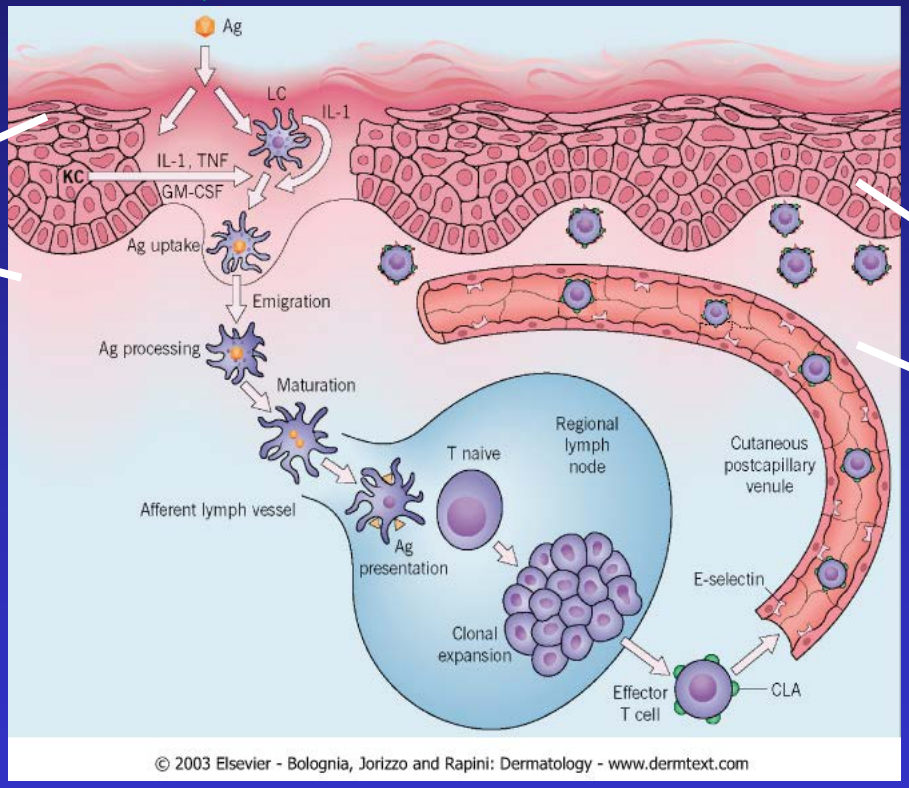
Cells that become lymphoma

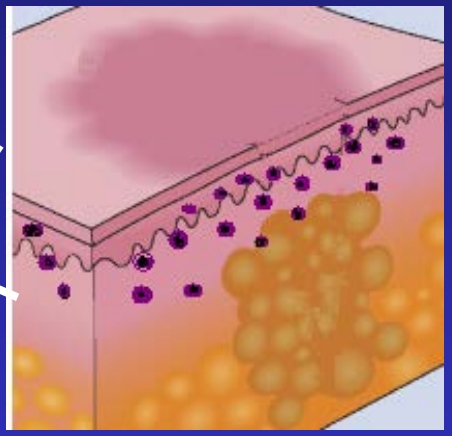


1. Orkin SH et al. *Cell*. 2008;132(4):631-644.
2. Uckun FM. *Blood*. 1990;76(10):1908-1923.
3. Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.

Immune cells protect the skin

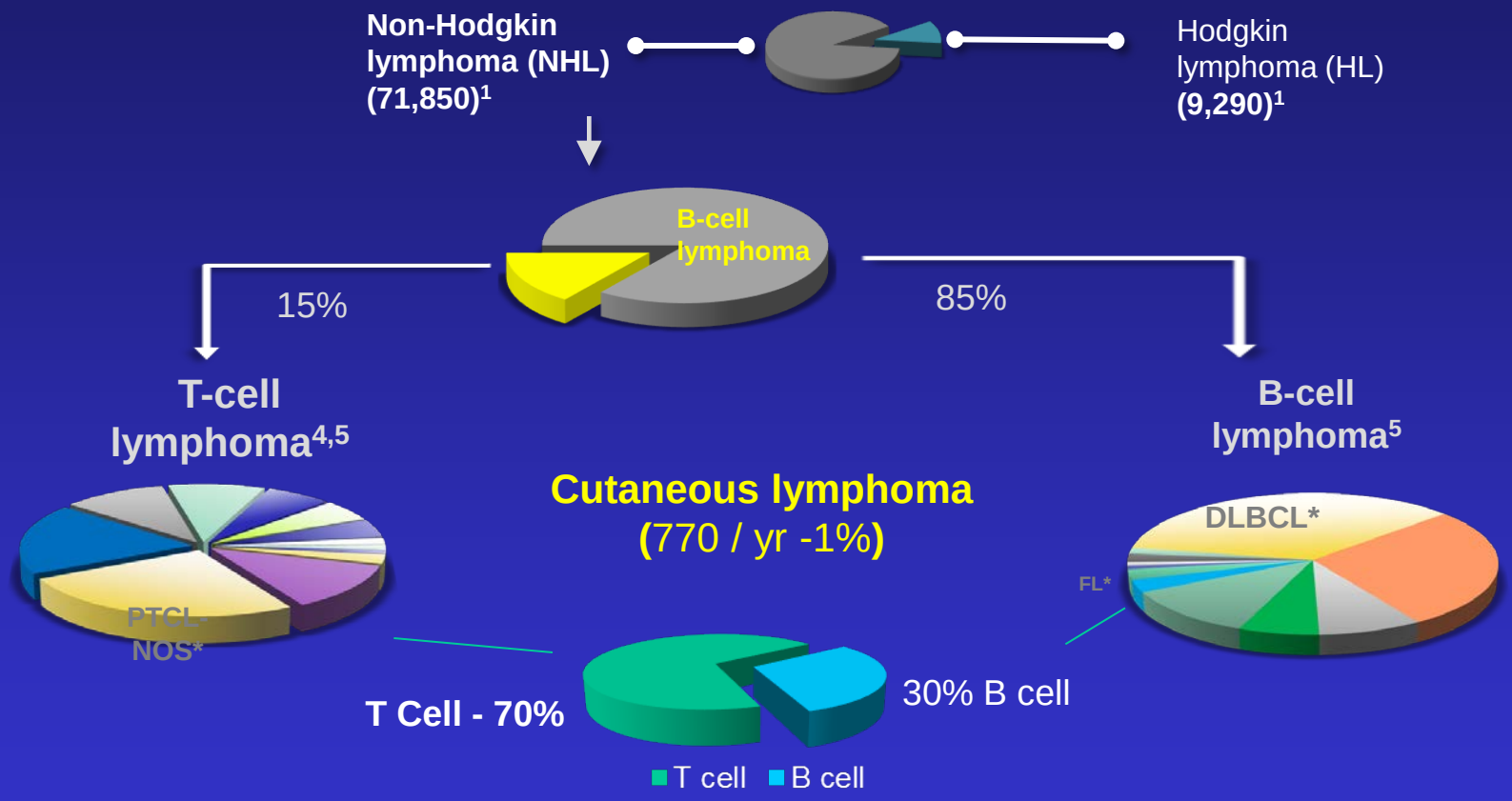






T and B cell cells migrate to the skin to guard. T cells more often. Persistance of abnormal cells is associated with skin disease.

Cutaneous Lymphoma : How common?

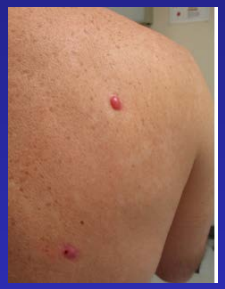


References: 1. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta, GA: American Cancer Society; 2013. **2.** Types of non-Hodgkin lymphoma. American Cancer Society Web site. http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-types-of-non-hodgkin-lymphoma. Updated November 14, 2013. Accessed December 19, 2013. **3.** Küppers R. *Nat Rev Cancer*. 2009;9(1):15-27. **4.** International T-Cell Lymphoma Project. *J Clin Oncol*. 2008;26(25):4124-4130. **5.** Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008. **Note:** B-cell and T-cell sub-classifications are illustrated on slides 10 and 11, respectively.

