Associazione Italiana Radioterapia Oncologica

Giardini Naxos, 27 Ottobre 2013

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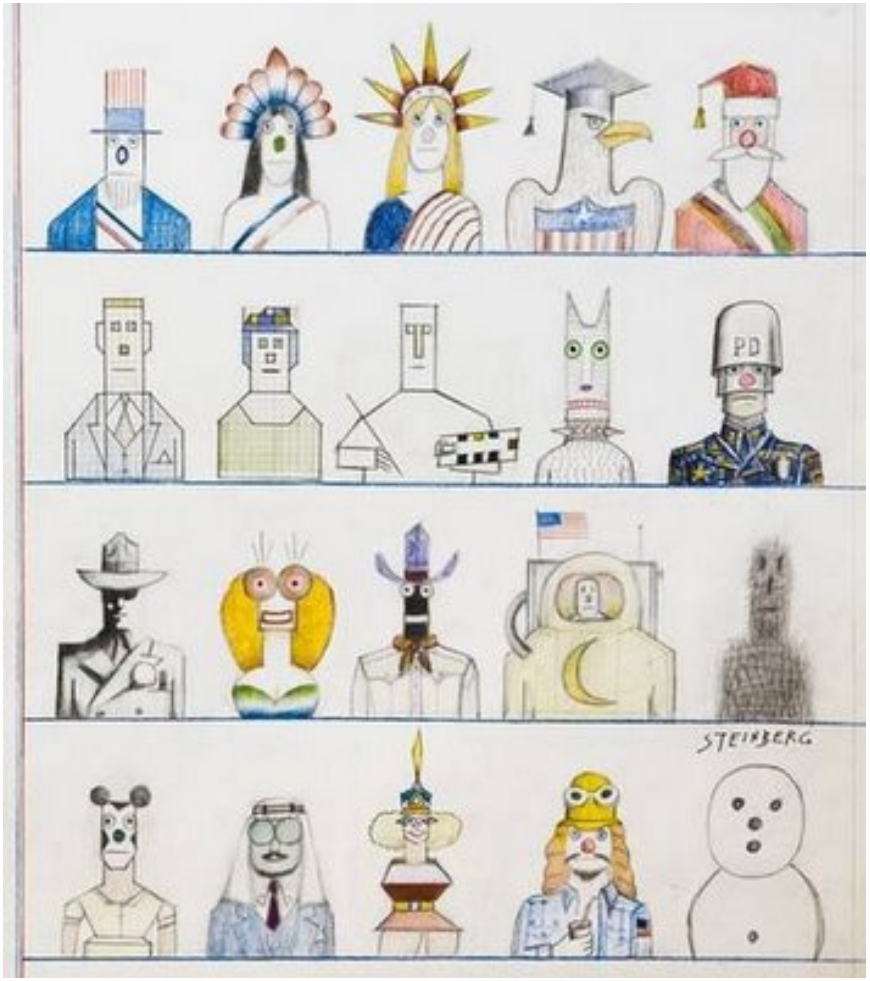
Frequently Asked Questions

- What are the most common clinical-pathological entities?
- Is the staging system the same as for nodal non-Hodgkin's lymphomas?
- What are the classification systems?
- What are the staging procedures at diagnosis?
- What is the prognosis of the most common subtypes?
- What is the best therapy?



Very heterogeneous group of diseases for:

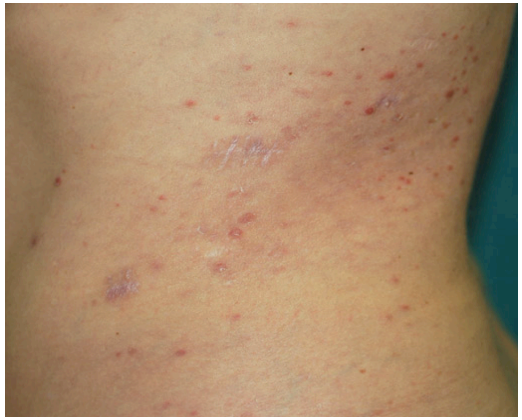
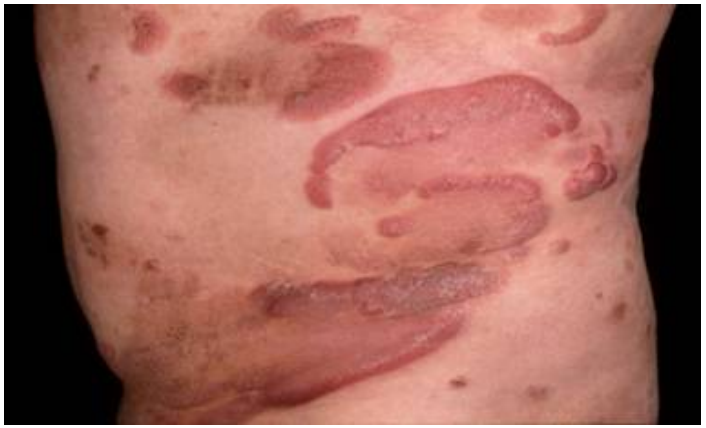
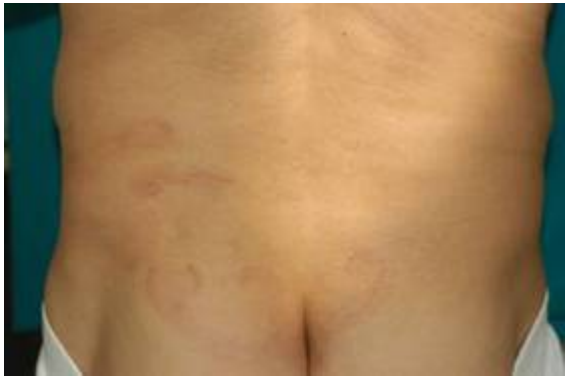
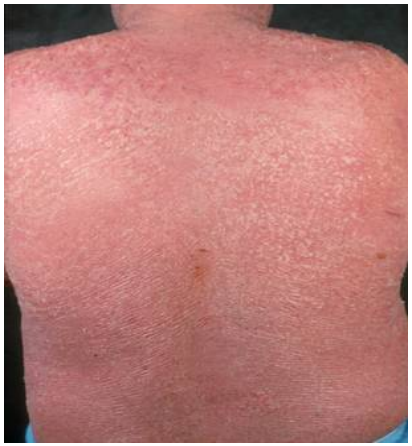
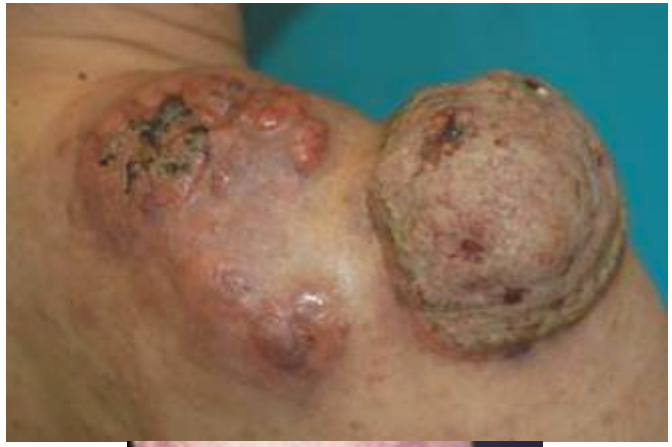
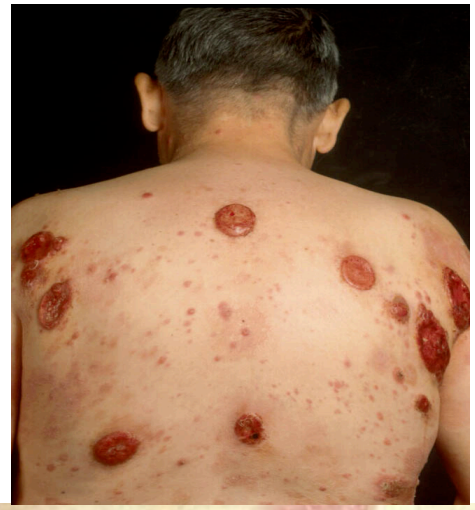
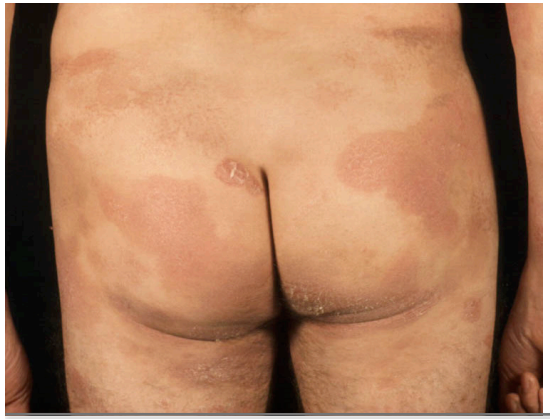
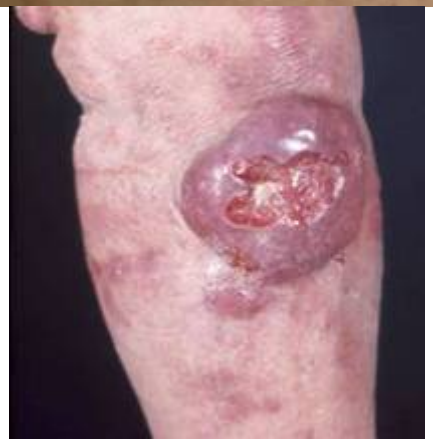
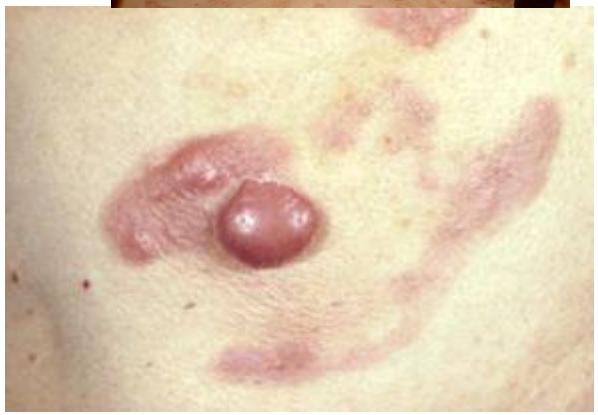
- clinical manifestations
- immuno-pathological characteristics
- prognosis

Table 1. Annual Incidence Rates of Cutaneous T-Cell Lymphoma in the United States (9 Registries), 1973-2002[a]

Variable	Incidence Rate (95% Confidence Interval)[b]	No. of Cases[c]
Period		
1973-1977	2.8 (2.4-3.1)	228
1978-1982	3.8 (3.4-4.1)	357
1983-1987	5.3 (4.9-5.8)	526
1988-1992	6.3 (5.8-6.7)	675
1993-1997	8.5 (8.0-9.0)	1007
1998-2002	9.6 (9.1-10.1)	1236
Race		
White	6.1 (5.9-6.3)	3226
Black	9.0 (6.4-9.7)	487
Other	4.9 (4.3-5.4)	223
Sex		
Men	8.7 (8.4-9.1)	2449
White	8.4 (8.0-8.7)	1975
Black	11.3 (10.2-12.4)	266
Other	7.4 (6.4-8.4)	154
Women	4.6 (4.4-4.8)	1580
White	4.3 (4.1-4.5)	1251
Black	7.3 (6.5-8.2)	221
Other	2.7 (2.1-3.3)	69
Age, y		
0-9	0.1 (0.08-0.2)	14
10-19	0.3 (0.2-0.4)	33
20-29	1.2 (1.0-1.4)	131
30-39	2.9 (2.6-3.2)	317
40-49	6.4 (5.9-7.0)	573
50-59	11.2 (10.4-12.0)	766
60-69	17.7 (16.5-18.8)	917
70-79	24.6 (23.0-26.2)	863
≥80	22.9 (20.7-25.1)	415

- Rising incidence
- Male prevalence
- Advanced age

Arch Dermatol 2007

WHO-EORTC classification for cutaneous lymphomas

Rein Willemze, Elaine S. Jaffe, Günter Burg, Lorenzo Cerroni, Emilio Berti, Steven H. Swerdlow, Elisabeth Ralfkiaer, Sergio Chimenti, José L. Diaz-Perez, Lyn M. Duncan, Florent Grange, Nancy Lee Harris, Werner Kempf, Helmut Kerl, Michael Kurrer, Robert Knobler, Nicola Pimpinelli, Christian Sander, Marco Santucci, Wolfram Sterry, Maarten H. Vermeer, Janine Wechsler, Sean Whittaker, and Chris J. L. M. Meijer

Classification based on:

- clinical, histopathological, immunophenotypic, cytogenetic and molecular features

Blood 2005;105:3768-3785

World Health Organization/European Organization for Research and Treatment of Cancer classification [3]

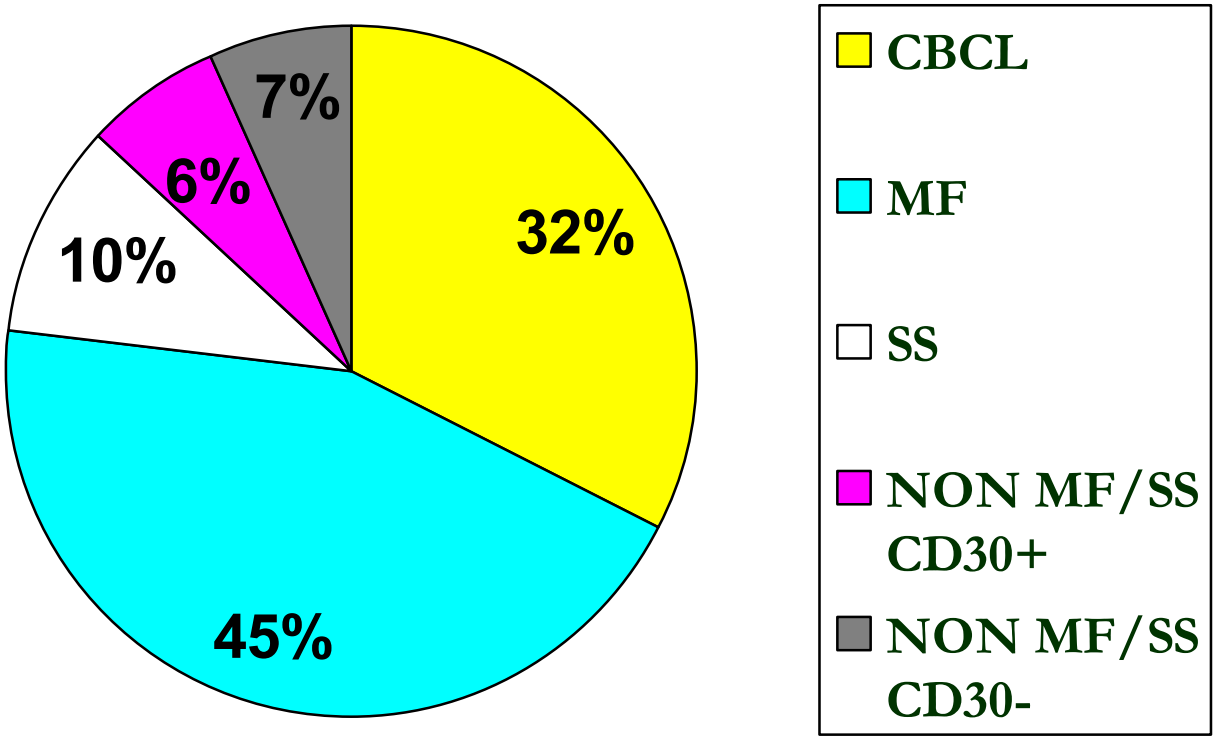
Cutaneous T-cell and NK-cell lymphomas	**Cutaneous B-cell lymphomas**
Mycosis fungoides	Primary cutaneous marginal zone B-cell lymphoma
Mycosis fungoides variants and subtypes	Primary cutaneous follicle center lymphoma
• Folliculotropic MF	Primary cutaneous diffuse large B-cell lymphoma, leg type
• Pagetoid reticulosis	Primary cutameous diffuse large B-cell lymphoma, other
• Granulomatous slack skin	
Sézary syndrome	• intravascular large B-cell lymphoma
Adult T-cell leukemia/lymphoma	
Primary cutaneous CD30-positive lymphoproliferative disorders	
• Primary cutaneous anaplastic large cell lymphoma	
• Lymphomatoid papulosis	**Precursor hematologic neoplasm**
Subcutaneous panniculitis-like T-cell lymphoma*	CD4+/CD56+ hematodermic neoplasm (blastic NK cell lymphoma)†
Extranodal NK/T-cell lymphoma, nasal type	
Primary cutaneous peripheral T-cell lymphoma, unspecified	
• Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (provisional)	
• Cutaneous γ/δ T-cell lymphoma (provisional)	
• Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	

Table 2. Relative frequency and disease-specific 5-year survival of 1905 primary cutaneous lymphomas classified according to the WHO-EORTC classification

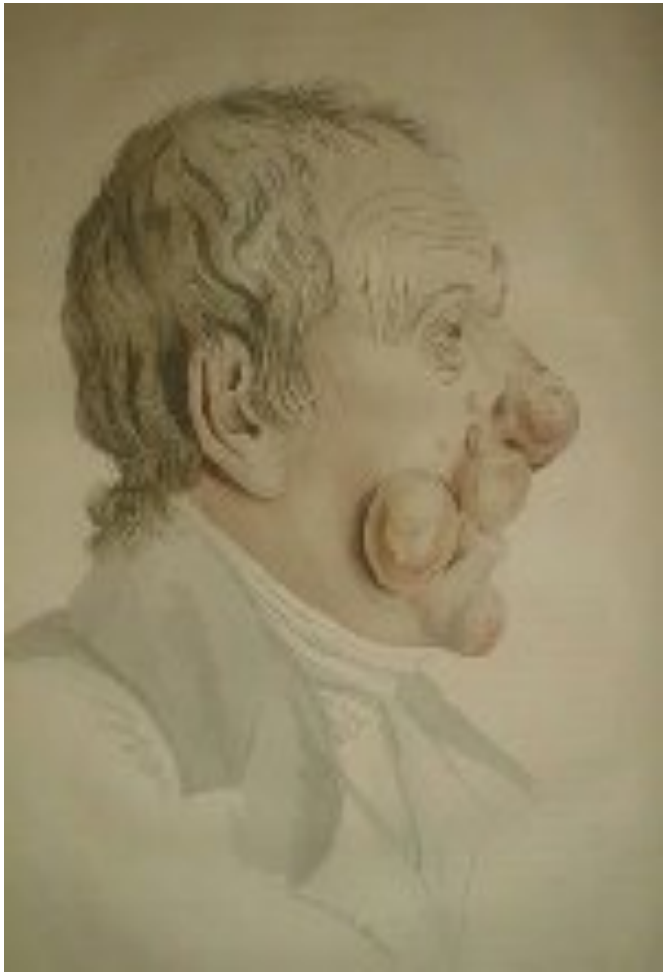
WHO-EORTC classification	No.	Frequency, %*	Disease-specific 5-year survival, %
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	< 1	100
Granulomatous slack skin	4	< 1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous $CD4^+$ small/medium pleomorphic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	< 1	NR
Primary cutaneous aggressive CD8+ T-cell lymphoma†	14	< 1	18
Primary cutaneous γ/δ T-cell lymphoma†	13	< 1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16
Cutaneous B-cell lymphoma			
Indolent clinical behavior			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95
Intermediate clinical behavior			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	< 1	50
Primary cutaneous intravascular large B-cell lymphoma	6	< 1	65

NR indicates not reached.
*Data are based on 1905 patients with a primary cutaneous lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.
†Primary cutaneous peripheral T-cell lymphoma, unspecified excluding the three provisional entities indicated with a double dagger (‡).