WHO/EORTC Lymphoma Classification

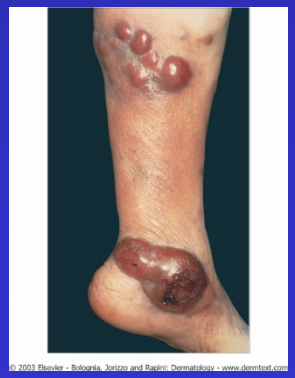
Skin Lymphomas

B cell



Primary cutaneous marginal zone B cell lymphoma

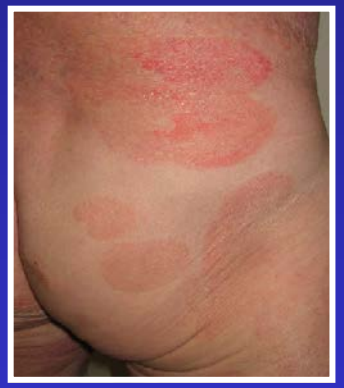
Primary cutaneous follicular center



Primary cutaneous diffuse large B cell – leg type

T cell

Primary cutaneous CD30+ T cell disorder



Mycosis fungoides

Sezary syndrome

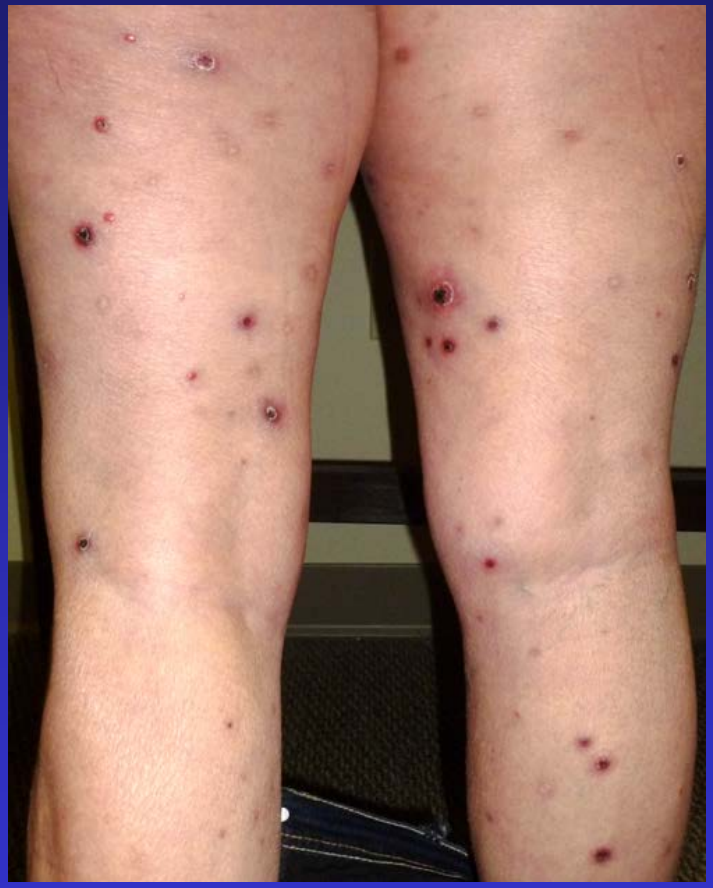
Primary cutaneous γδ TCL

Peripheral TCL-NOS

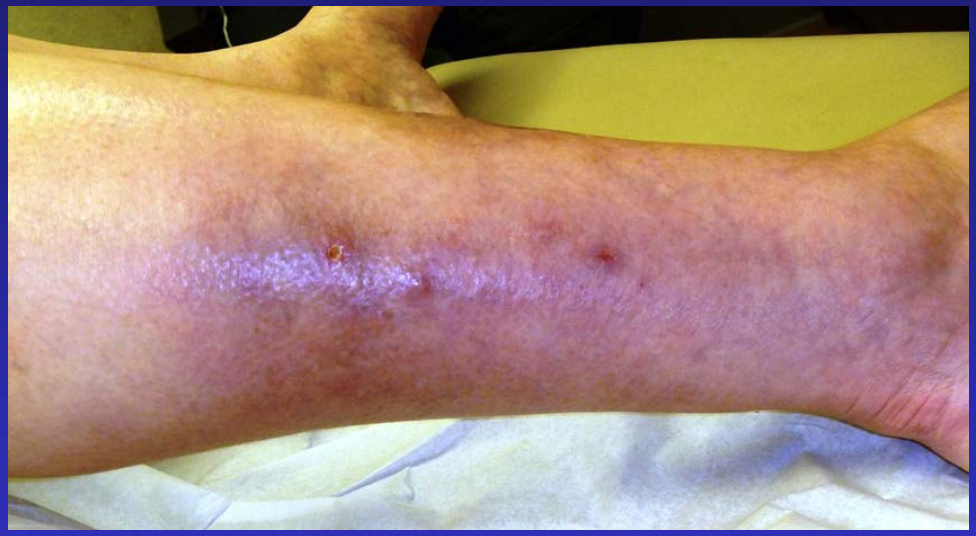
Subcutaneous panniculitic-like TCL

Variable presentation of cutaneous lymphoma

CD30+ Lymphoproliferation

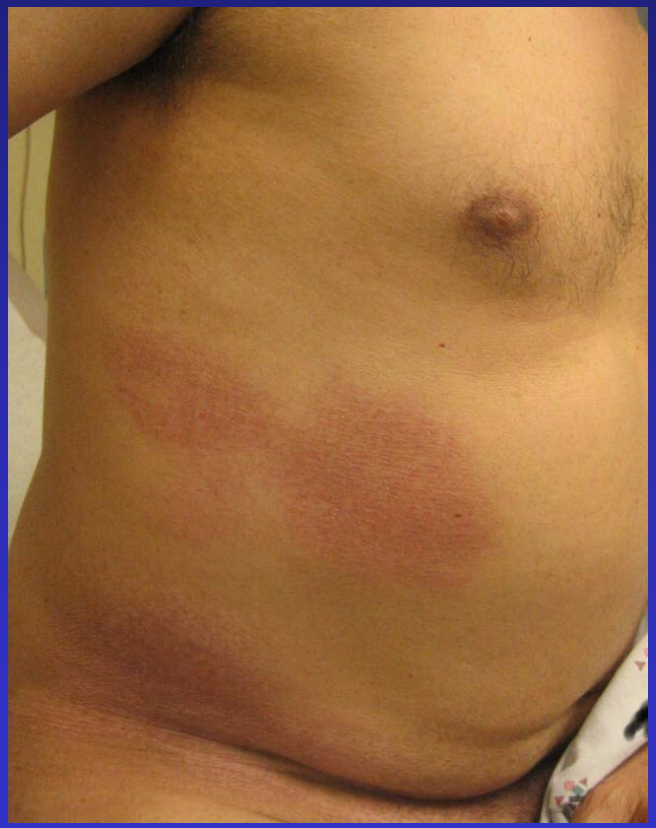


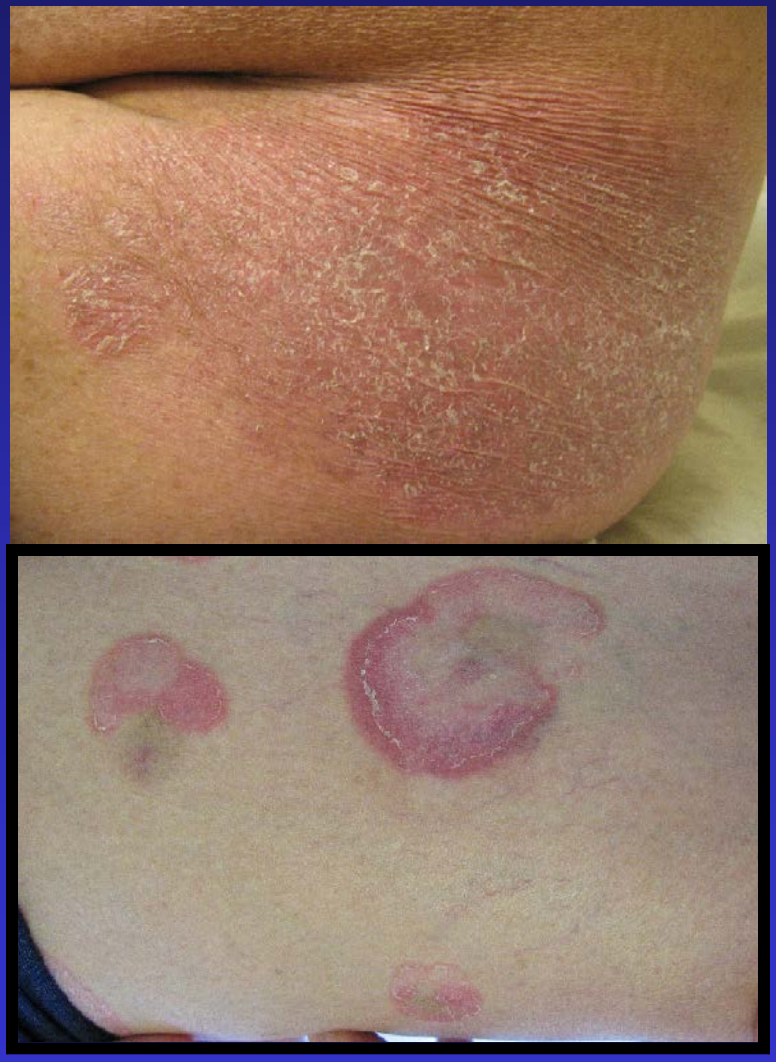
Lymphomatoid Papulosis



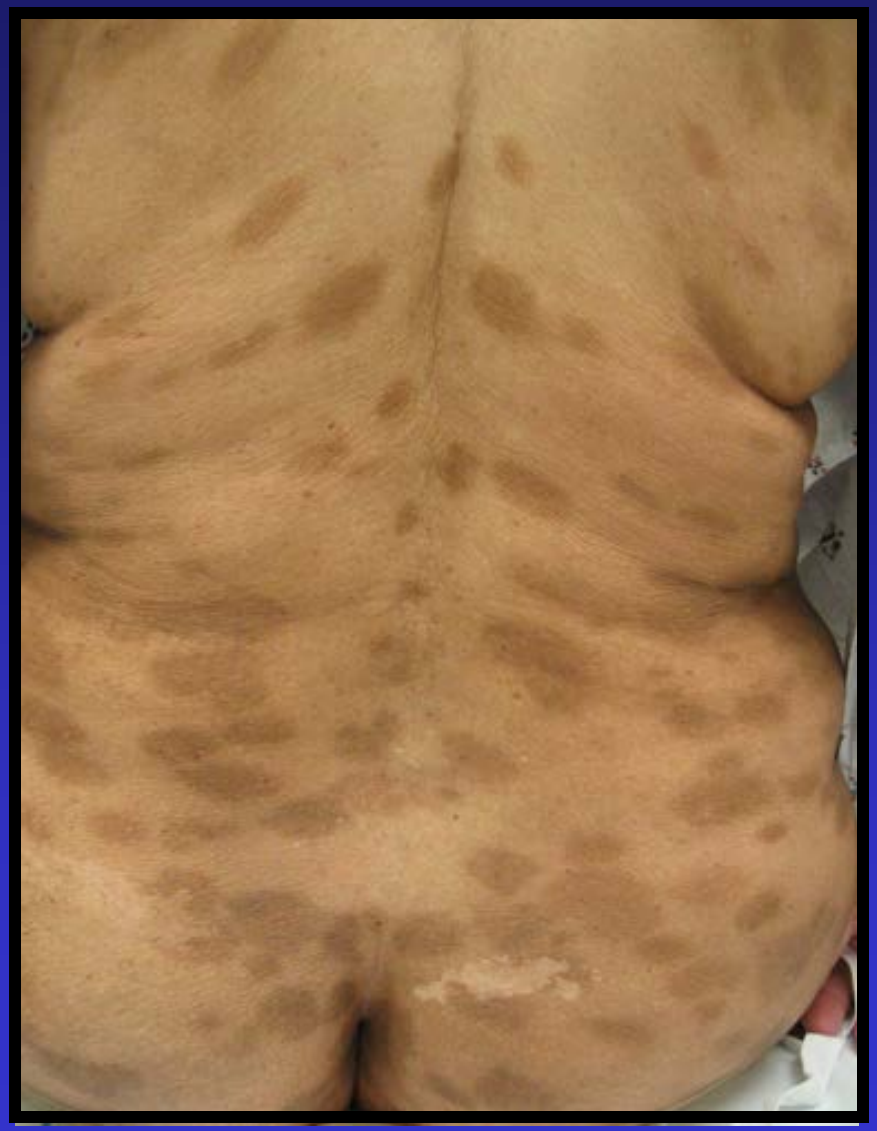
CD30+ Anaplastic large cell lymphoma (ALCL)

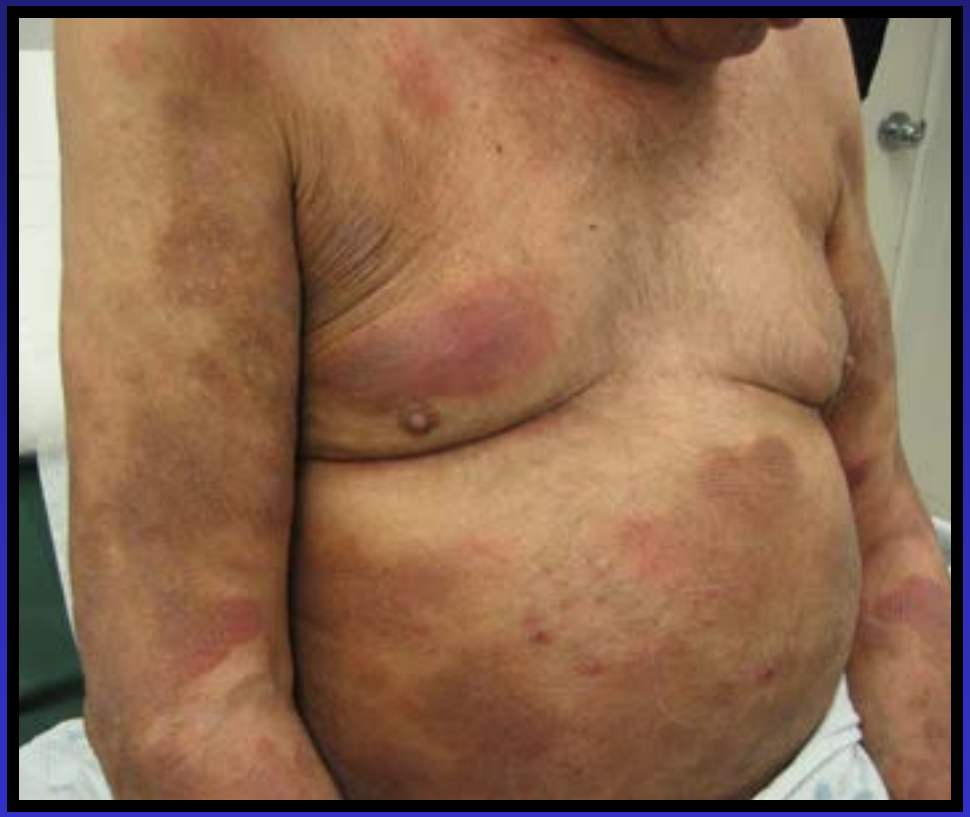
CTCL: Scaly patches



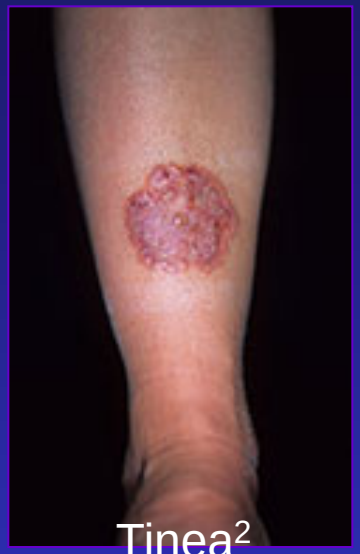


CTCL : Patches and plqaues

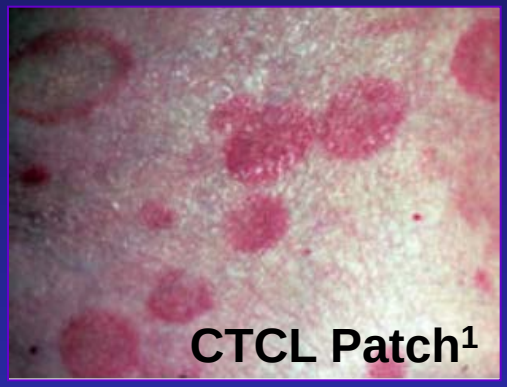




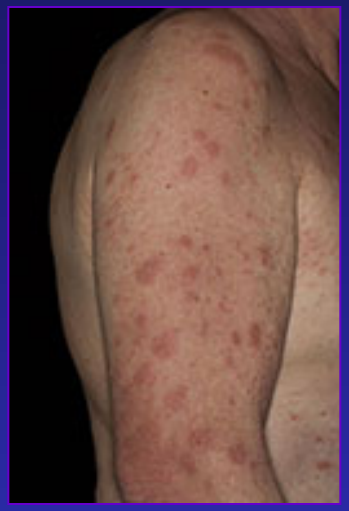
Cutaneous T-Cell Lymphoma (MF/SS) Common Mimickers



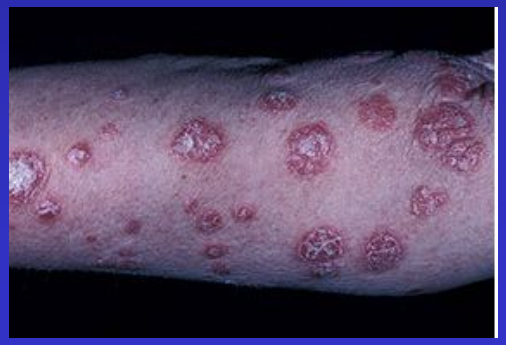
Tinea[2]



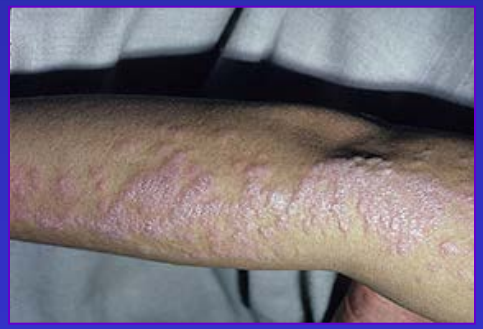
CTCL Patch[1]



Eczema[2]



Psoriasis[2]



Lichen Planus[2]

1. New Zealand Dermatological Society Incorporated. Published online at: http://www.dermnetnz.org
2. http://www.dermnet.com

Mycosis Fungoides (MF)

Epidemiology

- Described in 1806 by Alibert
- 3% of non-Hodgkin's lymphoma – etiology unclear
- Annual incidence: 0.36-0.90/100,000
- Median age 55 - 60 years
- 2:1 male predominance
- African americans affected greater than caucasian
- Leukemic phase - Sézary Syndrome
  - Atypical Sézary cells in the peripheral blood

1. Hoppe RT et al. In: Mauch PM et al, eds*Non-Hodgkin s Lymphoma*. Philadelphia, Pa: Lippincott Williams & Wilkins,2004:307-318
2. Kim YH, Hoppe RT. *Semin Oncol*1999;26:276-.289.
3. Kim YH et al. *Arch Dermatol* 2003;139:857-866
4. Weinstock M 1999 Amer J Pub Health 89:1240-1244