University of Turin - Cutaneous Lymphomas Registry
1975-2010
1273 pts

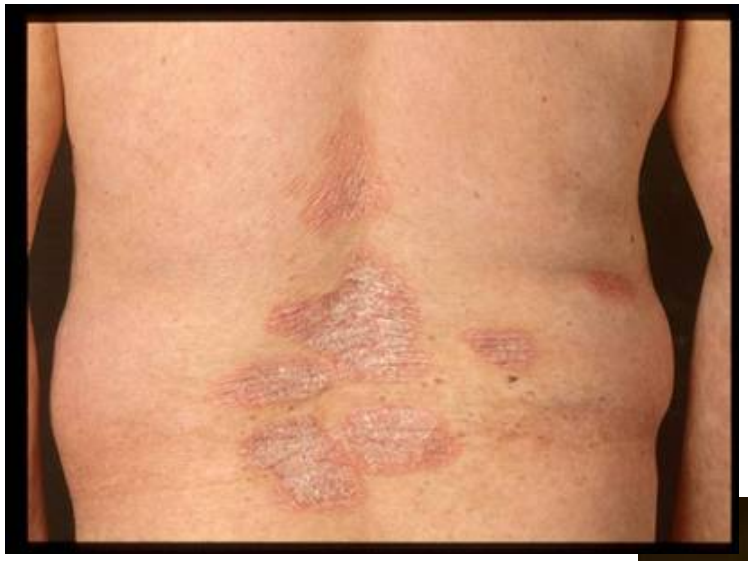


Mycosis Fungoides



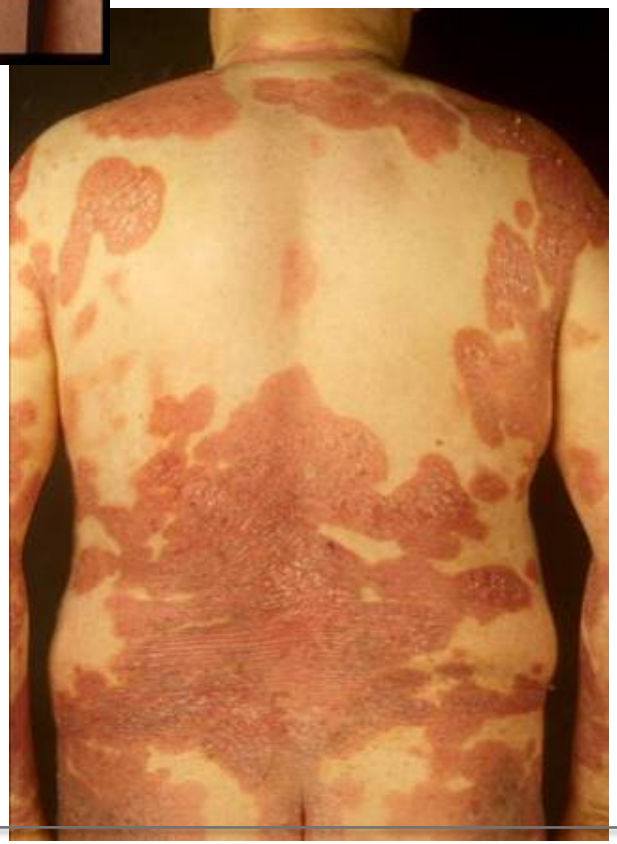
Alibert , 1806

- Most common type of CTCL
- Male prevalence
- Age >55 yrs
- Indolent chronic course
- Classical progression from patch lesions to plaques, nodular-tumors and erythroderma

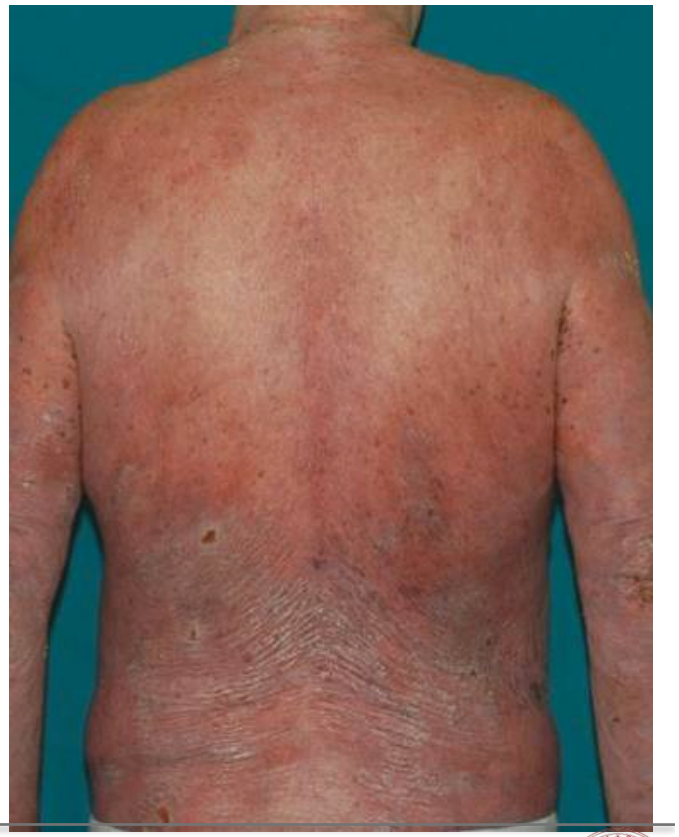


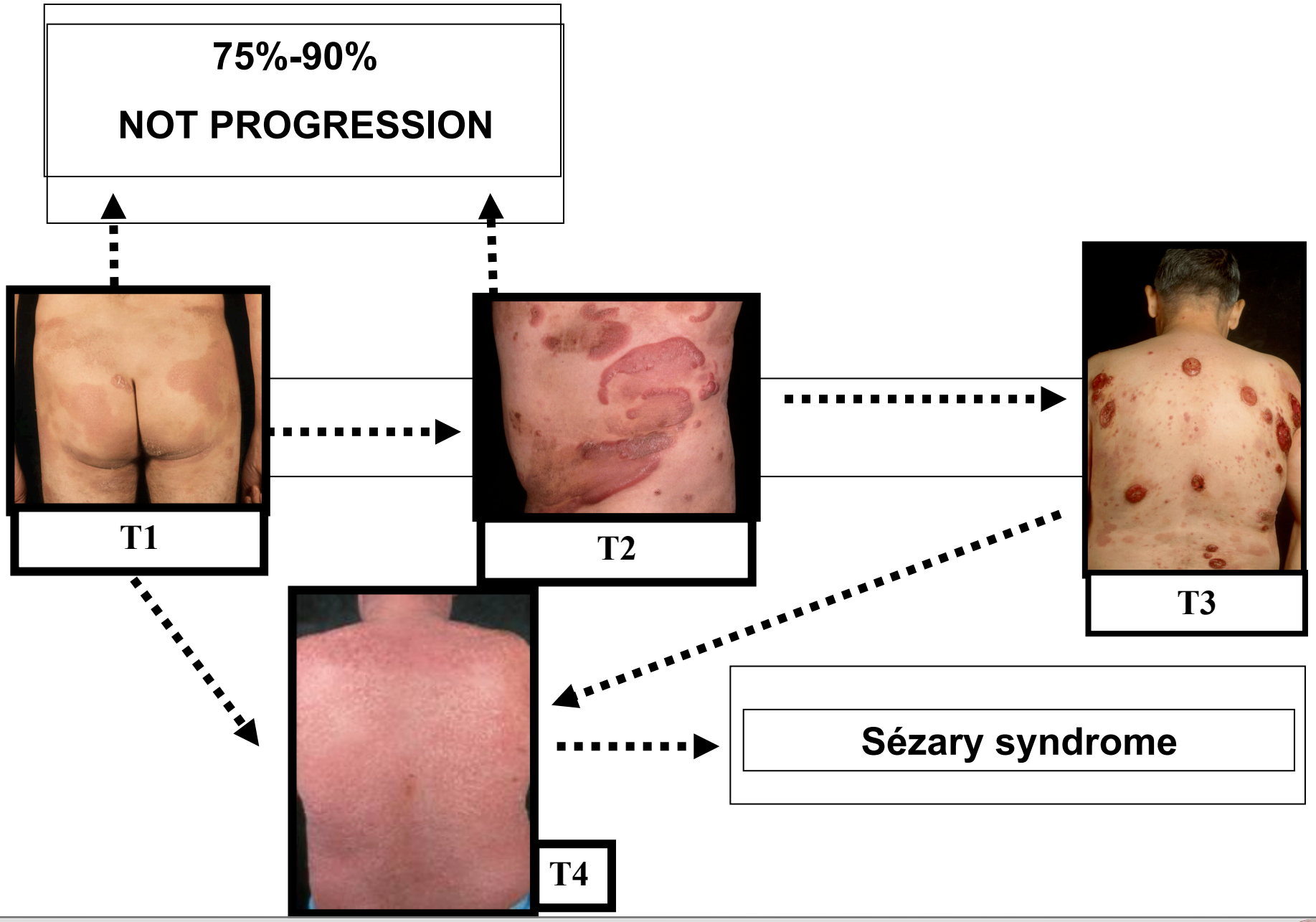
1992

2009

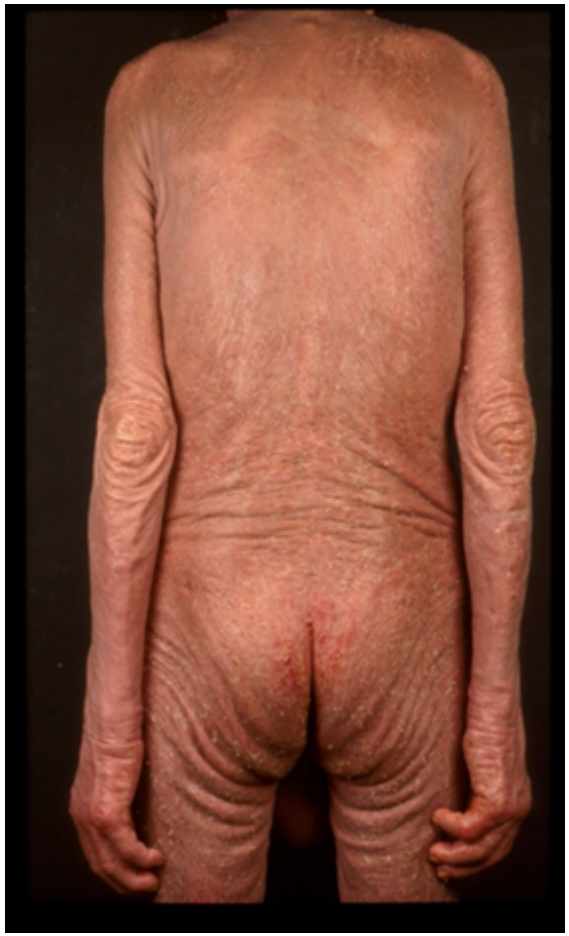


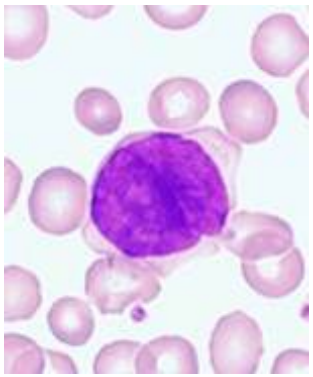
1999

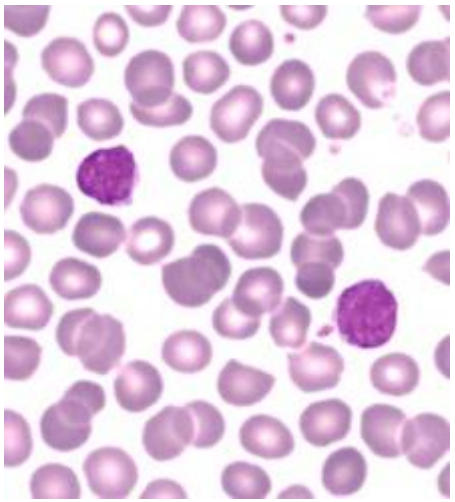


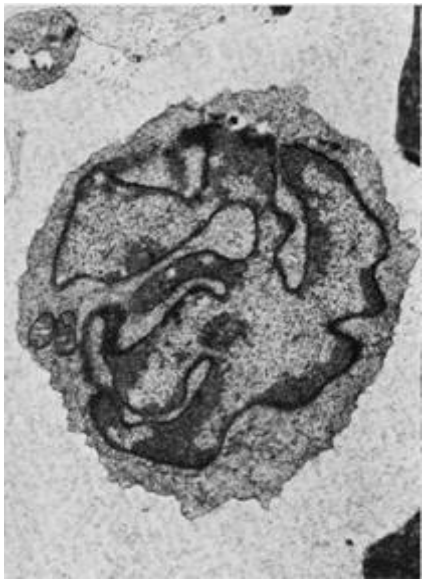

75%-90%
NOT PROGRESSION
T1
T2
T3
T4
Sézary syndrome

Sezary's syndrome









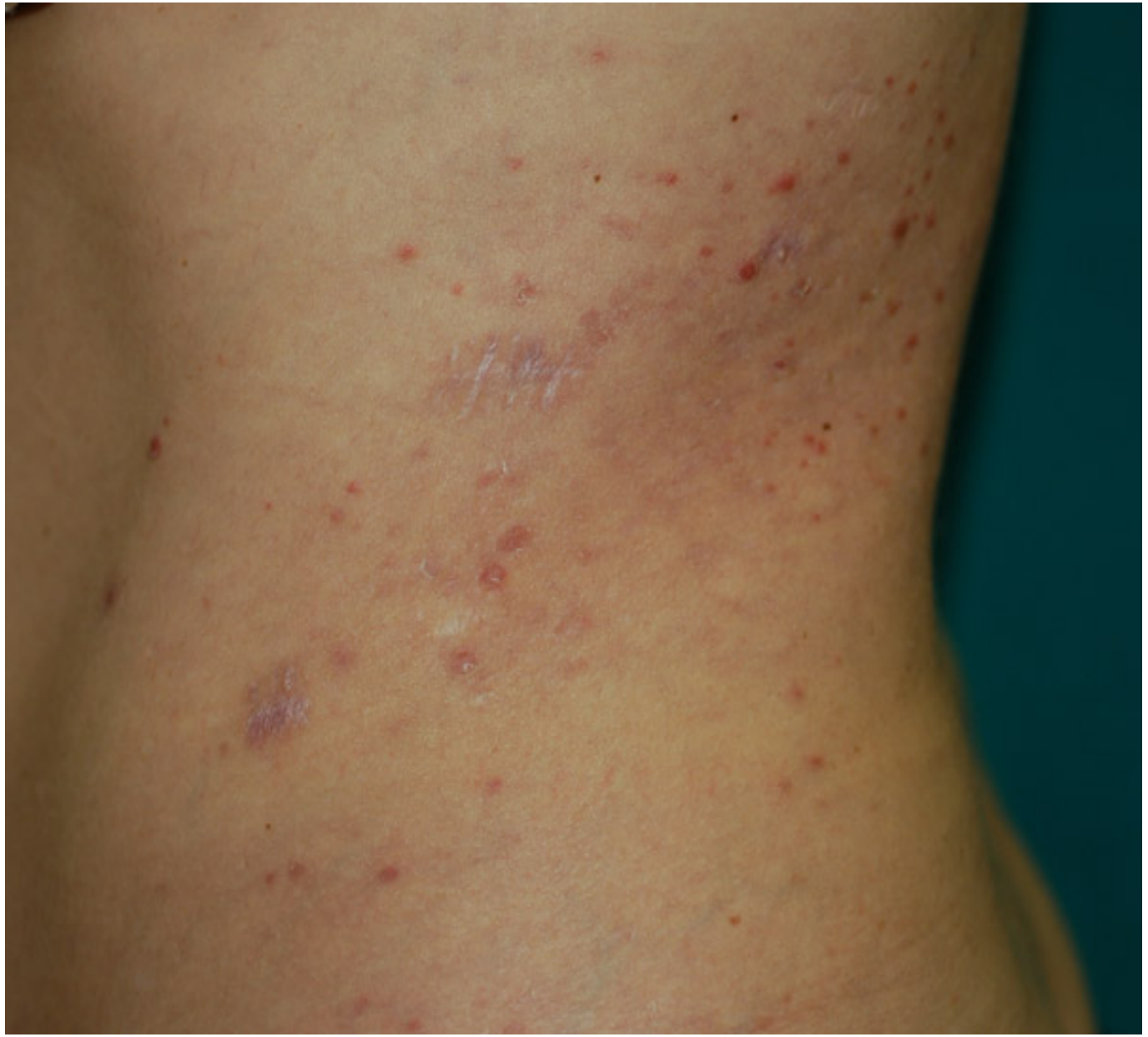
Sézary A, Bouvrain Y: Erytrodermie avec présence de cellules monstrueuses dans le derme et dans le sang circulant . 1938; Bull Soc Fr Derm Symph 45:254.
Baccaredda A: Reticulohistiocytosis cutanea hyperplastica benigna cum melanodermia. 1939; Archiv Dermatol Sifil 179:210.

Cutaneous T Lymphomas
NO MF/SS CD30+

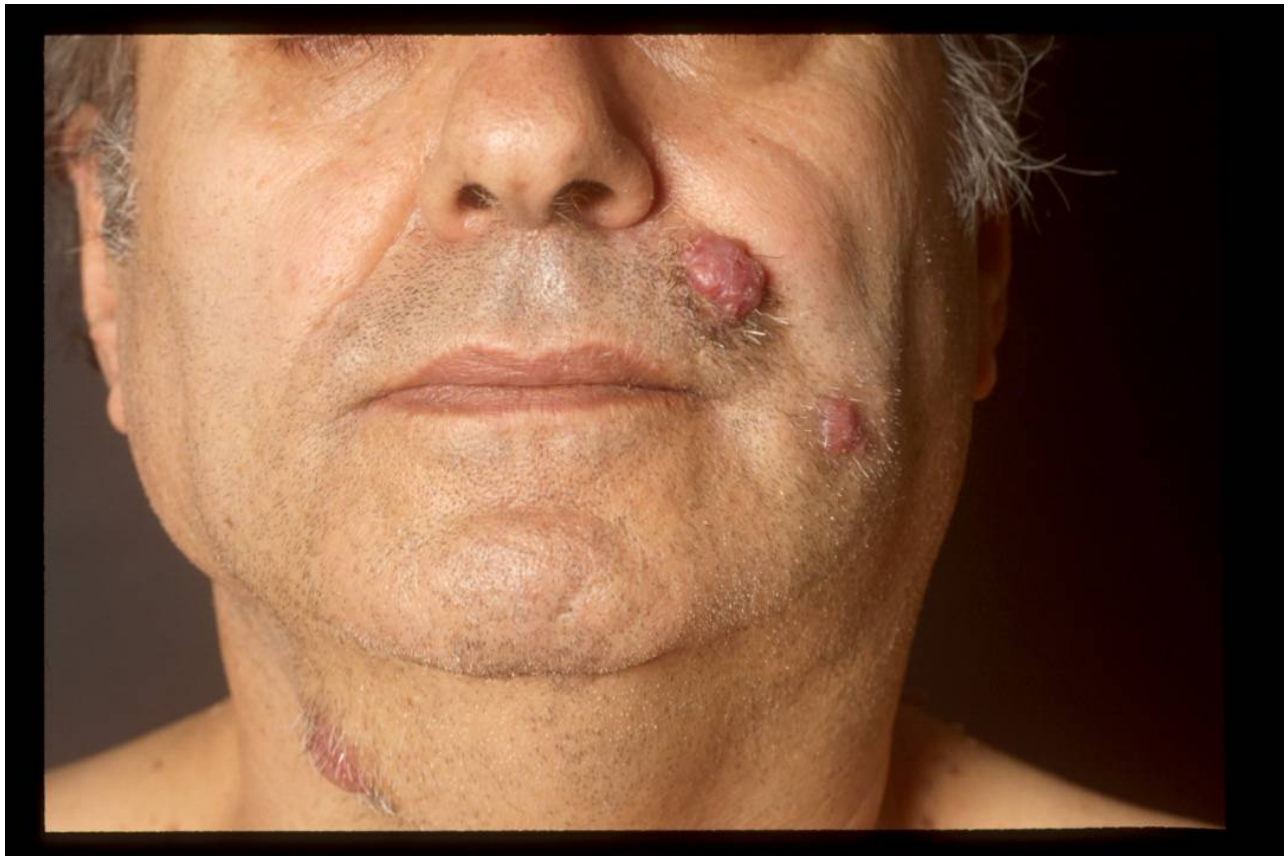
- Anaplastic Large Cell Lymphoma (ALCL)
- Lymphomatoid papulosis
- Borderline Cases