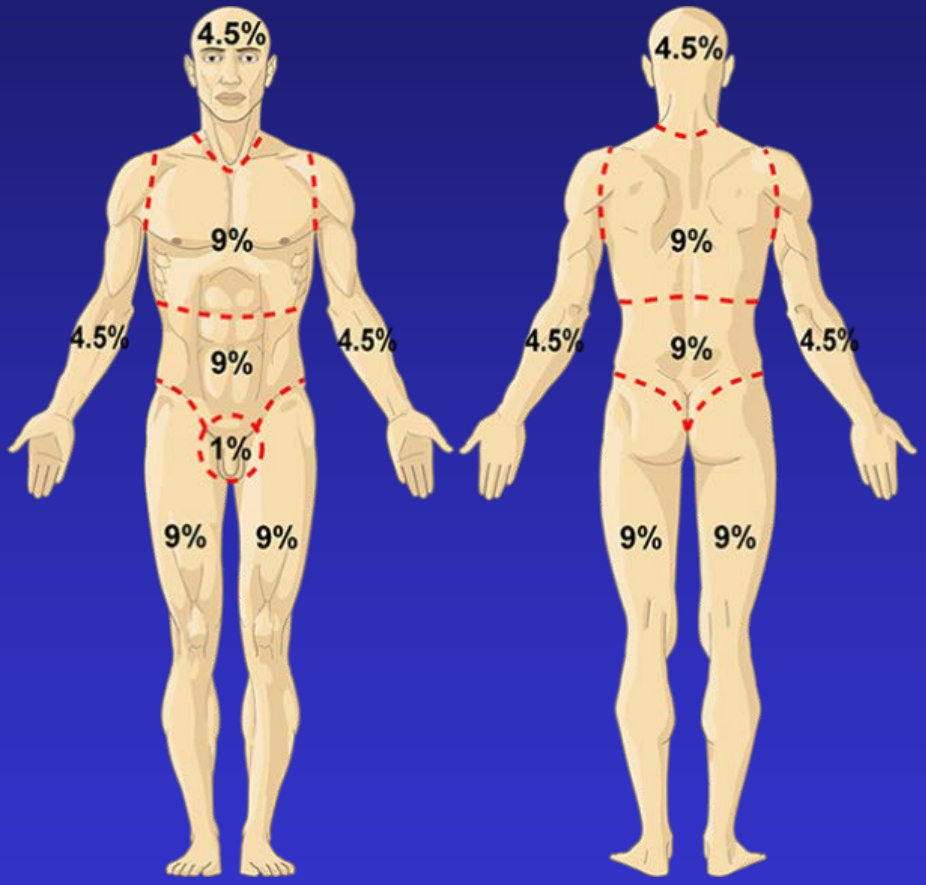
MF Clinical History

- Indolent for many years, “premycotic stage”
- Minimal symptoms in early stage
- Bathing trunk distribution
- Thin patches with cigarette paper atropy, ‘poikiolodermatous’ appearance
- Symptoms of itchiness with late disease
- Progresses on skin before internal involvement
- Fevers, chills, secondary infections with late stage disease

Diagnosis / Staging

- Complete physical exam
- Skin biopsy of suspicious lesion
  - Multiple biopsies may be necessary of early stage lesions
  - Immunohistochemistry – CD3, CD4, CD45, CD5, CD7
  - TCR gene clonality studies
- Blood count with differential, chemistry, liver function test, lactate dehydrogenase LDH, Sezary studies
- Imaging - CT or PET/CT if lymph node palpable
- Lymph node biopsy if palpable

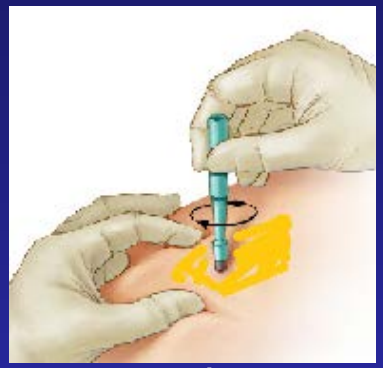
Body surface area – T staging



T1	< 10% BSA	IA
T2	>10% < 80%BSA	IB
T3	tumor	IIB
T4	> 80% BSA	III-IV

Diagnosis

Clinically suspicious skin lesion



Monitor

Not CTCL

Suspicious for CTCL

Diagnostic for CTCL

Immunehisto - TCRGR (-)

Immunehisto+ TCRGR (-)

Immunehisto - TCRGR (+)

Research

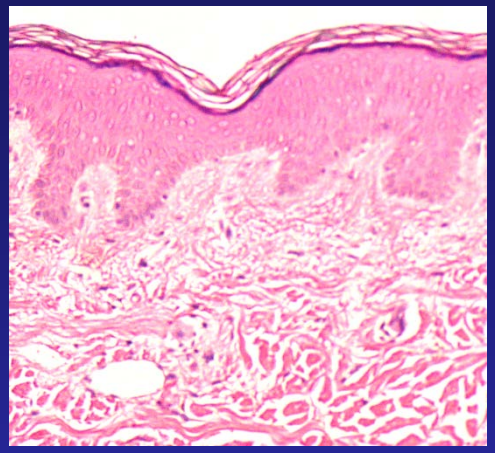
+ Clinical morphology

Close follow-up Repeat biopsy

Treat for CTCL

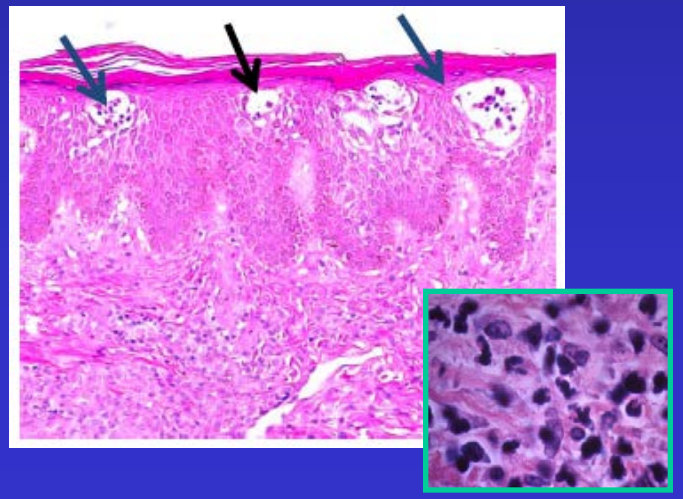
Histopathology

- Historically “classic” features
  - Epidermotropism without spongiosis
  - Atypical lymphocytes
  - Pautrier microabscesses
- Other features
  - Haloed lymphocytes
  - Solitary lymphocytes in the basal layer
  - Lymphocytes in epidermis larger than those in dermis
  - Dermal collagen fibrosis

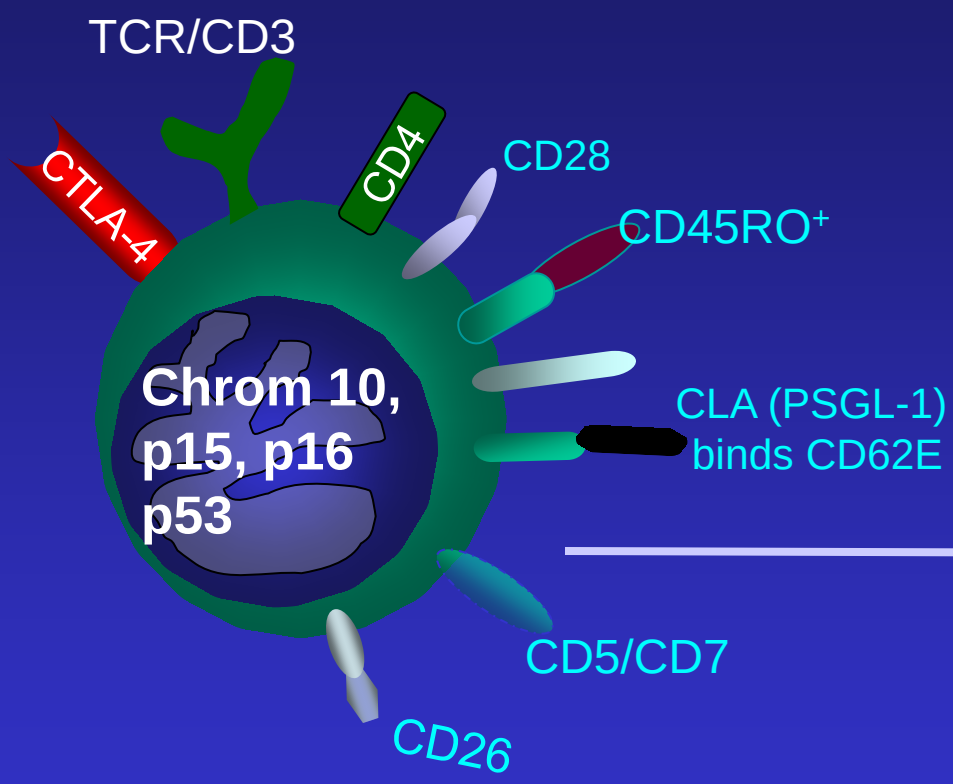


Normal

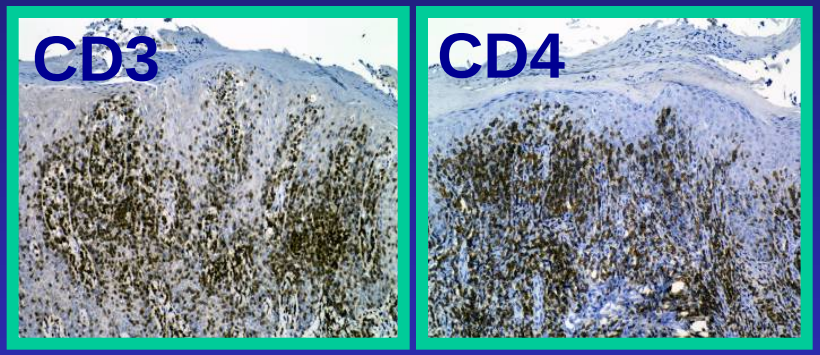
Mycosis fungoides



Immune markers of CTCL



Antigens expressed



Antigens lost

Clonality and Molecular Analysis

- Dominant clone (Standard)
  - DNA analysis for clonality
    - PCR-based techniques
    - TCR-gamma gene
    - (threshold 1%; sensitivity 80%)

- Novel markers (Research)
  - Surface markers – CD158, CD164
  - Molecular cellular markers - Tox
  - Epigenetic markers – TWIST1, PLS3

Diagnosis of Early MF: 4 Points Required*

Criteria	Major (2 Points)	Minor (1 Point)
Clinical Persistent and/or progressive patches/thin plaques plus 1) Non–sun-exposed location 2) Size/shape variation 3) Poikiloderma	Any 2	Any 1
Histopathological Superficial lymphoid infiltrate plus 1) Epidermotropism 2) Lymphoid atypia	Both	Either
Molecular Clonal TCR gene rearrangement		Present
Immunopathological 1) CD2, 3, 5 <50% 2) CD7 <10% 3) Epidermal/dermal discordance		Any 1