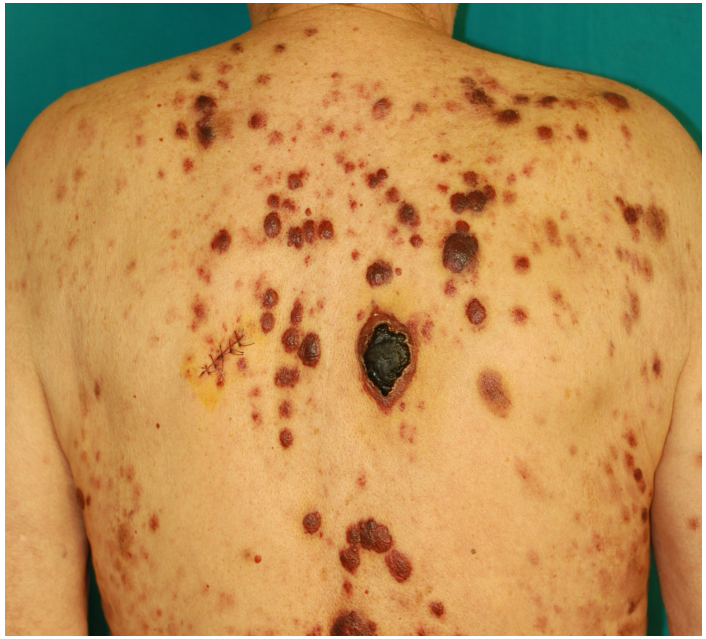
Lymphomatoid papulosis

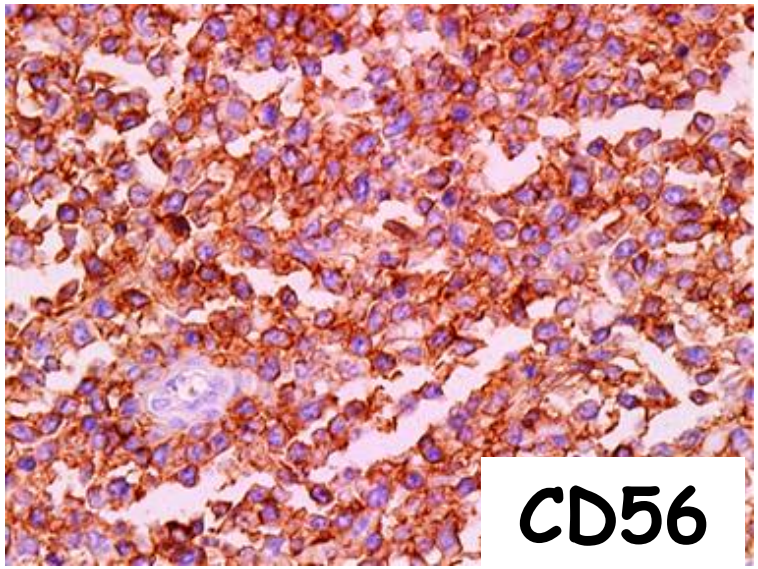
- **Papular lesions, necrotic papules, pustules, nodular poussée with spontaneous remission**
  - **LyP tipo A:** not epidermotropic CD30+
  - **Lyp tipo B:** MF
  - **Lyp tipo C:** large cells CD30+

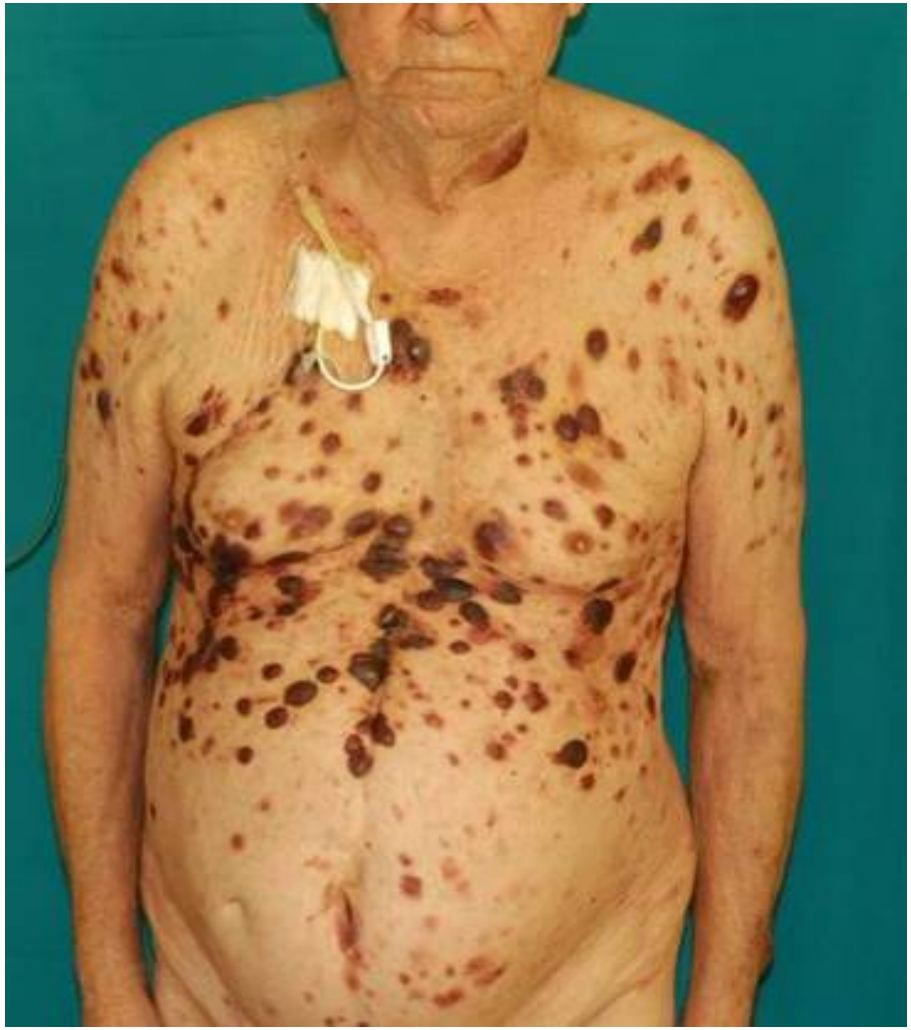


Large cell lymphoma CD30+

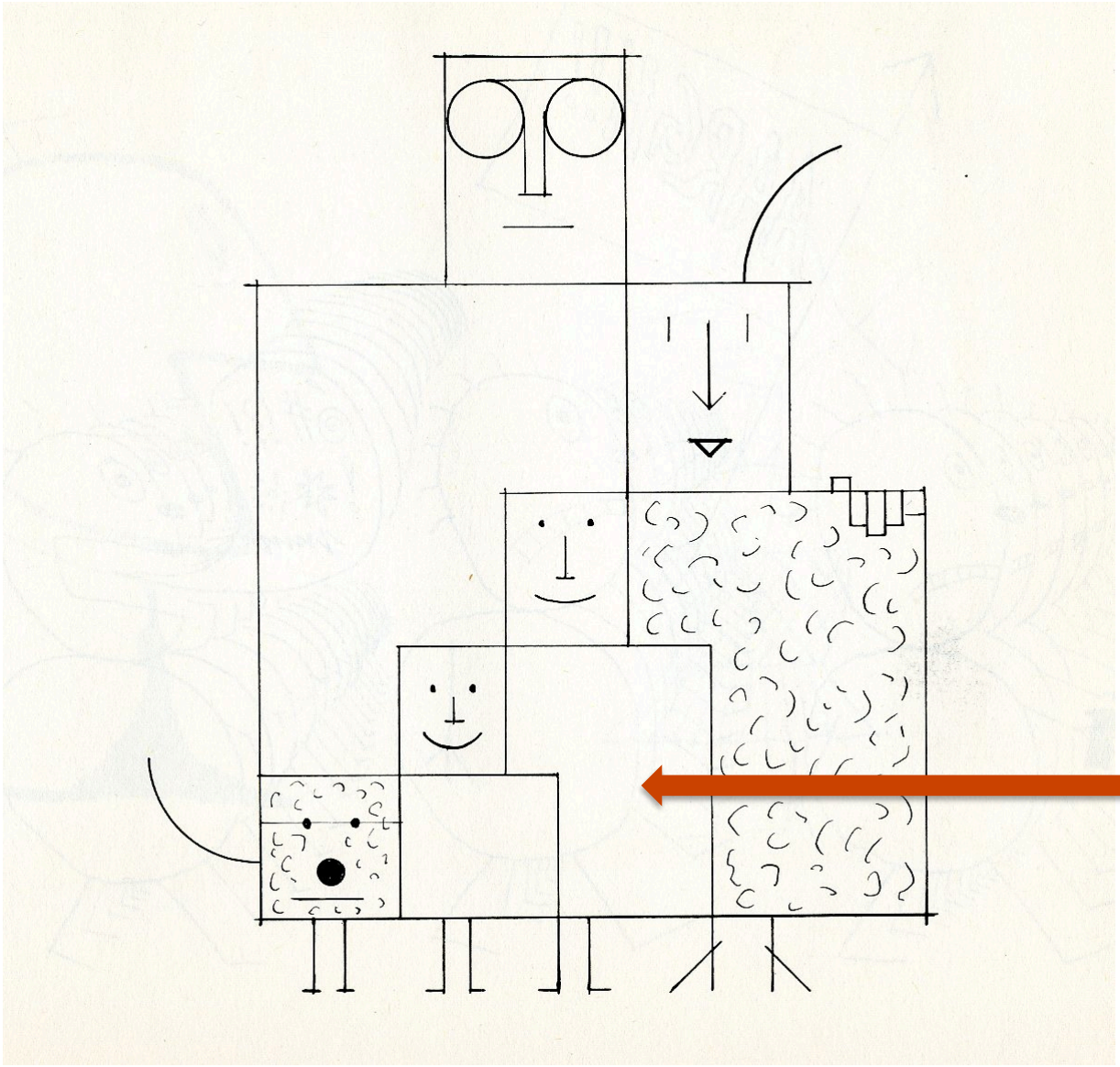






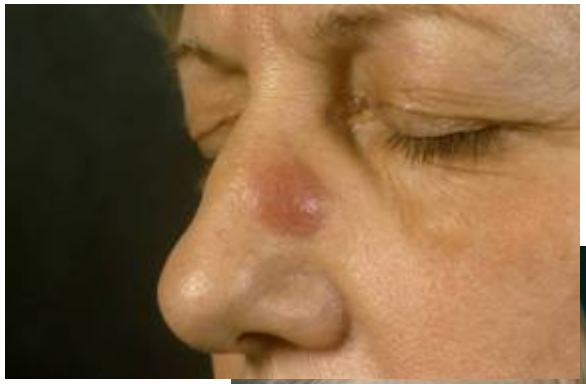


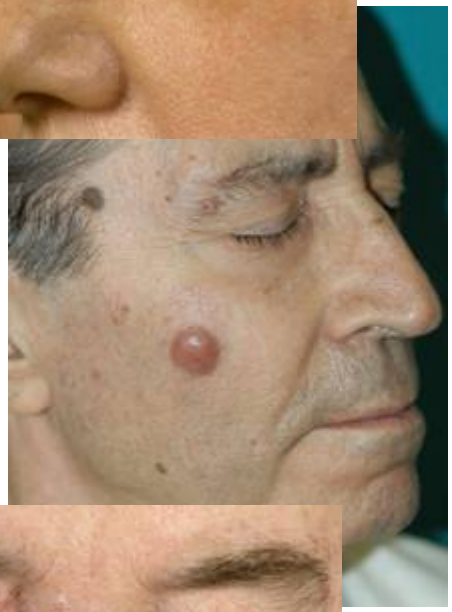
BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN)

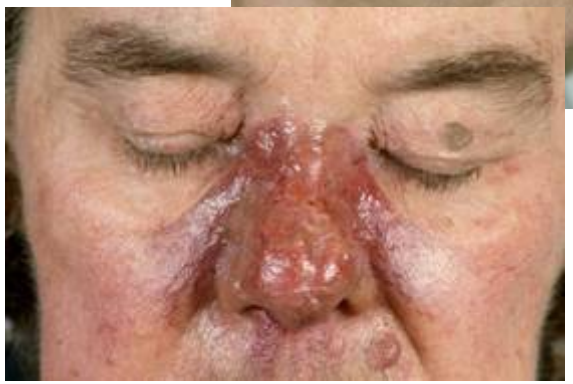


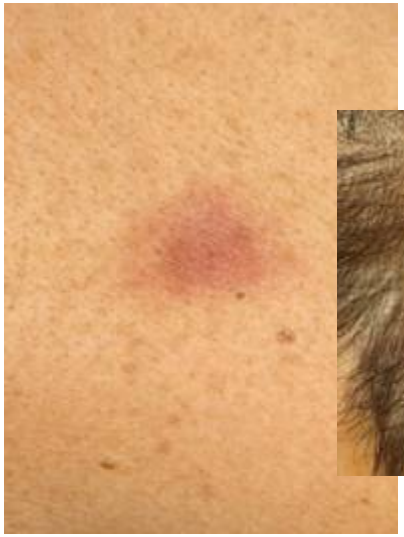
B-cell Cutaneous Lymphomas

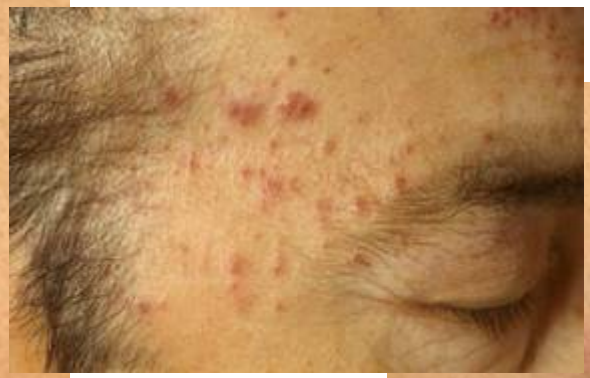
PCMZL

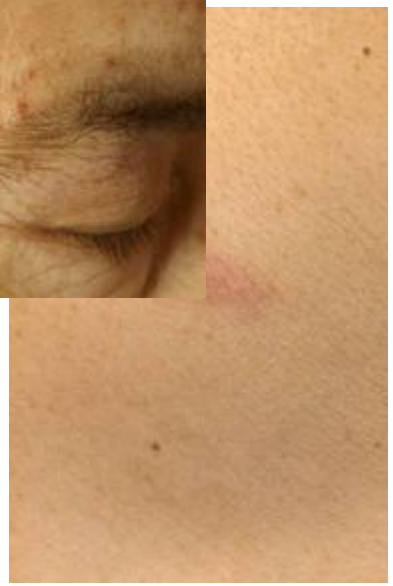


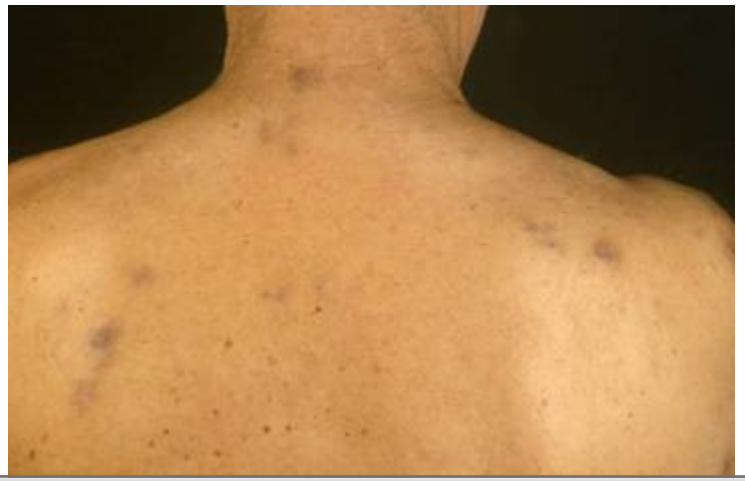












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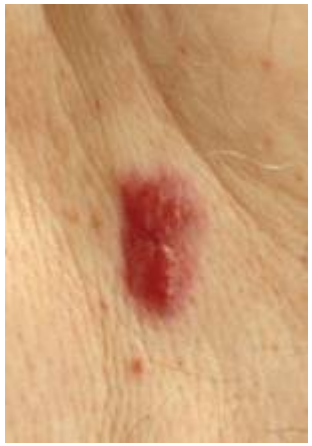
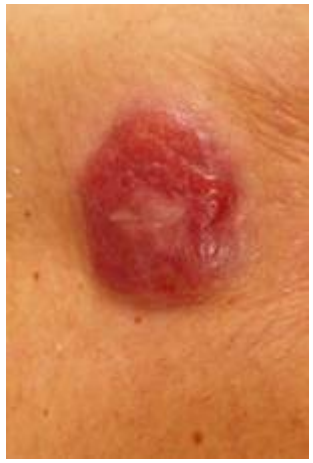
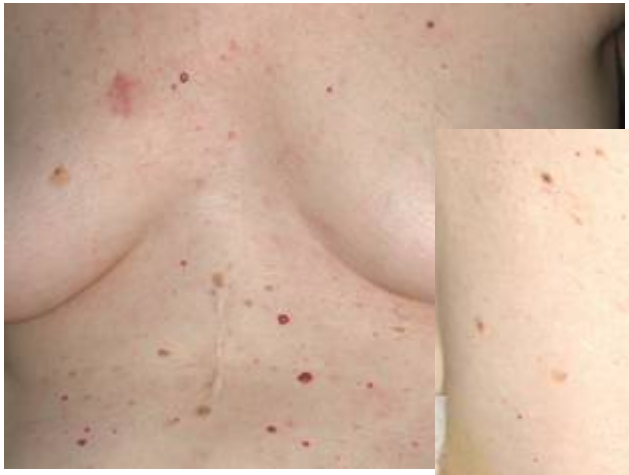
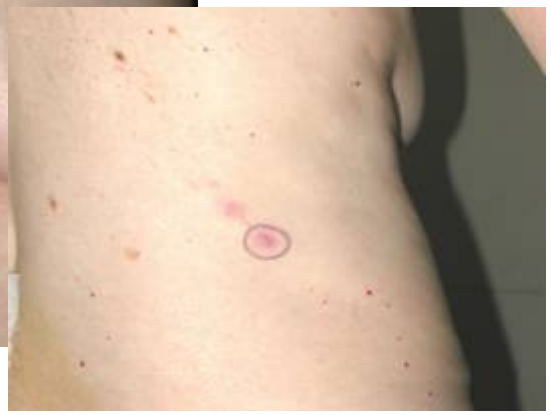
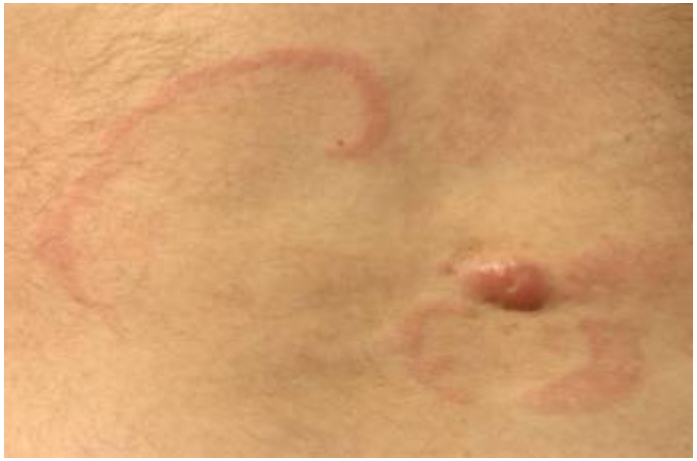
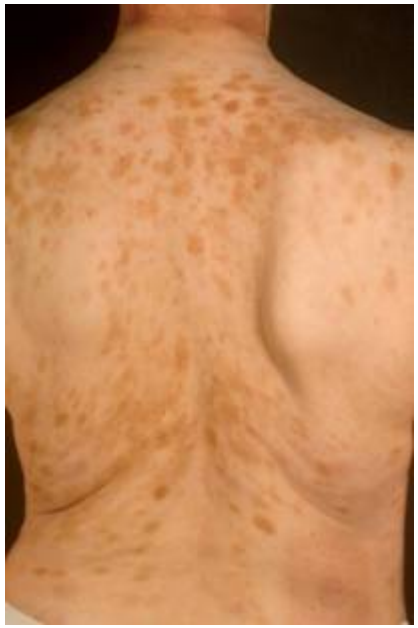


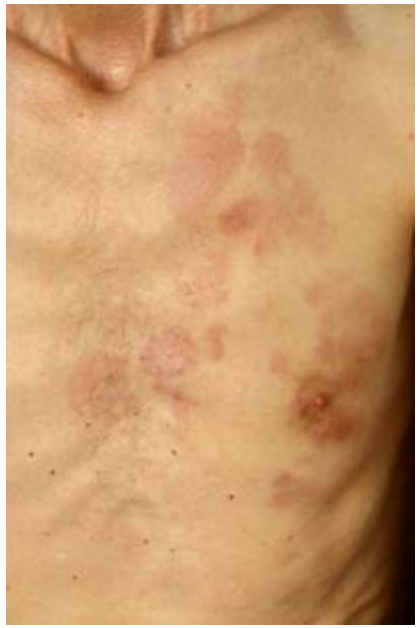




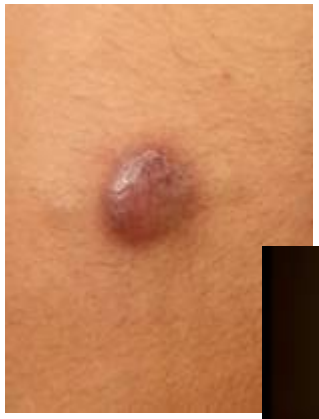


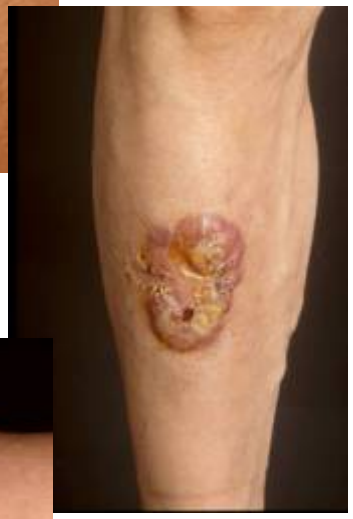


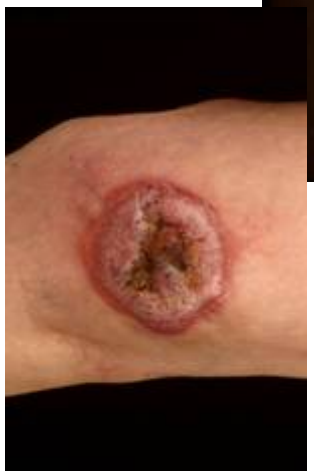


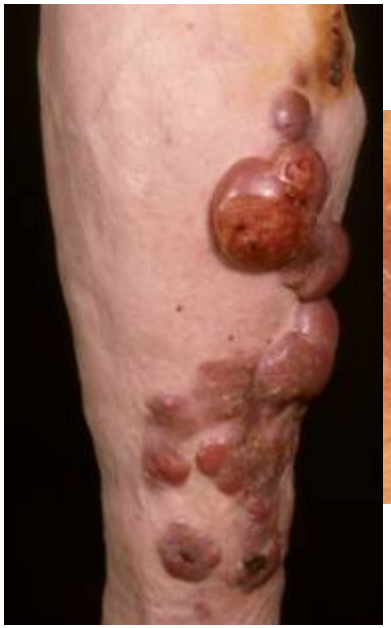


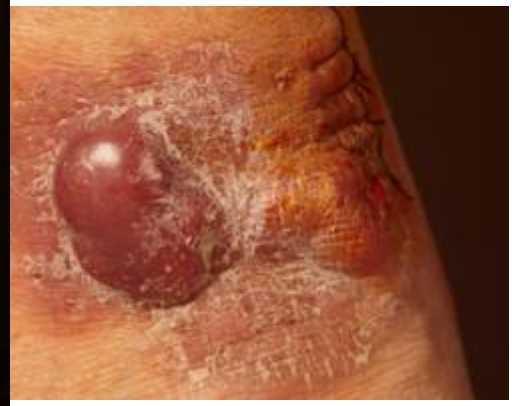
PCLBCL

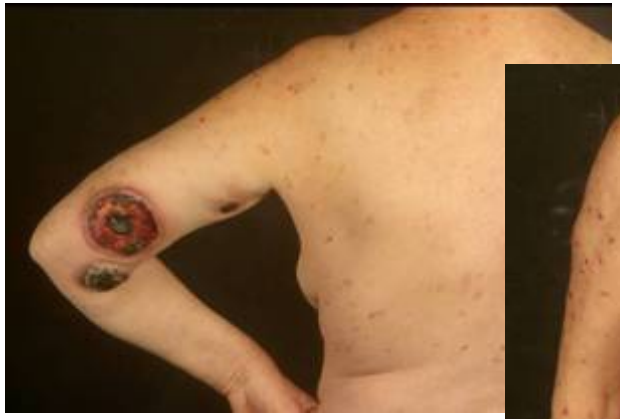


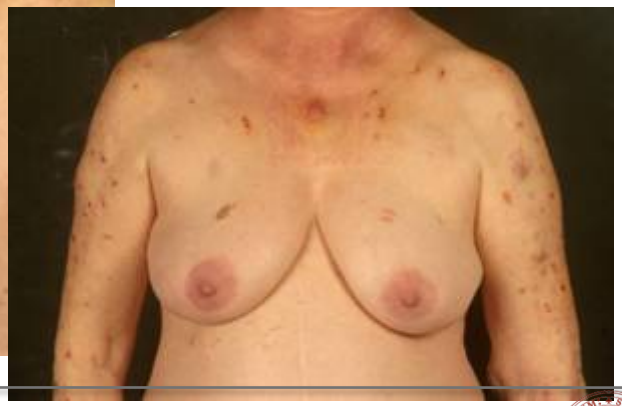






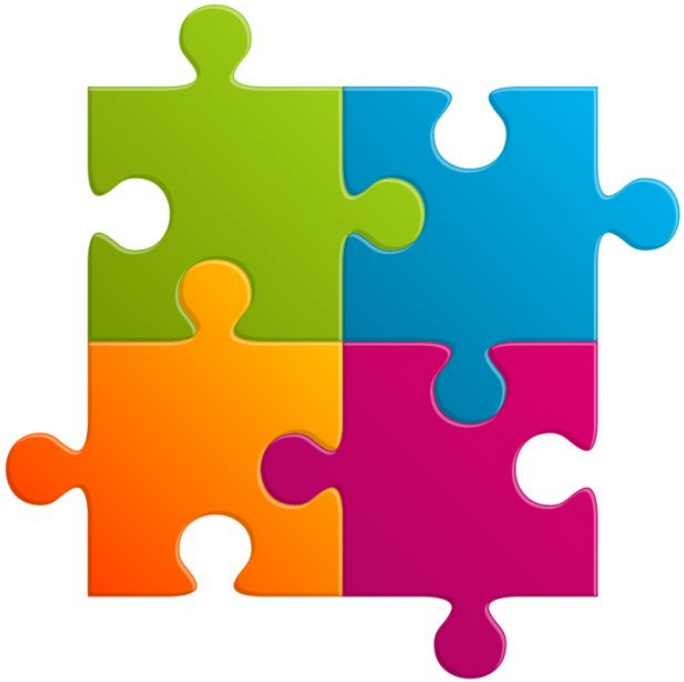






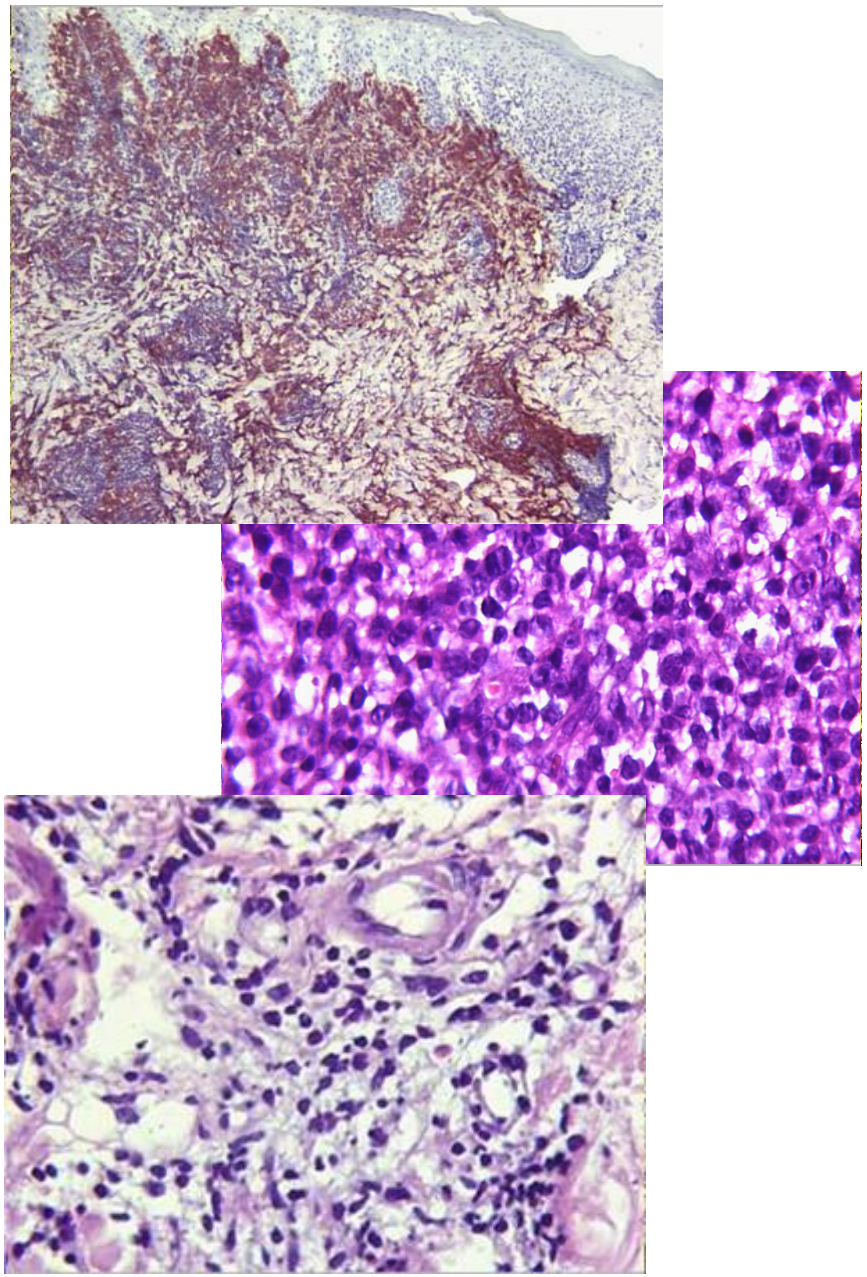
CLASSIFICATION & STAGING

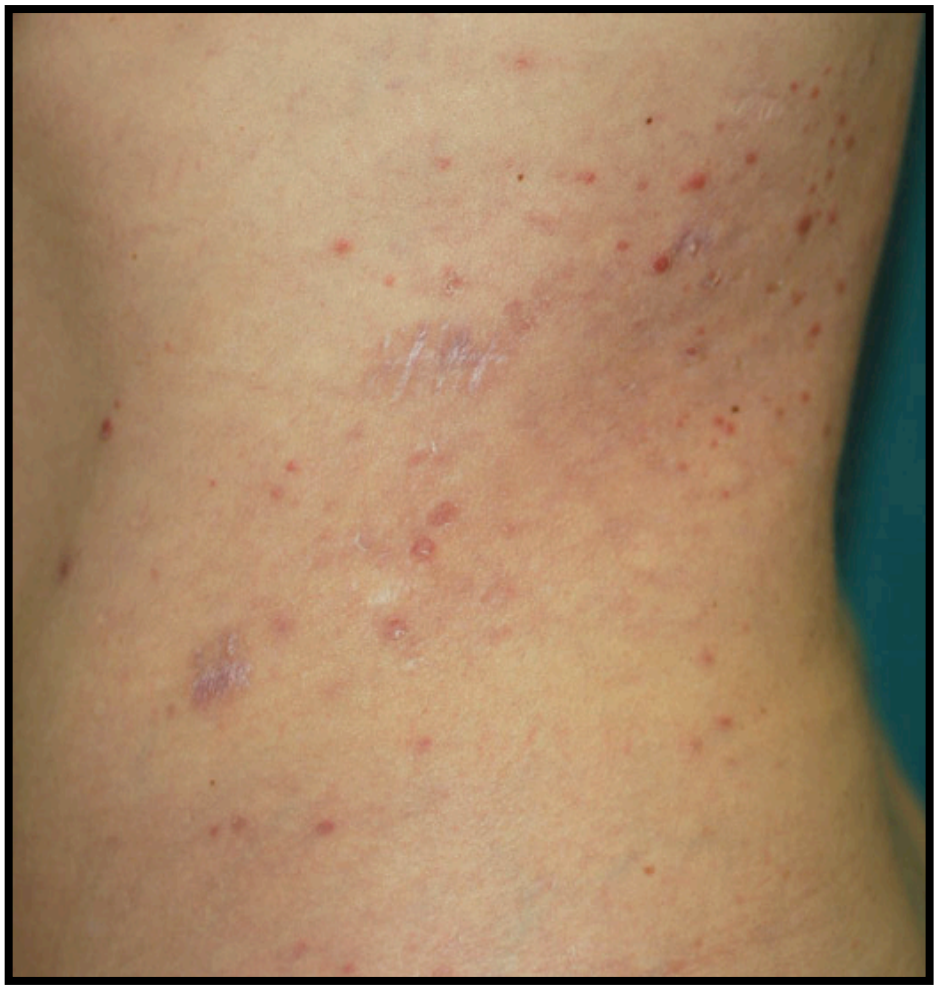
- In nodal lymphomas: the Ann Arbor system and the International Prognostic Index
- The Ann Arbor system was not designed for staging cutaneous lymphomas
- In 1979 → MF co-operative group lead to TNM classification of CTCL

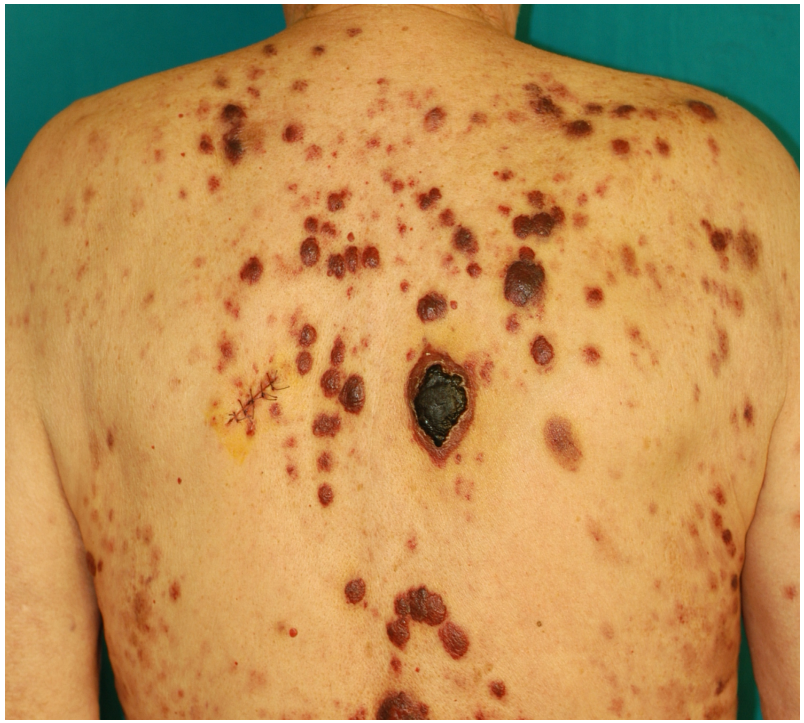


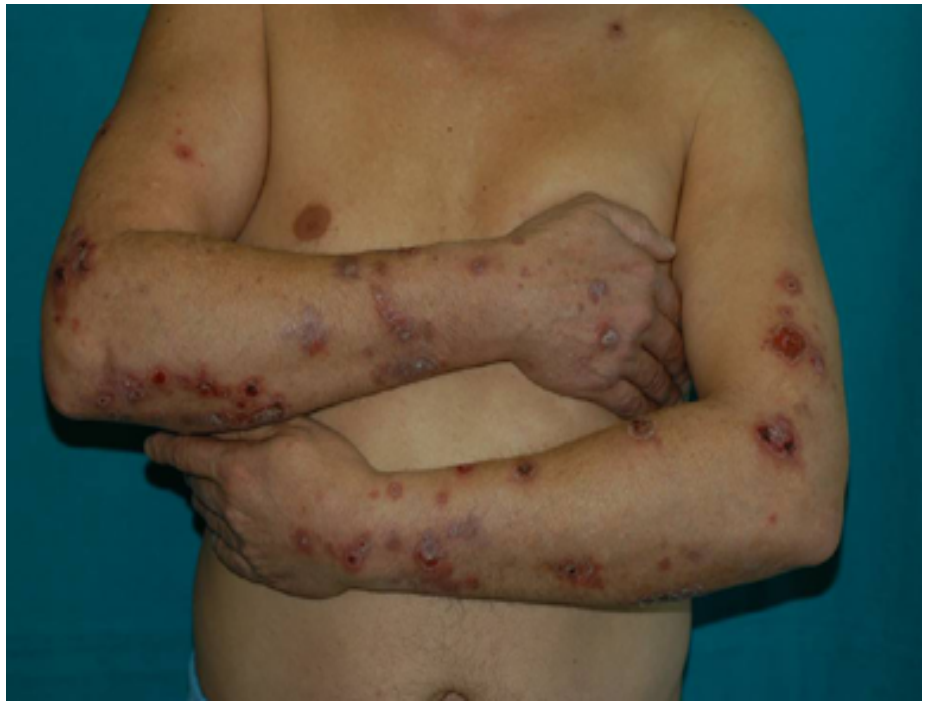
- Clinical
- Histology
- Immunopathology
- Molecular Biology