*Pimpinelli, et al. ISCL Criteria. (2005) JAAD 53:1053-1063

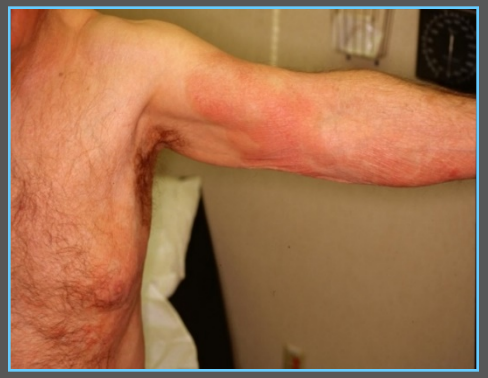
Mycosis Fungoides and Sézary Syndrome Clinical Staging System

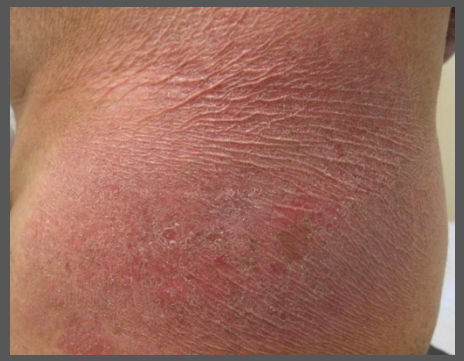
Stages		TNM Classification*				
IA	Patches/plaques < 10% BSA	T1	N0	M0	B0,1	**Skin localized**
IB	Patches/plaques > 10% BSA	T2	N0	M0	B0,1	
IIA	Palpable nodes	T1-2	N1	M0	B0,1	
IIB	Tumors	T3	N0-1	M0	B0,1	
IIIA	Erythroderma	T4	N0	M0	B0	
IIIB		T4	N1	M0	B1	
IVA	Nodes positive	T1-4	N2-3	M0	B 2	**Beyond skin**
IVB	Visceral disease	T1-4	N0-3	M1	B0-2	