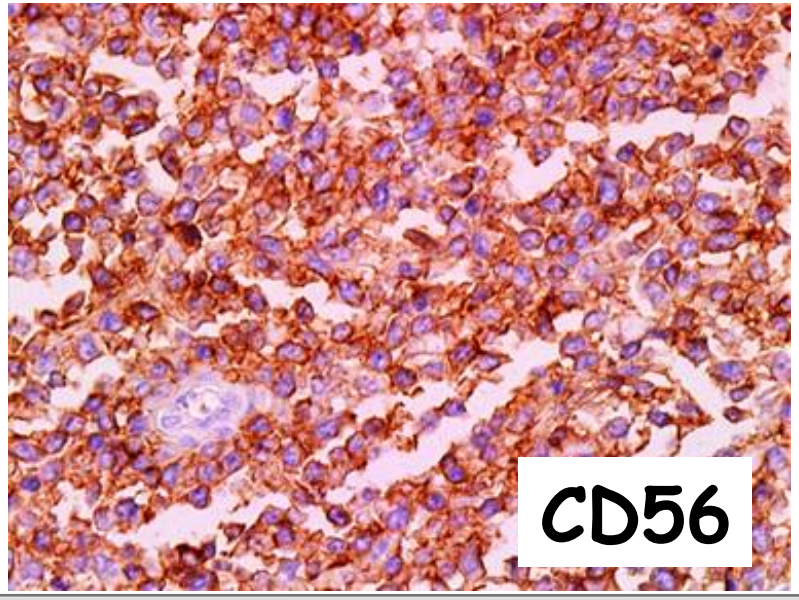
Lymphomatoid papulosis

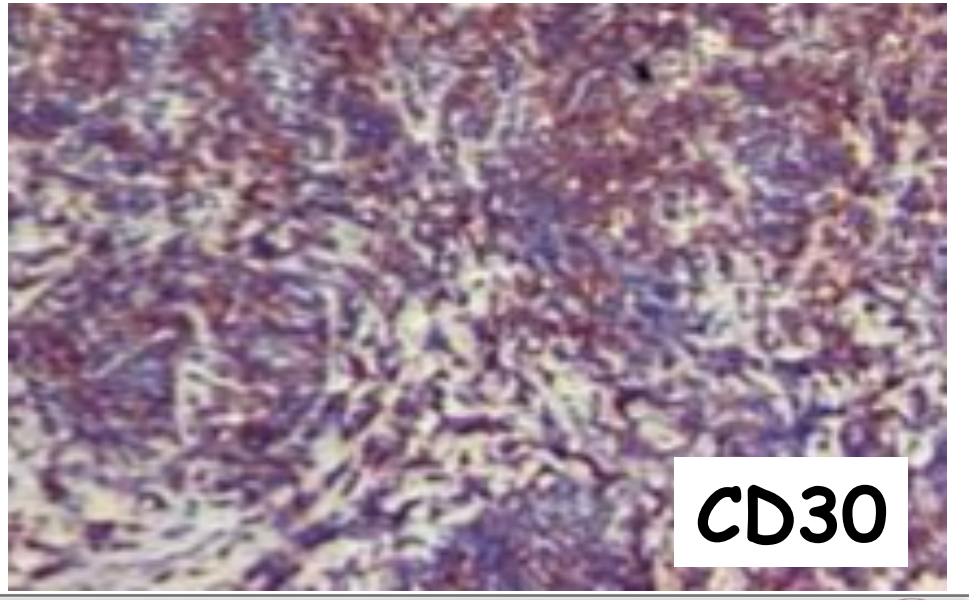









CD56


CD30

STAGING SYSTEM

B and T LYMPHOMAS NO MF/SS

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*
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
T3b: multiple lesions involving ≥3 body regions

Kim YH, Blood 2007

Table 4. ISCL/EORTC revision to the classification of mycosis fungoides and Sézary syndrome

TNMB stages	
Skin	
T_1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥ 10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors‡ (≥ 1-cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B_{0a}	Clone negative#
B_{0b}	Clone positive#
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative#
B_{1b}	Clone positive#
B2	High blood tumor burden: ≥ 1000/μL Sézary cells‖ with positive clone#

Olsen E et al. Blood 2007; 110: 1713

Table 7. ISCL/EORTC revision to the staging of mycosis fungoides and Sézary syndrome

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Olsen E et al. Blood 2007; 110: 1713

HISTORY

↓

CLINICAL

↓

HISTO-
IMMUNOPHATOLOGY

↓

DEFINITIVE DIAGNOSIS

Algorithm for the Diagnosis of Early MF

Criteria	Major (2 Points)	Minor (1 Point)
CLINICAL Persistent and/or progressive patches and 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) Atypia	Both	Either
MOLECULAR/ BIOLOGICAL Clonal TCR gene rearrangement		Present
IMMUNOPATHOLOGICAL 1) CD2,3,5 <50% of T cells 2) CD7< 10% of T cells 3) Epidermal discordance from expression of CD2,3,5 and 7 on dermal T cells		Any 1

Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005; 53: 1053-1063.

Revisions to the staging and classification of 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)

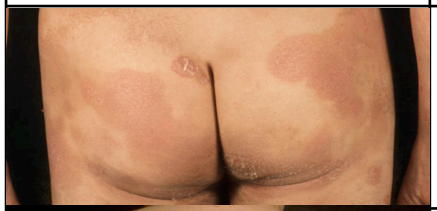
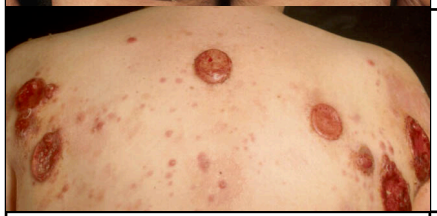
Elise Olsen,[1] Eric Vonderheid,[2] Nicola Pimpinelli,[3] Rein Willemze,[4] Youn Kim,[5] Robert Knobler,[6] Herschel Zackheim,[7] Madeleine Duvic,[8] Teresa Estrach,[9] Stanford Lamberg,[2] Gary Wood,[10] Reinhard Dummer,[11] Annamari Ranki,[12] Gunter Burg,[11] Peter Heald,[13] Mark Pittelkow,[14] Maria-Grazia Bernengo,[15] Wolfram Sterry,[16] Liliane Laroche,[17] Franz Trautinger,[6] and Sean Whittaker,[18] for the ISCL/EORTC

	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
Advanced-stage disease[11]				
IIB	3	0-2	0	0, 1
III	4	0-2	0	0, 1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Leukemic Blood Involvement

- Absolute Sézary cell count > 1,000/mm^3
- CD4/CD8 ratio> 10
- CD4+CD7- >= 40%
- Aberrant expression of T cell markers
- Evidence of a T cell clone (SB, PCR)
- A chromosomally-abnormal T cell clone
- CD4+CD26- circulating > 30%

Staging Exams

		Rx/Eco	TC/PET	B.O.
	MF IA-IIA	+	-	-
	MF IIB-IVB	-	+	High grade or stage IV
	SEZARY	-	+	-
	PAP. LINF.	-	-	-

Original Article

Time Course, Clinical Pathways, and Long-Term Hazards Risk Trends of Disease Progression in Patients With Classic Mycosis Fungoides

A Multicenter, Retrospective Follow-Up Study From the Italian Group of Cutaneous Lymphomas

Pietro Quaglino, MD[1]; Nicola Pimpinelli, MD[2]; Emilio Berti, MD[3]; Piergiacomo Calzavara-Pinton, MD[4]; Giuseppe Alfonso Lombardo, MD[5]; Serena Rupoli, MD[6]; Mauro Alaibac, MD[7]; Ugo Bottoni, MD[8,9]; Angelo Carbone, MD[10]; Paolo Fava, MD[1]; Michele Fimiani, MD[11]; Angela Maria Mamusa, MD[12]; Stefano Titli, MD[1]; Pier Luigi Zinzani, MD[13]; Maria Grazia Bernengo, MD[1]; and On behalf of the Gruppo Italiano Linfomi Cutanei (GILC)

GILC: retrospective MF series (n=1422)

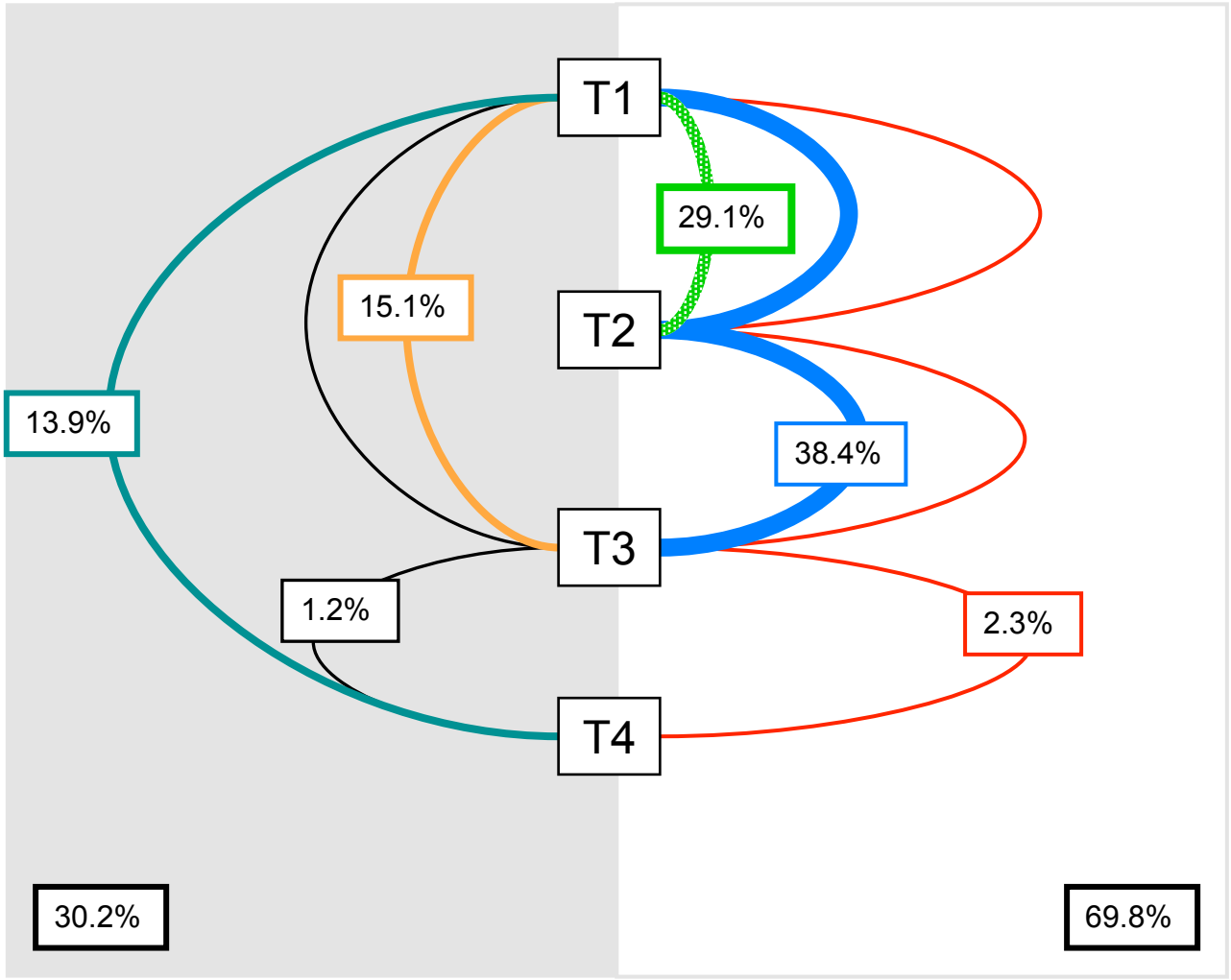
Table 2. Disease Stage Progression According to the Initial Stage of Disease at Diagnosis[a]

Maximum stage Stage at diagnosis	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB	Disease Stage Progression
IA (n=552)	412 (74.6%)	40 (7.2%)	20 (3.6%)	37 (6.7%)	16 (2.9%)	1 (0.2%)	12 (2.2%)	5 (0.9%)	9 (1.6%)	140 (25.4%)
IB (n=556)		396 (71.2%)	24 (4.3%)	63 (11.3%)	29 (5.2%)	7 (1.3%)	14 (2.5%)	12 (2.2%)	11 (2.0%)	160 (28.8%)
IIA (n=122)			73 (59.8%)	12 (9.8%)	12 (9.8%)	2 (1.6%)	9 (7.4%)	11 (9.0%)	3 (2.5%)	49 (40.2%)
IIB (n=78)				44 (56.4%)	6 (7.7%)	0	10 (12.8%)	10 (12.8%)	8 (10.2%)	34 (43.6%)
IIIA (n=82)					50 (61.0%)	7 (8.5%)	15 (18.3%)	7 (8.5%)	3 (3.7%)	32 (39.0%)
IIIB (n=11)						5 (45.5%)	4 (36.4%)	2 (18.2%)	0	6 (54.5%)
IVA1 (n=1)							1	0	0	–
IVA2 (n=9)								8 (88.9%)	1 (11.1%)	1
IVB (n=1)									1	–

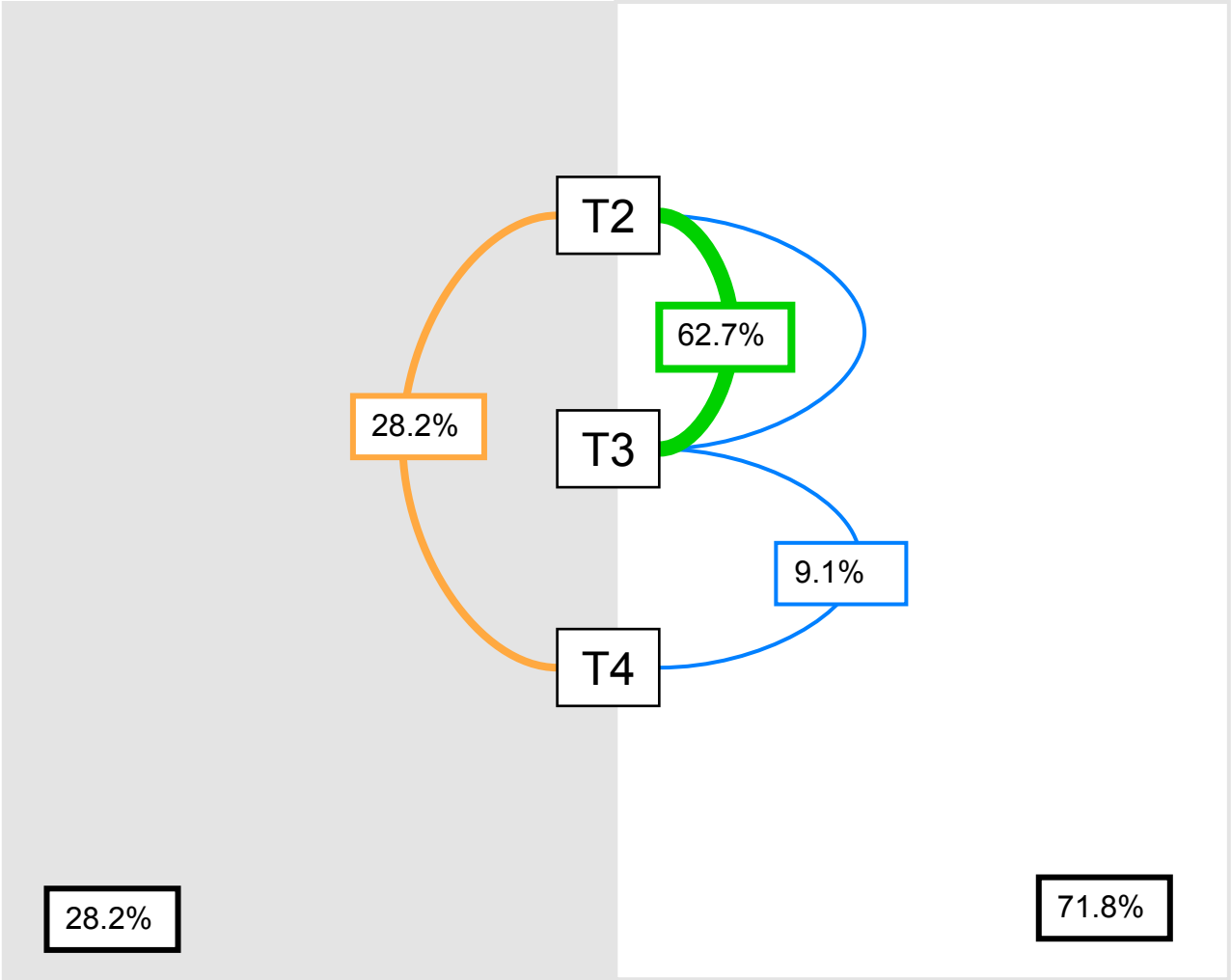
[a] The number reported is the number of patients (percentages set in parentheses were calculated based on the total number of patients for each stage of disease). Gray-shaded cells represent patients who maintained the stage of disease noted at the time of the initial diagnosis to the end of the follow-up period.

Quaglino P, GILC study, Cancer 2012

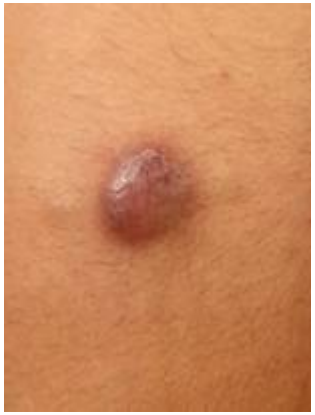
GILC: retrospective MF series (n=1422)

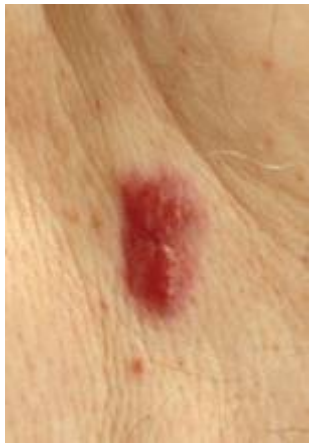


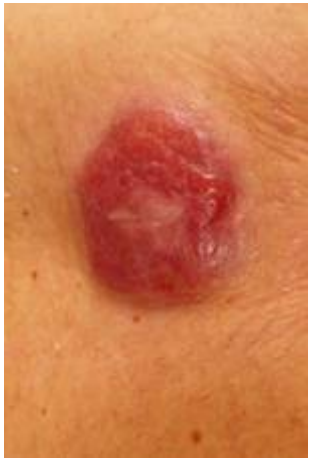
GILC: retrospective MF series (n=1422)

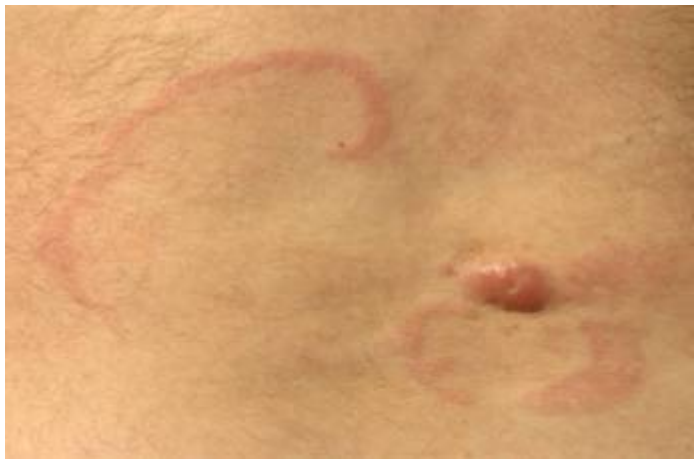


Cutaneous B-Cells Lymphomas









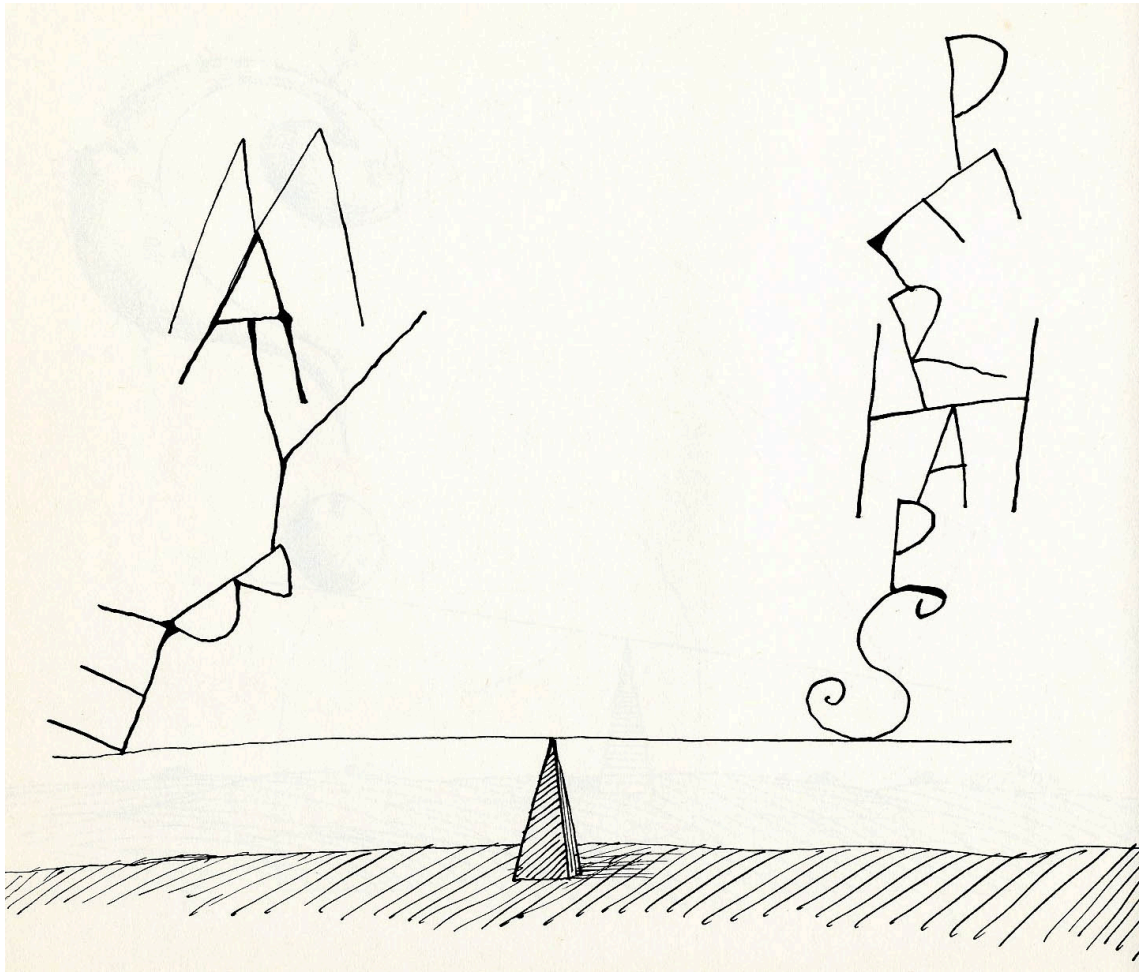
Primary or secondary?