B1 >5% Sezary cell; B2 Sezary cell >1000/mcl

Olsen et al. (2007) Blood 110:1713; Kim YH et al.(2003) ArchDerm 139:857

Skin Lesions in Early Stage Mycosis Fungoides

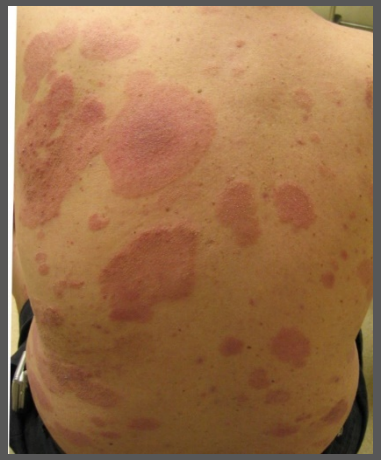


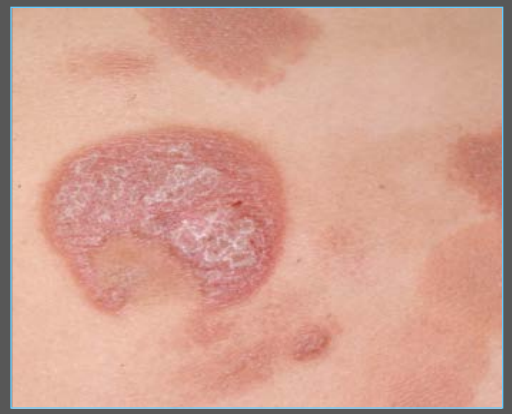


Patches

IA / T1 = <10%

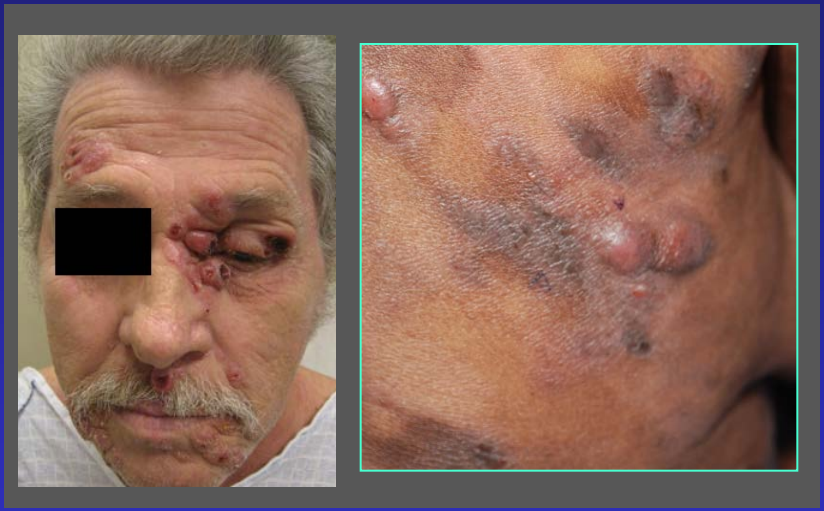
IB / T2 = >10%



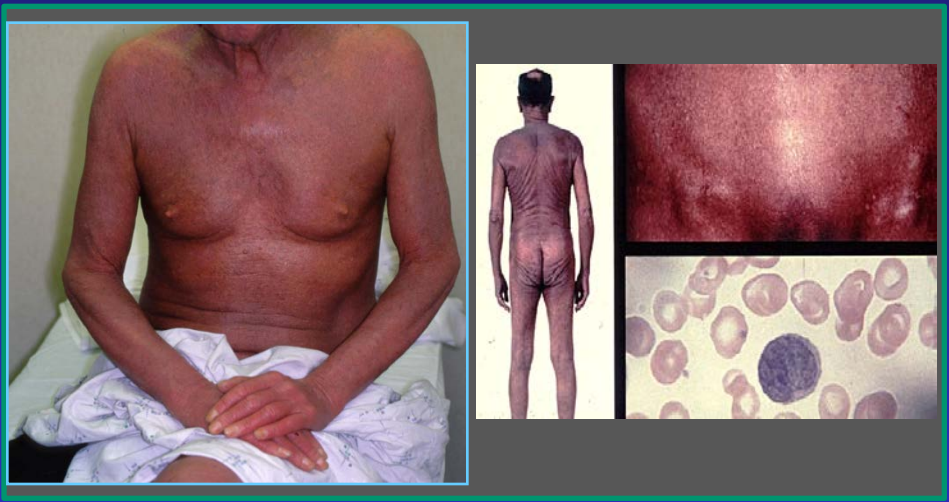


Plaques

Advanced Stage Lesions in Mycosis Fungoides



T3 Tumor

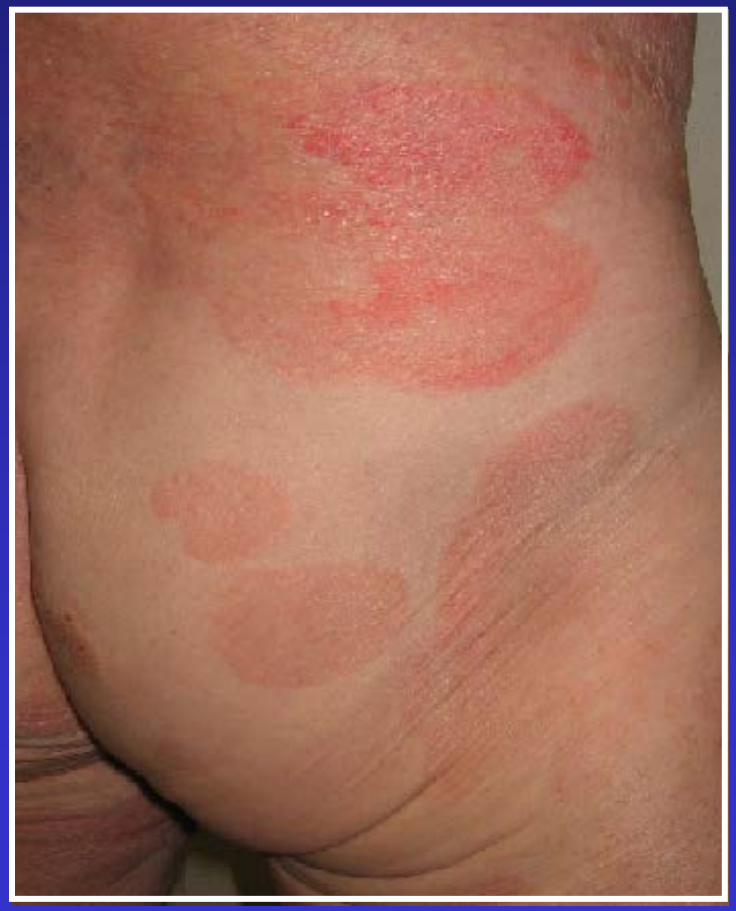


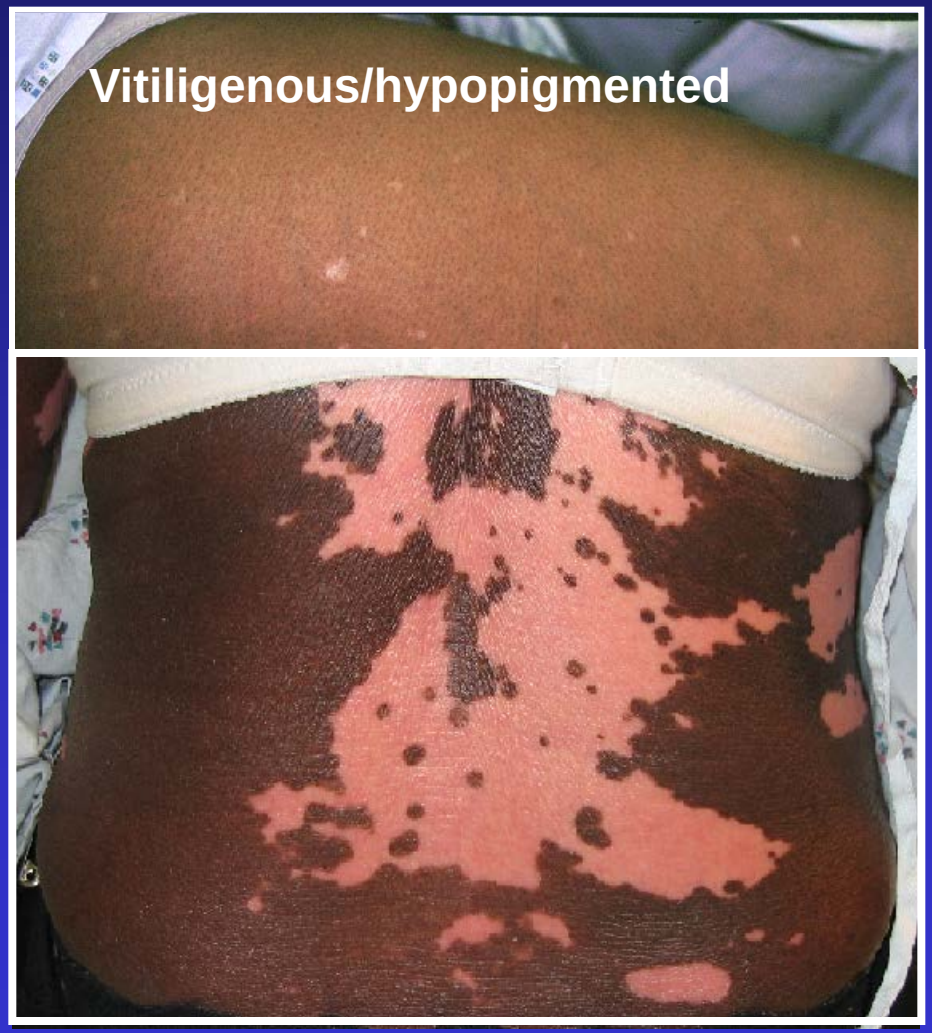
T4 Erythroderma

1. Hoppe RT et al. In: Mauch PM et al, eds. *Non-Hodgkin's Lymphoma*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:307-318.
2. Kim YH, Hoppe RT. *Semin Oncol.* 1999;26:276-289.

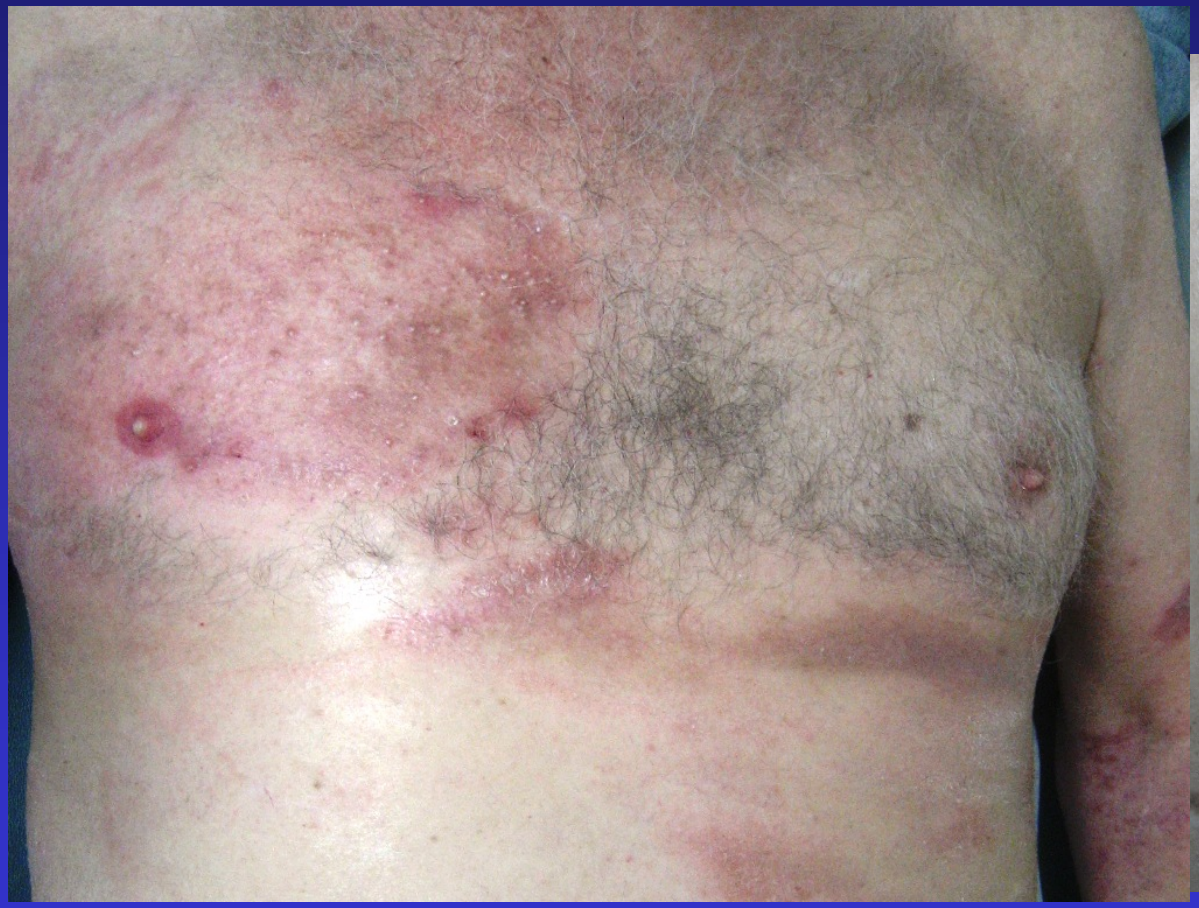
Clinical CTCL Variants

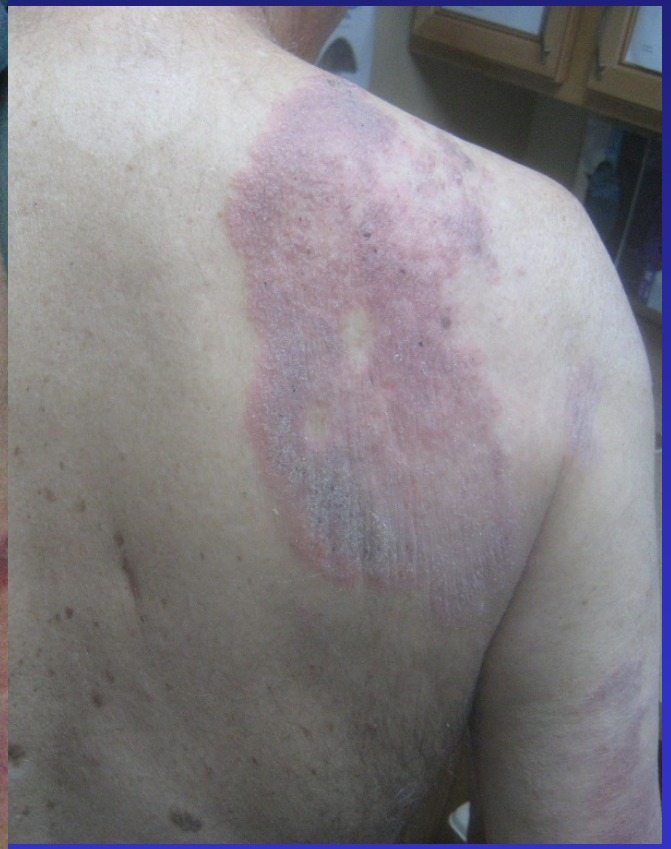
Alibert-Bazin





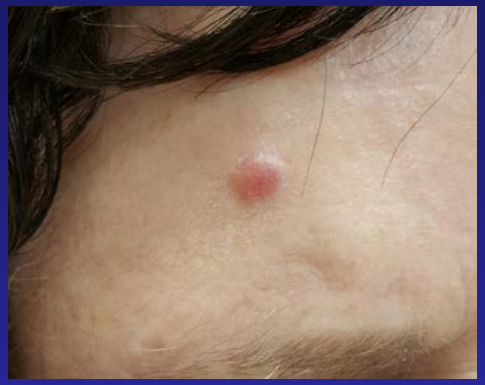
CTCL-Follicular MF



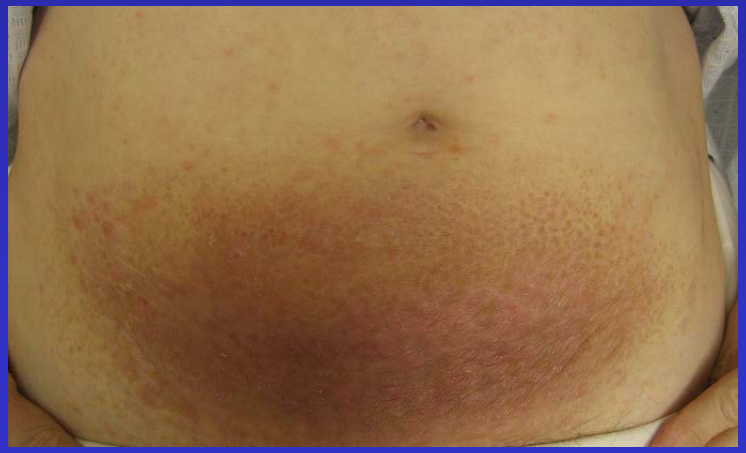


Variants of CTCL

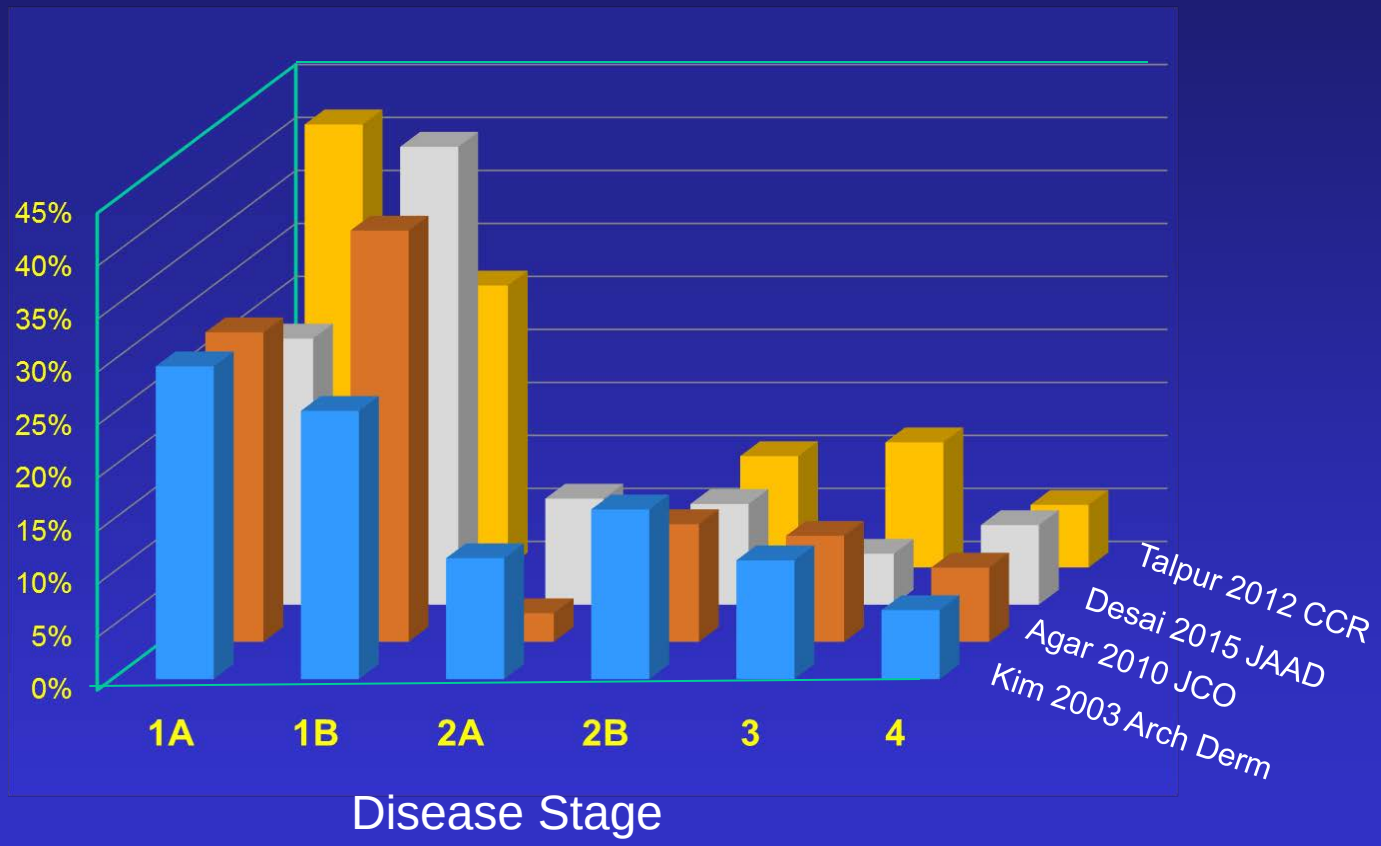
- Small medium pleomorphic CD4+ TCL



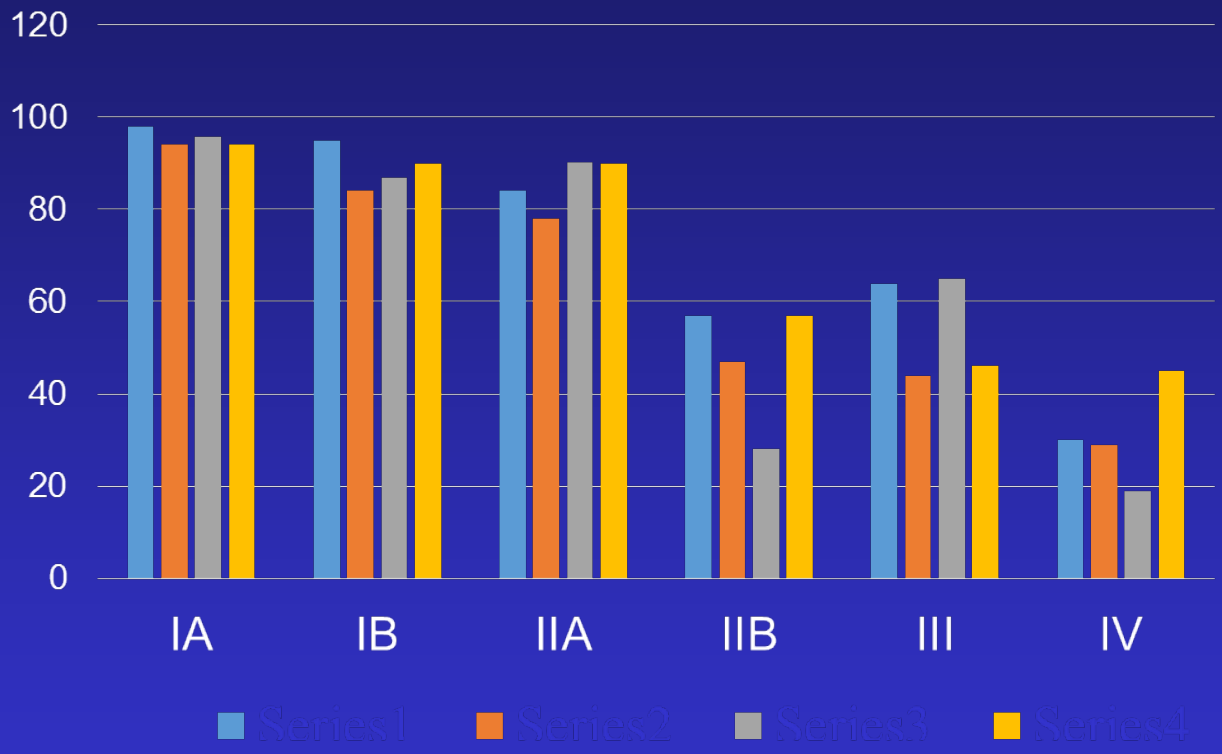
Granulomatous slack skin



CTCL distribution by stage (n=3683)

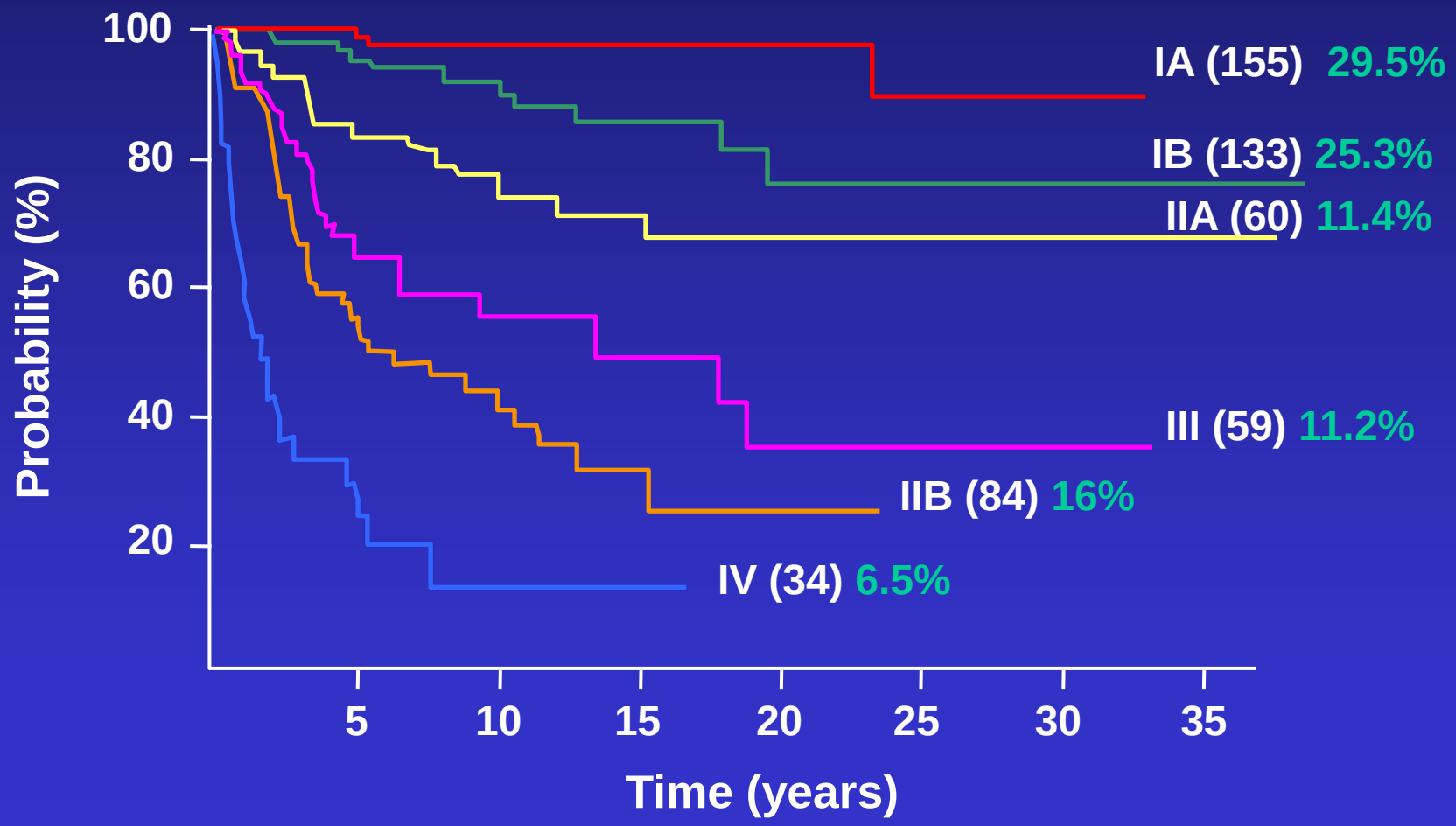


Survival (%) at 5 years



Kim (2003)	Agar (2010)	Desai (2015)	Talpur (2012)
Arch Derm	J ClinOnc	JAAD	ClinCanRes
US (n=525)	Europe (n=1502)	US (n=393)	US (n=1263)