Table 1. Clinical Characteristics of 467 Patients With PCBCL

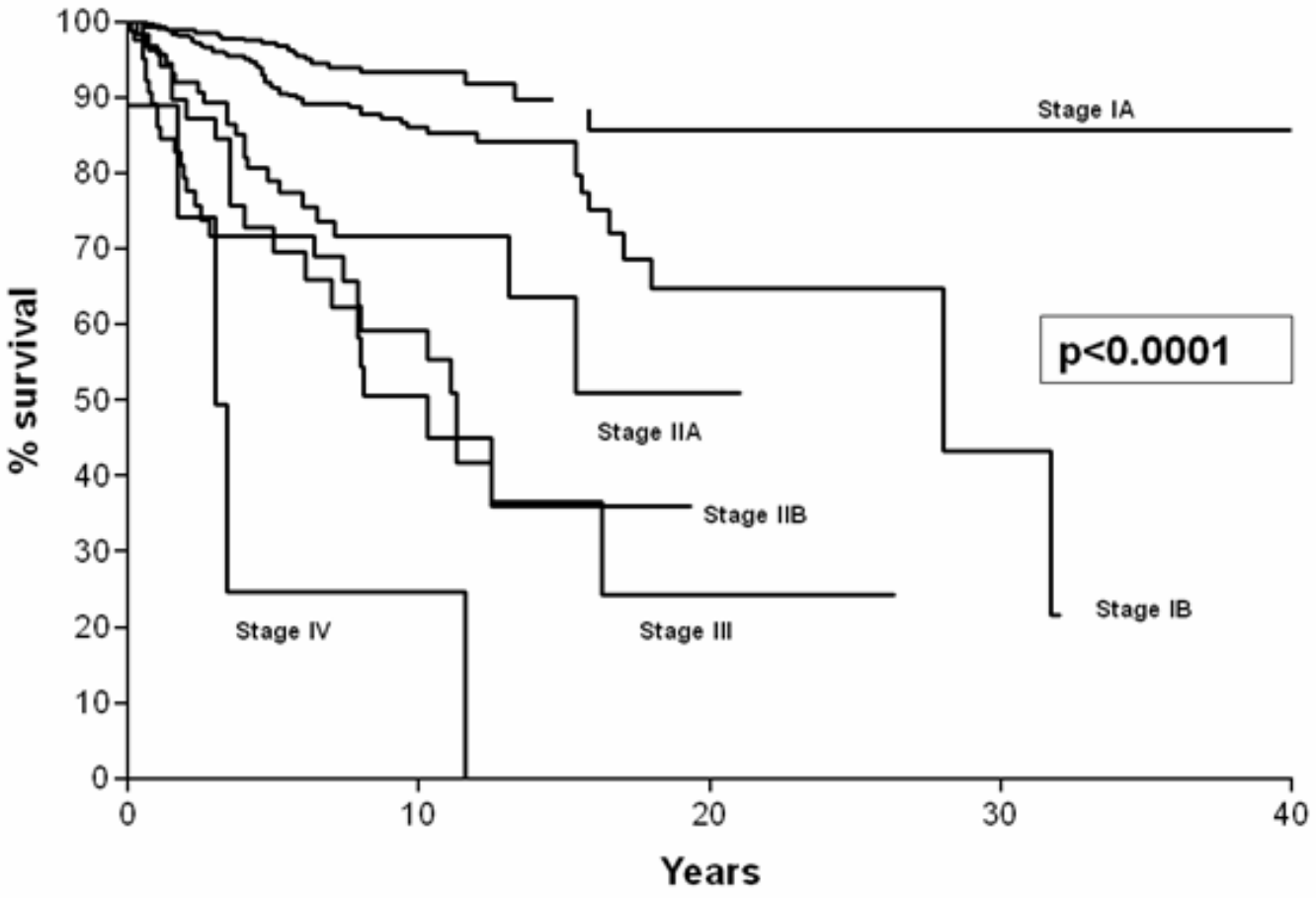
Characteristic	All Patients		MZL		FCL		DLBCL, Leg Type	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total No. of patients	467		151	31.4	265	56.7	51	10.9
Age, years								
Median	54		55		51		70	
Range	17-94		18-84		17-89		41-94	
Sex								
Male	278		92		159		27	
Female	189		59		106		24	
Ratio male/female	1.5		1.56		1.05		1.1	
Site of cutaneous involvement								
Head-neck	91	19.5	20	13.2	70	26.4	1	2
Trunk	206	44.1	70	46.4	132	49.8	4	7.8
Upper limb	49	10.5	26	17.2	22	8.3	1	2
Lower limb	52	11.1	9	6	9	3.4	34	66.6
Disseminated	69	14.8	26	17.2	32	12.1	11*	21.6
Extent of cutaneous involvement								
Single lesion	256	54.8	88	58.3	151	57	17	33.3
Regional	142	30.4	37	24.5	82	30.9	23	45.1
Disseminated	69	14.8	26	17.2	32	12.1	11	21.6
First-line therapy								
Surgery	106	22.7	39	25.8	64	24.2	3	5.9
Radiotherapy	245	52.5	83	55	134	50.6	28	54.9
Chemotherapy	116	24.8	29	19.2	67	25.3	20	39.2
Response to treatment								
CR rate	429 of 467	91.9	144 of 151	95.4	243 of 265	91.7	42 of 51	82.3
Relapse rate	200 of 429	46.7	64 of 144	44.4	113 of 243	46.5	23 of 42	54.8
Two or more relapses	102 of 429	23.8	27 of 144	18.7	58 of 243	23.9	17 of 42	40.5
Extracutaneous involvement	42 of 429	9.8	9 of 144	6.2	26 of 243	10.7	7 of 42	16.7

Abbreviations: PCBCL, primary cutaneous B-cell lymphoma; MZL, marginal-zone B-cell lymphoma; FCL, follicle center lymphoma; DLBCL, diffuse large B-cell

Prognosis?



GILC: retrospective MF series (n=1422)



Quaglino P, GILC study, Cancer 2012

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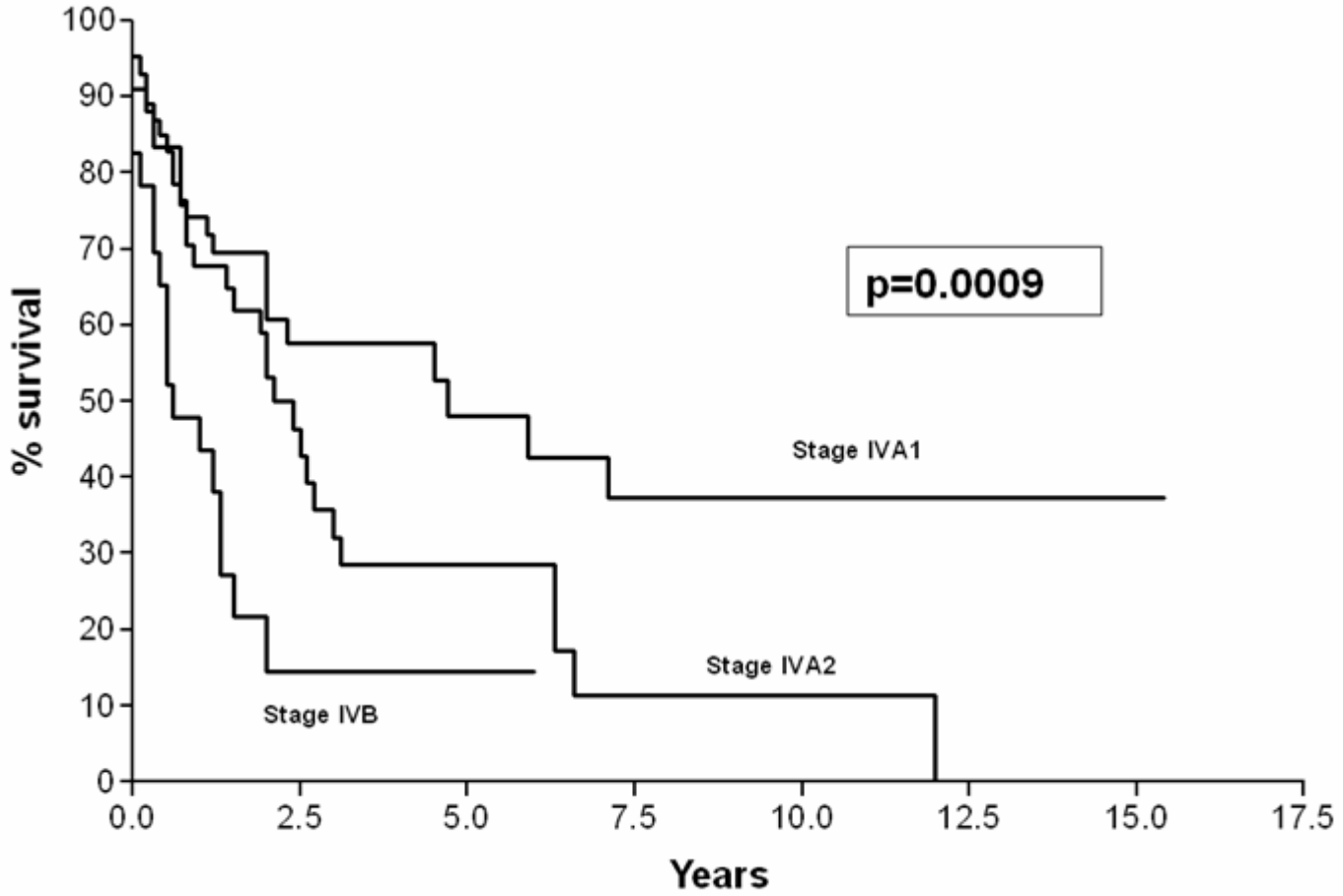
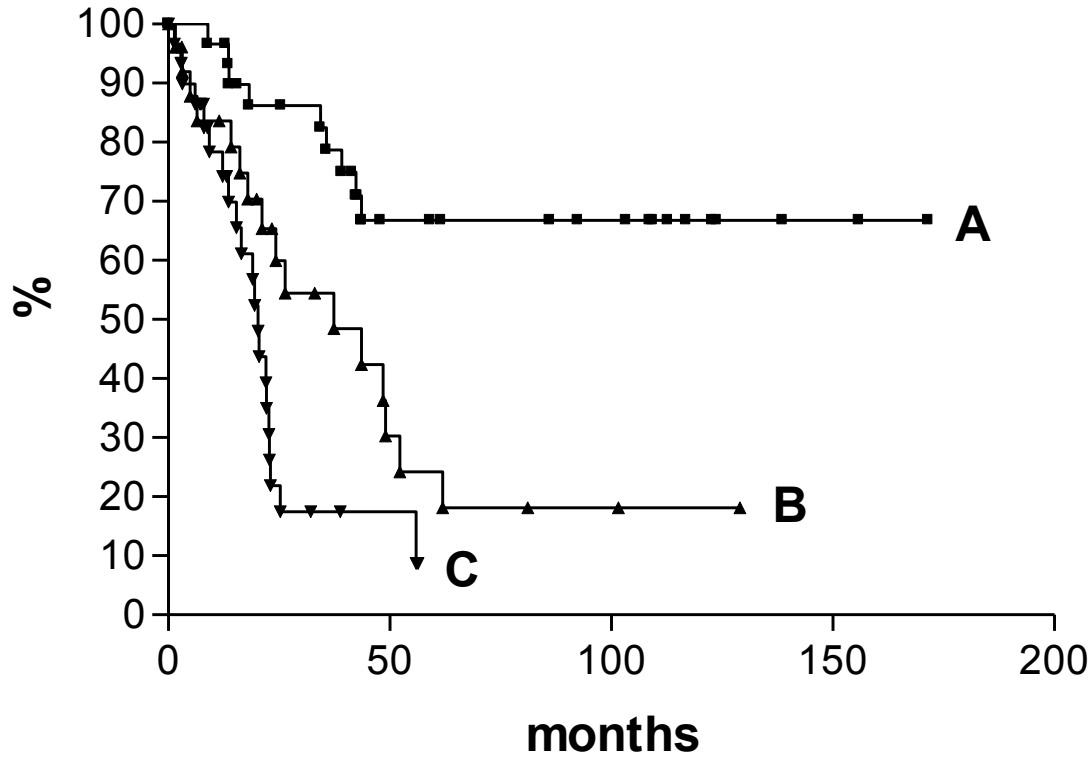


Quaglino P, GILC study, Cancer 2012

Sézary Sindrome: survival according to atipical circulating cell rate



A <1000
B >=1000 and >3000
C >=3000

A vs B p = 0.0024
A vs C p = 0.0001
B vs C p = 0.0449

VOLUME 24 · NUMBER 9 · MARCH 20 2006
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Prognostic Factors in Primary Cutaneous B-Cell Lymphoma: The Italian Study Group for Cutaneous Lymphomas

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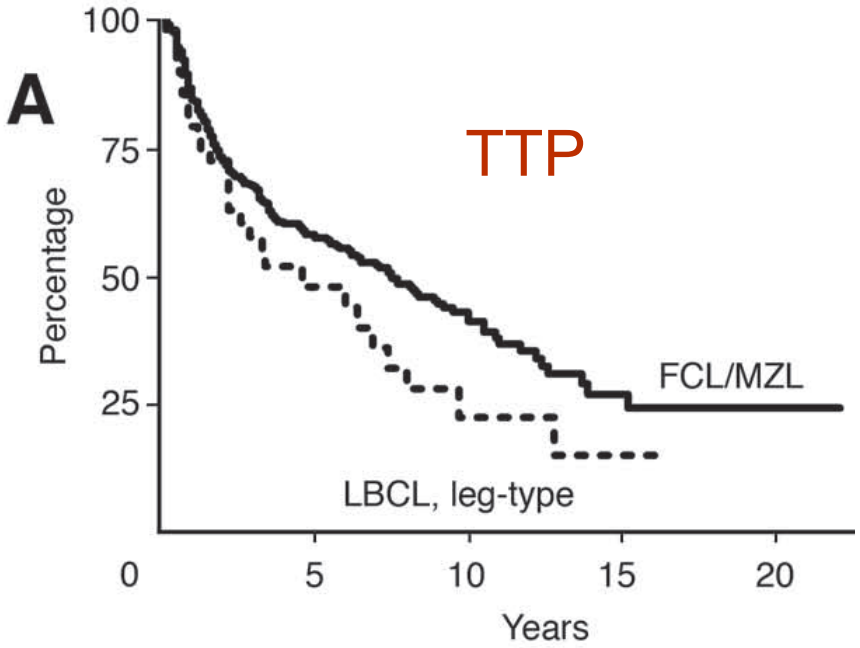

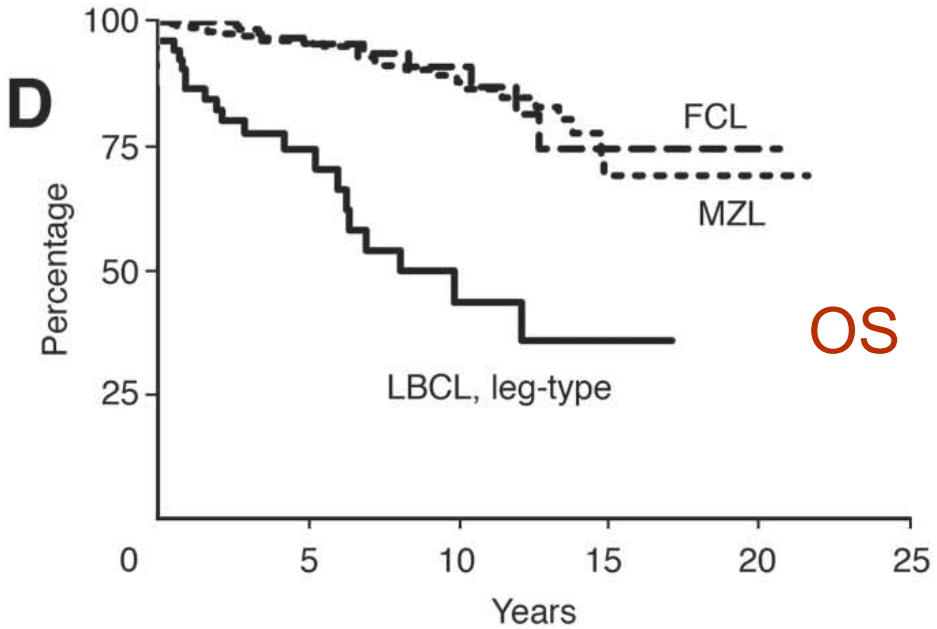

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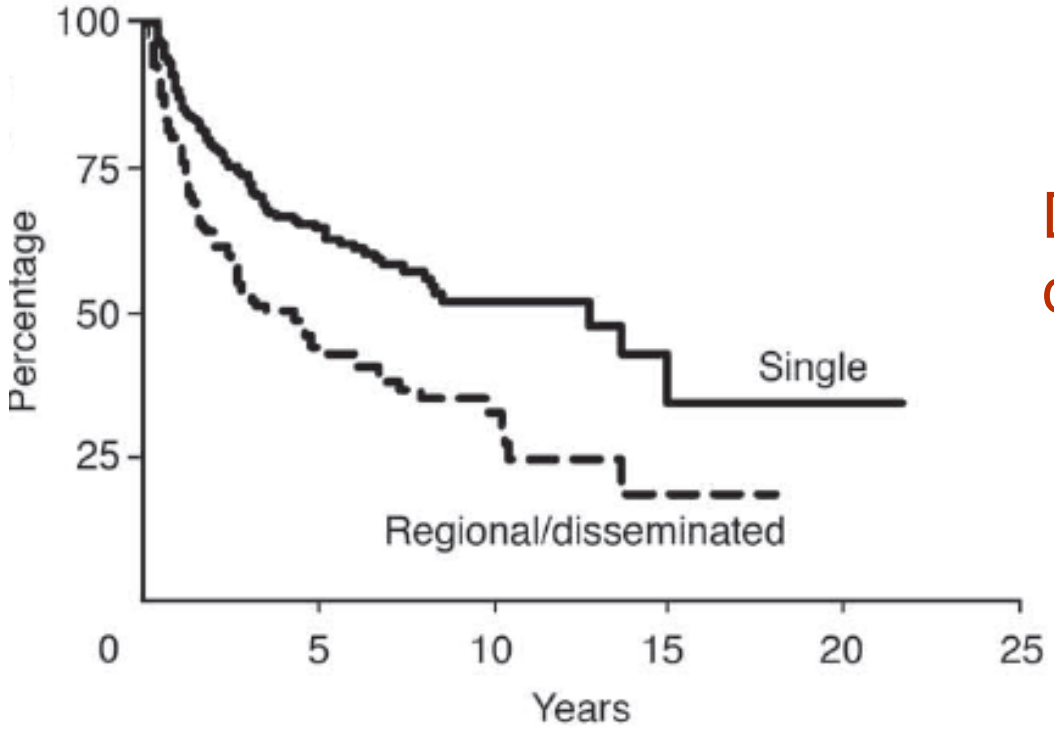

DFS according to disease extent

Therapy?