Mycosis Fungoides and Sézary Syndrome: Survival by Clinical Stage

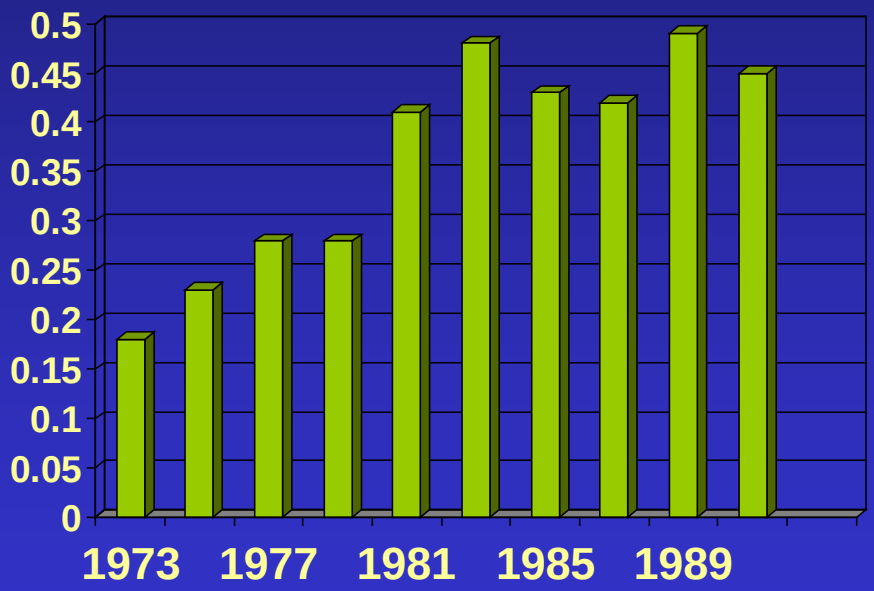


Kim Y. et al Arch Dermatol (2003) 39:857-866

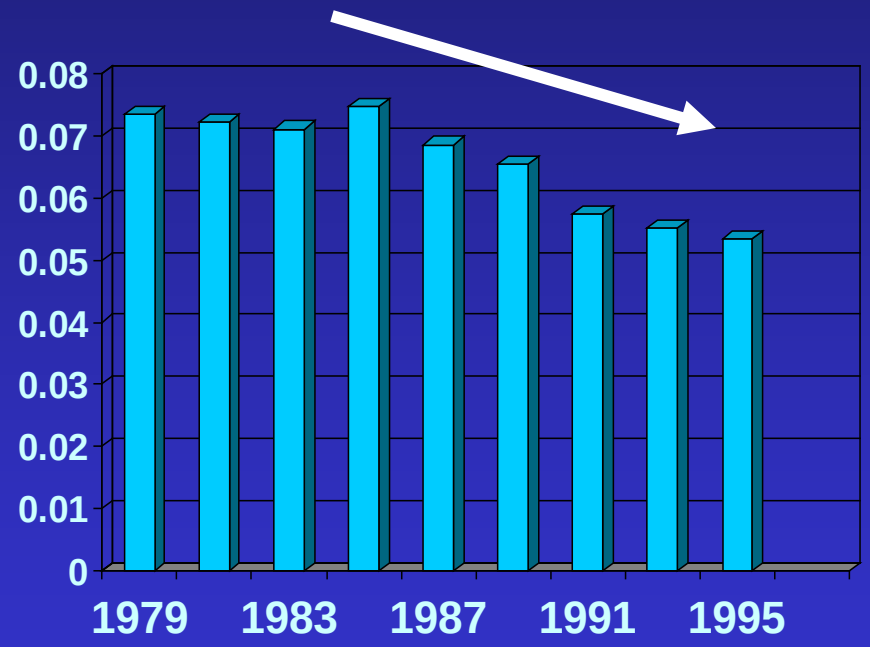
Mycosis fungoides statistics – US

Based on SEER database

Incidence /100,000



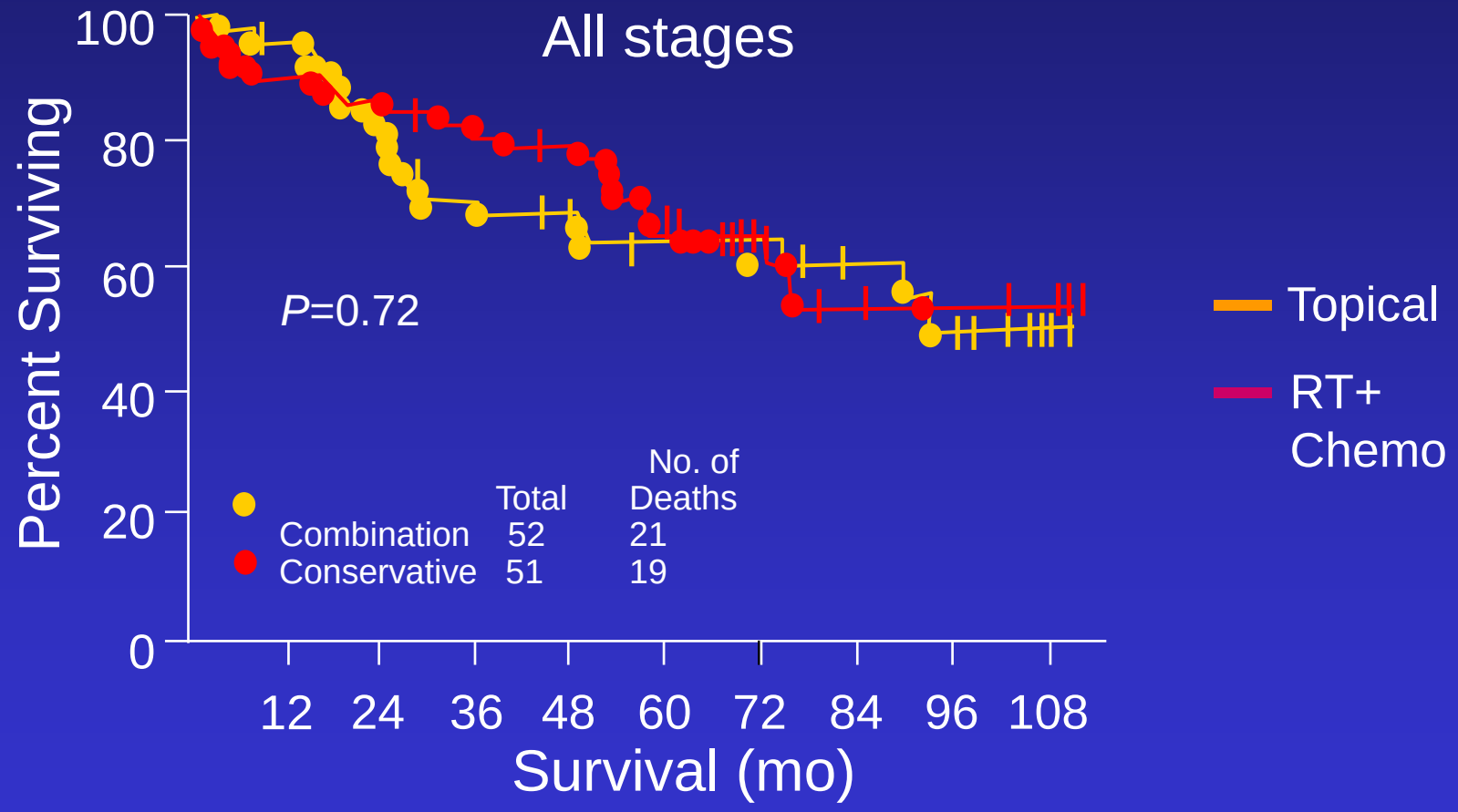
Mortality /100,000



Weinstock M 1999 Amer J Pub Health 89:1240-1244

Conservative or aggressive treatment ?

Kaye et al (1989) NEJM 321:1784



Survival Among Patients Receiving Either Combined Therapy or Conservative Therapy

Summary

- Cutaneous lymphomas are B or T cell cancers infiltrating the skin
  - Most common variant is mycosis fungoides type
- Diagnosis can be challenging in the early stages
  - Skin biopsy is important for diagnosis
  - Repeat biopsy in early stage may be necessary
- Clinical staging depends mainly on extent of skin invovlement
- Prognosis is dependent on clinical staging

Thank you