Table 2. Summary of treatment options for MF/SS

Therapy	MF		Sézary syndrome/ erythrodermic MF	Comments
	Early-stage disease	Advanced-stage disease		
Topical corticosteroids	++++	++	+++	Symptomatic control
PUVA	++++	+	+++	Availability may be restricted in nonmetropolitan areas
UVB	+++	+	++	More readily accessible than PUVA
Topical chemotherapy	+			If limited number of lesions
Imiquimod	+			If small lesions and limited number of lesions
Photodynamic therapy	+			If limited number of lesions; limited availability
Retinoids	+	+	+	Usually second line; less used since bexarotene became available
Bexarotene	++	+++	+++	Usually second line; can be used in combination with PUVA or IFN-α
Interferon-α	++	+++	++++	Second line
HDACi	+	+++	++++	Beyond second line
Oral MTX	+	+++	++	Low dose weekly
Localized radiotherapy	+	+++		If localized or large/plaques and tumor nodules
TSEB	+	++	+	For widespread disease
Systemic chemotherapy		++	++	Beyond second line
ECP		++++		If circulating clone detectable
Autologous transplantation		+	+	Very selected cases
Allogeneic transplantation		+	+	Very selected cases
Denileukin diftitox		++	++	Beyond second line
Alemtuzamab		+	+	Beyond second line; immunosuppressive
Proteasome inhibitors		+		Under investigation
Immunomodulatory agents (lenalidomide)		+		Under investigation

MF indicates mycosis fungoides; SS, Sézary syndrome; PUVA, psoralan ultraviolet A; UVB, ultraviolet B; ECP, extracorporeal photopheresis; HDACi, histone deacetylase inhibitors; and TSEB, total skin electron beam.

Crosses indicate frequency of use: ++++, almost always; +++, very frequently; ++, moderately frequently; and +, occasionally.

blood
2009 114: 4337-4353
Prepublished online August 20, 2009;
doi:10.1182/blood-2009-07-202895

How I treat mycosis fungoides and Sézary syndrome

H. Miles Prince, Sean Whittaker and Richard T. Hoppe

Table 7. Recommendations for treatment of MF stages IA, IB, and IIA

Treatment	Comments*
First-line	
"Expectant policy"	Usually suitable for those with stage IA disease in conjunction with symptomatic treatment if required; patients with single lesion may be considered for "curative therapy" with radiation therapy
PUVA	For patch/plaque disease; requires regular 2 or 3 times/week treatment; there may be limited availability of PUVA in nonmetropolitan areas; can be combined with retinoids/rexinoids
UVB	For patch stage disease as skin penetration not as deep as PUVA; requires regular 2 or 3 times/week treatment and generally more readily available than PUVA
Topical corticosteroids	Simple therapy; toxicities if extensive skin application for long periods
Topical bexarotene	For limited sites of disease; simple therapy; local reactions may occur
Topical NM	For limited sites of disease or generalized involvement; local reactions occasionally problematic; ointment causes fewer reactions; availability of NM worldwide has been a problem recently
Topical carmustine	Rarely used now; for limited sites of disease; local reactions may occur; causes telangiectasias
Localized radiotherapy	Especially for patients with limited number of lesions and/or thickened plaques; durable remissions achieved
TSEB	Patients with stage IB disease with relatively slow progression; limited availability; can take 6 to 10 weeks to complete
Second-line+	
Oral bexarotene	Generally well tolerated and convenient (oral capsule); some responses can be very durable; most common side effects are hypertriglyceridemia and hypothyroidism that usually require treatment; other relatively common side effects are rash and headache; can be used in conjunction with other therapies
IFN-α monotherapy	Major difficulty is tolerance and compliance; some responses can be very durable; somewhat inconvenient (daily subcutaneous injection); most common side effect is fatigue, particularly in older patients; requires moderately high doses aiming for 3 to 5+ MU/day; monitor FBC and thyroid function; IFN-α can also be combined with PUVA, retinoids, bexarotene
Low-dose MTX	Generally well tolerated and convenient (oral weekly); dose-response effect is common and usually starts at 20 to 30 mg/week (up to 60-70 mg/week); some responses can be very durable; most common side effects are cytopenias and long-term risk of liver disease; very effective in patients with coexistent lymphomatoid papulosis; can be used in conjunction with other therapies, such as steroids, ECP, PUVA, IFN-α
Vorinostat	Only approved HDACi currently; generally well tolerated and convenient (oral daily); there appears to be a dose-response effect in some patients; most common SEs are fatigue, lethargy, mild/moderate thrombocytopenia and elevated creatinine and taste changes; can improve itch even when skin lesions remain; some responses can be very durable; virtually no data on use in combination with other therapies, such as PUVA, IFN-α, MTX, chemotherapy
Denileukin diftitox	Generally considered after trial of bexarotene and/or HDACi; inconvenient administration requiring daily dosing times 5 days every 3 weeks (6-8 courses); patient's tumor must express CD25 (although responses are observed in patients with $CD25^-$ lesions); there can be substantial supportive care requirements for some patients during therapy who develop capillary leak syndrome; some responses can be very durable even in heavily pretreated patients
Novel agents within clinical trials	In patients with stage IA-IIA disease, chemotherapy is not recommended and novel agents within clinical trials are generally recommended before chemotherapy is considered (see Table 12)

blood

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How I treat mycosis fungoides and Sézary syndrome

H. Miles Prince, Sean Whittaker and Richard T. Hoppe

Table 8. Recommendations for treatment of MF stage IIB

Treatment	Comments*
First-line	
IFN-α	Can be effective even in patients with tumor and/or ulcerated lesions; see Table 7 for other comments; IFN-α can also be combined with PUVA, retinoids, bexarotene, MTX
TSEB and superficial X-irradiation	"Boosts" needed to site of thickened plaques/tumors; limited availability; can take 6 to 10 weeks to complete
PUVA	For patch/plaque disease; requires regular 2 or 3 times/week treatment; there may be limited availability of PUVA in nonmetropolitan areas; can be combined with retinoids/rexinoids, bexarotene, IFN-α
Second-line	
Bexarotene	See Table 7 for comments
Vorinostat	See Table 7 for comments
Denileukin diftitox	See Table 7 for comments
Novel agents within clinical trials	In patients with stage IIB disease, chemotherapy is recommended after bexarotene and/or and HDACi and/or DD; it is very acceptable to consider novel agents within clinical trials before chemotherapy is considered (see Table 12)
Chemotherapy	Choice of chemotherapy regimens is extensive (see Table 11), and choice depends on patient tolerance, risk of infection versus the relatively short duration of remission observed with most chemotherapy regimens; transplantation may be considered in highly selected persons

*For more details and detailed references, we refer the reader to the EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome.[7]

(POLI)-CHEMOTHERAPY in CTCL: where, how, when...

- **MF:** IIB (diffuse disease), III relapse/refractory
- **Sézary Sindrome:** (monoCT), alemtuzumab if high blood involvement
- **T noMF/SS CD30-:** diffuse lesions (single?)
- **T noMF/SS CD30+:** ONLY if diffuse lesions and rapid decrease (NO Lymphomatoid papulosis)

Table 11. Key clinical studies of systemic chemotherapy in cutaneous T-cell lymphoma

Therapy examples*	Efficacy	Comments
CHOP-based[67]	ORR stage IIB: 66%	Myelosuppression with risk of infection; very short remission duration
EPOCH[61]	ORR stage IIB-IV: 80%	Myelosuppression with risk of infection; short remission duration
CMED/ABV[42,62]	ORR stage III-IV: 81%	Myelosuppression with risk of infection; median DFS of 7 months and 27% 5-year DFS
Pegylated liposomal doxorubicin[65]	ORR stage IA-IV: 88%	Single agent; well tolerated; infusion-related events; no comparisons with standard anthracyclines
Pentostatin[64]	ORR stage IIB: 75% Stage III: 58% Stage IV: 50%	Numerous trials and regimens used; activity in PTCL; perhaps best activity in SS; prolonged therapy needed in some cases; lymphopenia
Fludarabine plus IFN-α[55]	ORR stage IIA-IVA: 58% stage IVB: 40%	Neutropenia common
Fludarabine plus cyclophosphamide[66]	ORR stage IIB-III: 55%	Appears higher RR to fludarabine-alone; lymphopenia and prolonged myelosuppression in some patients; stem cell collection yields are lower
Gemcitabine[63]	ORR stage IIB-III: 70%	Neutropenia; recent evidence that toxicities (rash, infection) may be higher in patients with CTCL (see "Systemic chemotherapy")
2-Chlorodeoxyadensine[68]	ORR stage IIA-IV: 28%	Median duration or response of 4.5 months; bone marrow suppression and infections in 62%

CR indicates complete response; CRR, complete response rate; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone; ORR, overall response rate; PR, partial response; PUVA, ultraviolet A light with oral methoxypsoralen; and DFS, disease-free survival.

*See "Systemic chemotherapy" for more details and other trial results.

Many “new” cards to play in CTCL…

- Bexarotene
- Gemcitabine, Peg-Doxo
- MoAbs (alemtuzumab, zanolimumab)
- Histone deacetylase inhibitors
- Forodesine
- Lenalidomide
- Bortezomib
- Brentuximab vedotin
- Pralatrexate

Table 1. Summary of the results obtained by new investigational drugs in CTCL patients

Drug	Ref.	Mechanism of action	No. pts	Clinical characteristics of patients included	Route of administration	% response rate	Side effects
Alemtuzumab	75	Monoclonal antibody anti-CD52	14	Sèzary syndrome	Subcutaneous	85%	Infections
Vorinostat	79	HDAC	33	Advanced, heavily pretreated CTCL including SS	Oral 400 mg per day	24,4%	Fatigue, anorexia, diarrhoea, thrombocytopenia, QT alterations
Vorinostat	80	HDAC	74	Relapsed CTCL	Oral 400 mg per day	29,5%	Fatigue, anorexia, diarrhoea, thrombocytopenia, QT alterations
Romidepsin	81-82	HDAC	96	Pre-treated CTCL	Intravenous	34%	Fatigue, anorexia, diarrhoea, thrombocytopenia, QT alterations
Pralatrexate	83	Anti-folate compound	31	Relapsed/refractory MF, SS, and anaplastic large-cell lymphoma	Intravenous 30 mg/m^2 every week	43%	Fatigue, mucositis, nausea, epistaxis
Bortezomib	84	Proteasome inhibitor	12	MF, peripheral CTCL	Intravenous 1,3 mg/m^2 days 1,4,8,11 every 21 days	67%	Myelosuppression, neuropathy
Forodesine	85	Inhibitor of purine nucleoside phosphorylase	9	Advanced CTCL	Oral	5/9	Nausea, fatigue, edema, dyspnea and urinary casts
Zanolimumab	86	Monoclonal antibody anti-CD4	47	Early and advanced stage CTCL	Intravenous	56%	Skin reactions, infections of skin and upper respiratory tract
Mogamulizumab	87	Monoclonal antibody anti-CCR-4	42	Relapsed, refractory CTCL including SS	Intravenous 1 mg/kg	42%	Lymphopenia, neutropenia, thrombocytopenia, acute infusion reaction and skin eruptions
Brentuximab vedotin	88	Monoclonal antibody anti-CD30	58	Relapsed, refractory systemic CD30 anaplastic large cell lymphoma	Intravenous 1,8 mg/kg	86%	Neutropenia, thrombocytopenia and peripheral neuropathy

Bernengo MG, Quaglino P, GIDV 2012

Table 3. Therapy results

Cumulative studies	Patients, N	CR, no. (%)	Relapse, no. (%)
PCMZL			
Radiotherapy	132	130/132 (99)	60/130 (46)
Excision	75	74/75 (99)	32/74 (43)
Interferon-α	8	8/8 (100)	2/8 (25)
Rituximab intralesional	9	8/9 (89)	5/8 (62)
Rituximab intravenous	3	2/3 (67)	1/2 (50)
Chlorambucil	14	9/14 (64)	3/9 (33)
Antibiotics	14	6/14 (43)	1/5 (20)*
Multiagent chemotherapy	33	28/33 (85)	16/28 (57)
PCFCL			
Radiotherapy	460	457/460 (99)	216/457 (47)
Multiagent chemotherapy	104	88/104 (85)	42/83 (51)*
R-CHOP	2	1/2 (50)	0/1 (0)
Interferon-α	7	7/7 (100)	2/7 (29)
Rituximab intralesional	12	10/12 (83)	4/10 (40)
Rituximab intravenous	28	21/28 (75)	4/19 (21)*
Excision	93	91/93 (98)	36/91 (40)
Chemoradiotherapy	7	7/7 (100)	1/7 (14)
PCLBCL, LT			
Radiotherapy	101	89/101 (88)	52/89 (58)
Multiagent chemotherapy	32	26/32 (81)	14/24 (58)*
R-CHOP	12	11/12 (92)	1/11 (9)†
Chemoradiotherapy	6	4/6 (67)	1/2 (50)*
Rituximab intravenous	13	5/13 (39)	0/4 (0)*

B-cells lymphomas

Table 4. Recommendations for initial management of the 3 main types of CBCL

Disease type and extent	First-line therapy	Alternative therapies
PCMZL		
Solitary/localized	Local radiotherapy Excision Antibiotics*	IFN-α i.l. Rituximab i.l. i.l. steroids
Multifocal	Wait-and-see Local radiotherapy Chlorambucil† Rituximab i.v. Antibiotics*	IFN-α i.l. Rituximab i.l. Topical or i.l. steroids
PCFCL		
Solitary/localized	Local radiotherapy Excision	IFN-α i.l. Rituximab i.l.
Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP‡
PCLBCL, LT		
Solitary/localized	R-CHOP ± IFRT	Local radiotherapy Rituximab i.v.
Multifocal	R-CHOP	Rituximab i.v.

IFRT indicates involved field radiotherapy; i.l., intralesional; and i.v., intravenous.

*In case of evidence for *B burgdorferi* infection.

†Or other single or combination regimens appropriate for low-grade B-cell lymphomas.

‡In exceptional cases or for patients developing extracutaneous disease.

B-cells lymphomas

Radiation Therapy Keynotes

STANFORD
RADIATION ONCOLOGY

A partnership with Emanuel Cancer Center

TSEB was developed at Stanford University in 1960, initially with a four-field technique and later a six-field technique

A 6 MeV modern LINAC in high-dose electron mode
Angled dual fields

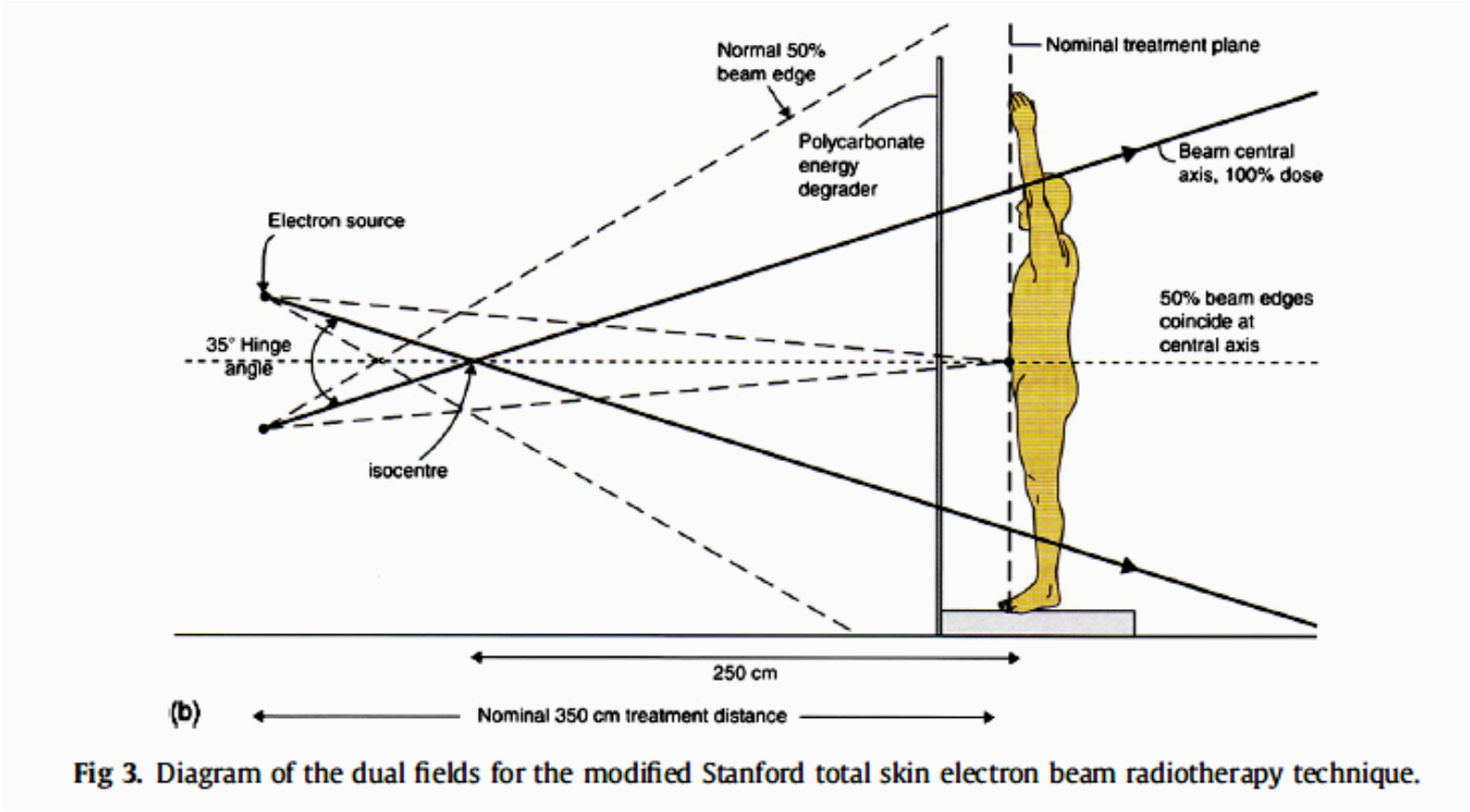
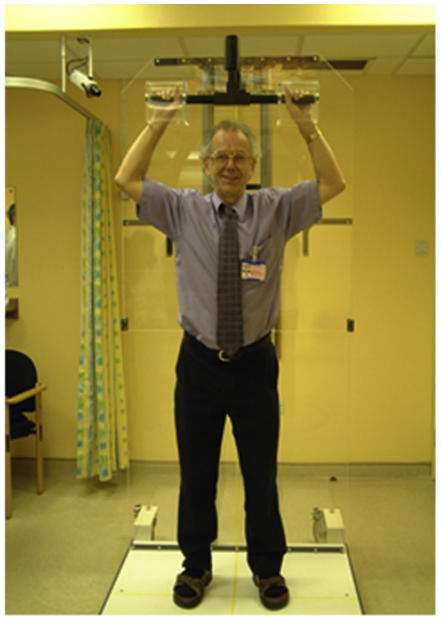
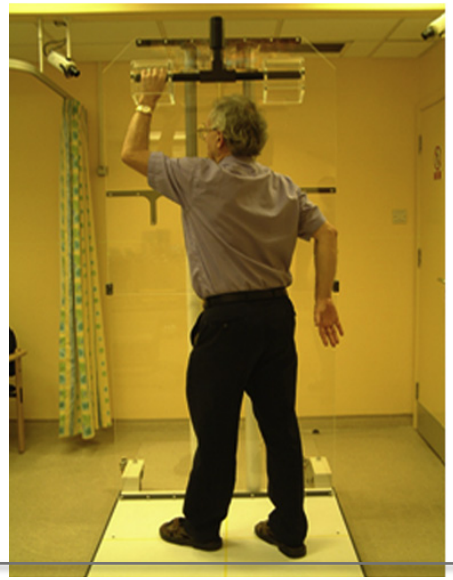
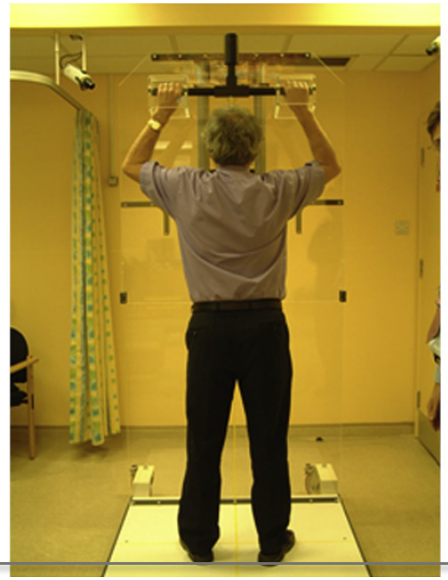


Fig 3. Diagram of the dual fields for the modified Stanford total skin electron beam radiotherapy technique.

The six standing positions for TSEB


A systematic review (metaanalysis) of mostly non-randomised studies

- CR rate is dependent on the stage of disease, skin surface dose and energy
- CR in stage IA/IB/IIA: 96%
- Greater skin surface dose (32-36 Gy) and higher energy (4-6 MeV electrons)

→ higher CR

- 5 year RFS: 10-23%

30-36 Gy Stanford

→ ORR 100%

→ CR 75% in T2, 47% in T3

→ Median response duration in CR: 29 months in T2, 9 months in T3

Jones et al, 1995

TSEB objectives (EORTC consensus)

Table I. Objectives of any method of total skin electron radiation

- To align the distribution of dose to the target volume
- To be practical, comfortable, and efficient for the patient
- To provide sufficient dose within the target volume
- To reliably attain cutaneous remission
- To minimize toxicity
- To produce beneficial long-term clinical results
- To accommodate repeated administration as required

Jones GW et al, 2002

• 3 positions each day → a full cycle of treatment to the 6 standing positions over 2 days

• DFT 30-36 Gy over 9-10 weeks (2 Gy per cycle)

• Possibility of a week gap if skin radiation reaction

Extra shielding:

- eyes
- hands
- wrists
- ears
- ankles
- feet
- penis

Clinical indications (EORTC consensus)

Table III. Clinical indications for total skin electron radiation

1. Patients with a new diagnosis of mycosis fungoides	
"Minimal" stage IA	Not recommended (consider local radiation only)
Stage IA & T1N1	A brief therapy with potential for long-term progression-free survival
Stage IB & T2N1	As in stage IA, consider combination therapy (eg, with psoralen plus UV light)
Stage IIB	Effective palliation, consider combination therapy
Stage III	Potential for long-term progression-free survival from erythroderma
Stage IVA	Consider the combination with involved-node photon-radiation
Stage IVB	Effective palliation, consider combination therapy
Sézary syndrome	Consider the combination with extracorporeal photochemotherapy
2. Patients for whom prior therapies failed	
IA - IIA	A brief therapy with potential for long-term progression-free survival
All others	Consider combination therapies
3. Patients considering repetition of total skin electron radiation	
Stable disease	Consider minicourse or complete course of total skin electron radiation
Progressive	Consider combination therapies

Jones GW et al, 2002

SIDE EFFECTS

- fatigue: common, but not severe or debilitating
- radiation dermatitis: mild to moderate
- alopecia: after 2 weeks of treatment
- nails toxicity
- oedema of the lower legs
- temporary epistaxis
- temporary gynaecomastia
- parotid swelling

Wilson, Arch Dermatol, 2003

To monitor for infection during treatment

→ in early disease the reported incidence of infection is 1%

→ in advanced disease the incidence of skin infection is higher

LONG-TERM LATE EFFECTS

- minor skin atrophy, usually around the wrist or lower leg area
- permanent alopecia
- fingernails and toenails dystrophy
- infertility: possible in men, but generally not an issue in women

Wilson, Arch Dermatol, 2003

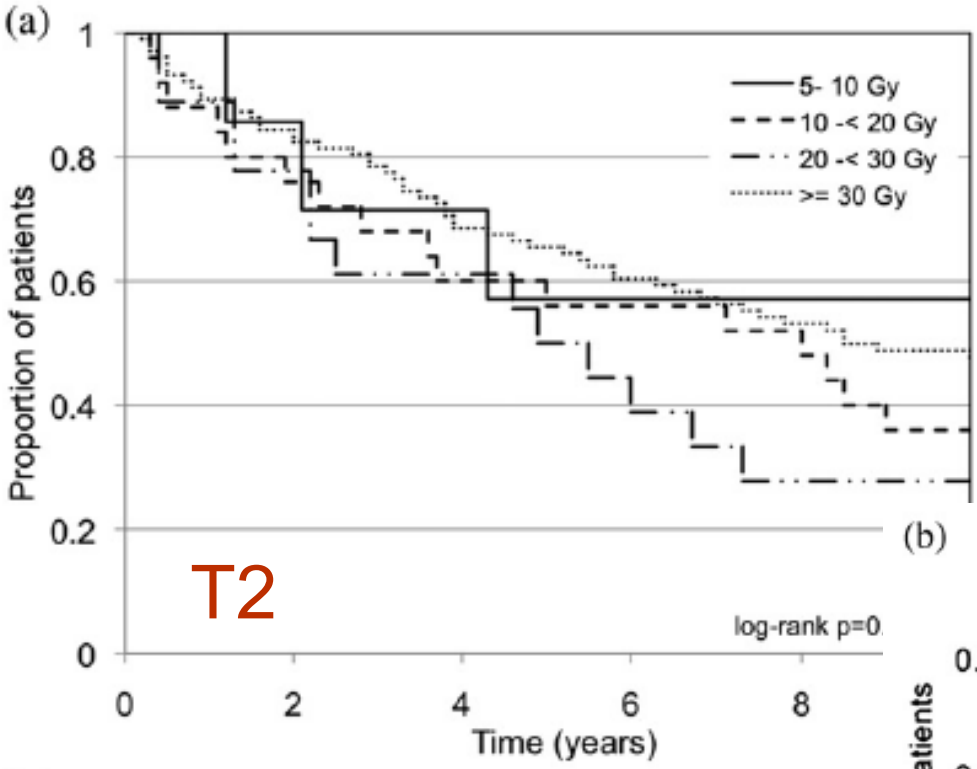
REVISITING LOW-DOSE TOTAL SKIN ELECTRON BEAM THERAPY IN MYCOSIS FUNGOIDES

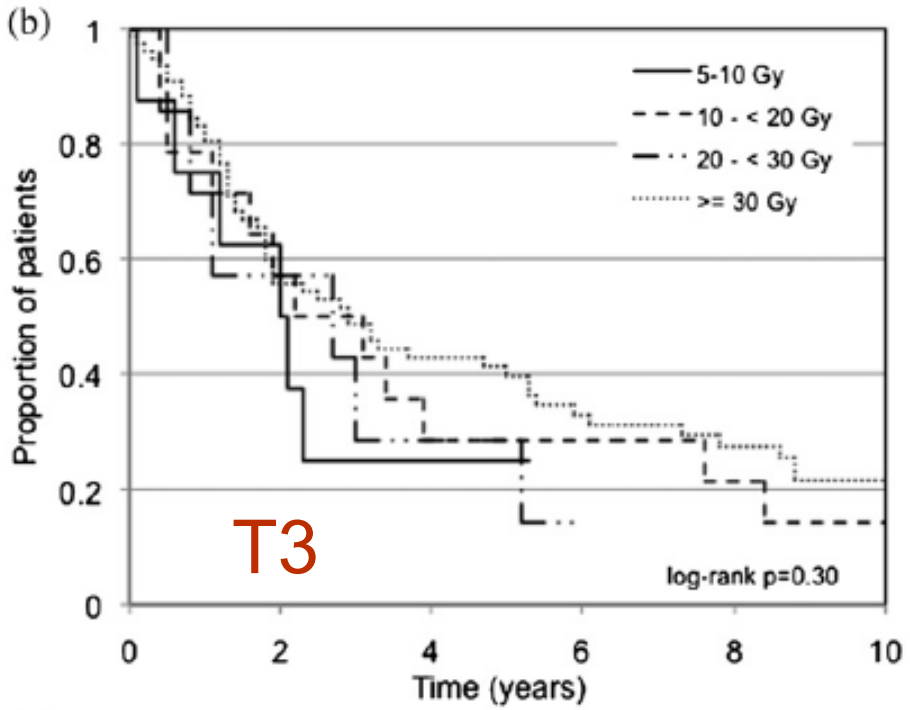
102 MF pts

Table 1. Initial course clinical response by dose

		No. of patients/total (%) per dose group			
T class or range	Response	5–<10 Gy	10–<20 Gy	20–<30 Gy	5–<30 Gy
T2	CR	1/7 (14)	13/25 (52)	7/19 (37)	21/51 (41)
	PR	5/7 (71)	11/25 (44)	12/19 (63)	28/51 (55)
	OR	6/7 (85)	24/25 (96)	19/19 (100)	49/51 (96)
T3	CR	2/8 (25)	1/14 (7)	2/7 (29)	5/29 (17)
	PR	5/8 (63)	13/14 (93)	5/7 (71)	23/29 (79)
	OR	7/8 (88)	14/14 (100)	7/7 (100)	28/29 (96)
T4	CR	0/4 (0)	4/12 (33)	2/6 (33)	6/22 (27)
	PR	4/4 (100)	8/12 (67)	3/6 (50)	15/22 (68)
	OR	4/4 (100)	12/12 (100)	5/6 (83)	21/22 (95)
T2–T4	CR	3/19 (16)	18/51 (35)	11/32 (34)	32/102 (31)
	PR	14/19 (74)	32/51 (63)	20/32 (63)	66/102 (65)
	OR	17/19 (90)	50/51 (98)	31/32 (97)	98/102 (96)

Harrison et al., IJROBP, 2011





Harrison et al., IJROBP, 2011

10 pts with histopathologically confirmed MF T2–T4 N0–N1 M0

TSEB 4 Gy in 4 fractions over 4 successive days

Table 1. Patient characteristics and treatment outcome

Patient no.	Sex	Age (y)	Stage*	Disease duration (y)	Prior therapy	Response	TBI before†	TBI after	Relapse (mo)
1	M	68	T2N1M0 IIB	<1	TS, Pred, MTX, PUVA	CR	3.3	0	3.5
2	F	61	T2N0M0 IB	9	TS, PUVA, X-ray, CHOP, MTX, TSEBT‡	PR	4	3	3
3	F	76	T3N0M0 IC	<1	TS, PUVA	PR	5.3	2	1
4	M	82	T3N0M0 IC	<1	TS, PUVA	PR	5.3	2	3.5§
5	M	64	T2N0M0 IB	2	TS, PUVA, X-ray, Pred	PR	3.3	3.3	2.7
6	F	56	T2N0M0 IB	<1	TS, PUVA	CR	4	0	3.5
7	M	81	T2N0M0 IB	16	TS, PUVA, UVB, HumaxCD4	NR	4	4	0
8	M	69	T2N0M0 IB	19	TS, PUVA, HumaxCD4	PR	4	4	1
9	M	75	T2N0M0 IB	<1	TS, PUVA, MTX, UVB	NA‖	4	NA	NA
10	F	55	T3N0M0 IIB	<1	TS, PUVA, X-ray	PR	4.3	4.3	1

Abbreviations: TBI = tumor burden index; M = male; F = female; TS = topical steroids; Pred = prednisolone; MTX = methotrexate; PUVA = psoralen plus ultraviolet-A; CR = complete response; X-ray = local field X-ray; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; TSEBT = total skin electron beam therapy; PR = partial response; NR = no response; NA = not applicable; UVB = ultraviolet-B.

Duration indicates interval from histopathologically verified diagnosis of mycosis fungoides to low-dose TSEBT.

Kamstrup et al., IJROBP, 2008

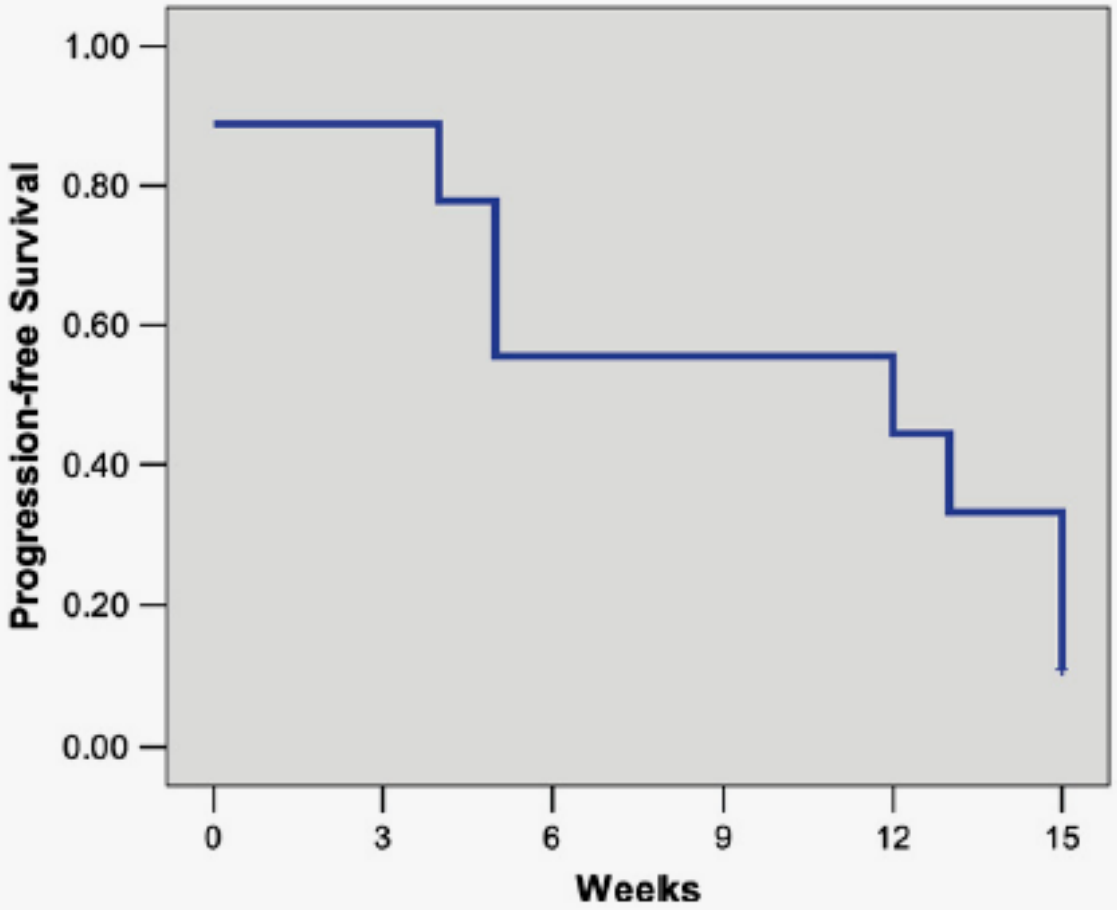


Fig. 1. Progression-free survival after low-dose total skin electron beam therapy. One patient (Patient 4) was censored after 3.5 months.

Kamstrup et al., IJROBP, 2008

Int. J. Radiation Oncology Biol. Phys., Vol. 40, No. 1, pp. 109–115, 1998

LOCAL SUPERFICIAL RADIOTHERAPY IN THE MANAGEMENT OF MINIMAL STAGE IA CUTANEOUS T-CELL LYMPHOMA (MYCOSIS FUNGOIDES)

LYNN D. WILSON, M.D., M.P.H.,* BARRY M. KACINSKI, M.D., PH.D.* AND GLENN W. JONES, B.SC., M.D., F.R.C.P.C., M.SC.†

Rarely mycosis fungoides can present as a solitary patch and plaque

In this setting local radiotherapy may be curative and the doses used have been between **20 and 30 Gy**

Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 2, pp. 361–364, 1998

RADIOTHERAPY FOR UNILESIONAL MYCOSIS FUNGOIDES

BIZHAN MICAILY, M.D.,* CURTIS MIYAMOTO, M.D.,* GARY KANTOR, M.D.,† STUART LESSIN, M.D.,‡ ALAIN ROOK, M.D.,‡ LUTHER BRADY, M.D.,* ROBERT GOODMAN, M.D.* AND ERIC C. VONDERHEID, M.D.*

Mycosis fungoides: radiation therapy

Dose response:

PR with doses as low as 1 Gy
CR with doses of 7 Gy or higher
Response rate > 90%

Recurrence rate:

< 10 Gy → 42%
10-20 Gy → 32%
20-30 Gy → 21%

Hoppe, Dermatologic Therapy, 2003

31 pts with MF:

82 symptomatic sites

4 Gy in 2 fx → 70% failed
8 Gy in 2 fx → CR 92%

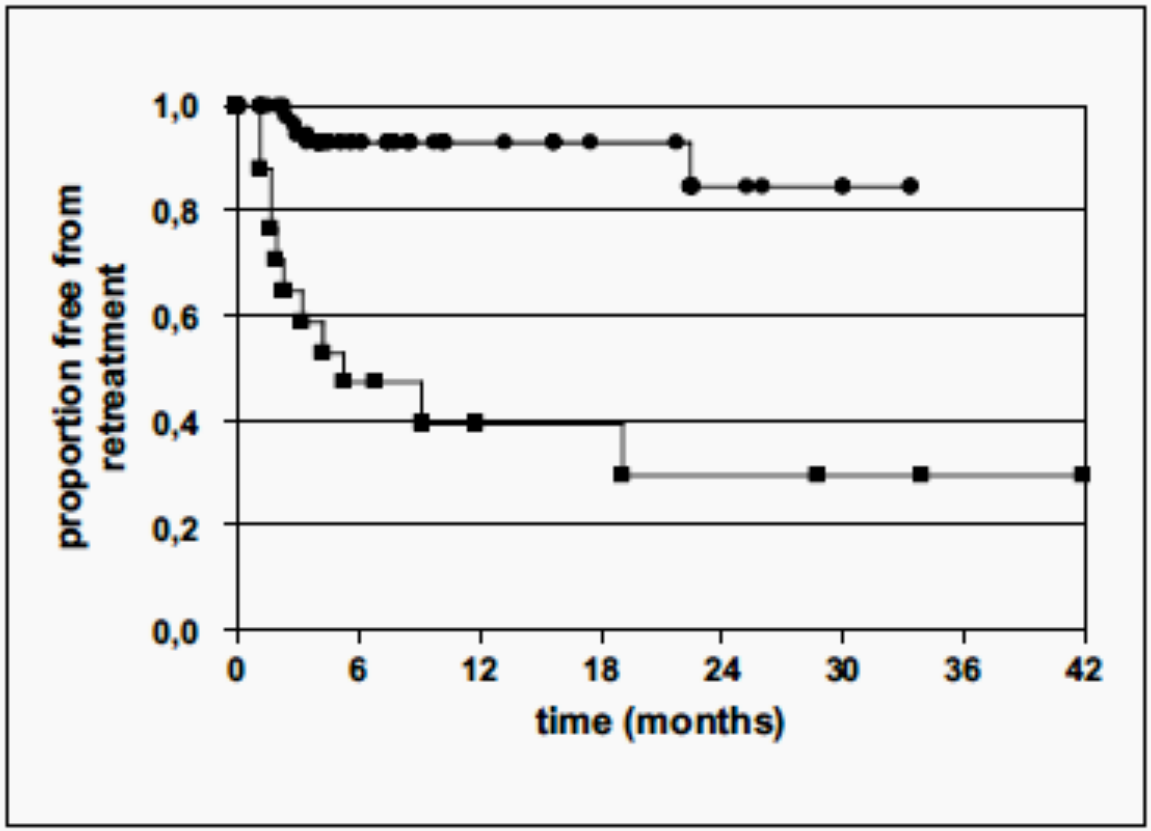


Fig. 2. Actuarial proportion free of retreatment for MF lesions treated with low-dose palliative radiotherapy (2 x 4 Gy, $n = 65$ [upper curve] and 2 × 2 Gy, $n = 17$ [lower curve]).

Neelis et al., IJROBP, 2009

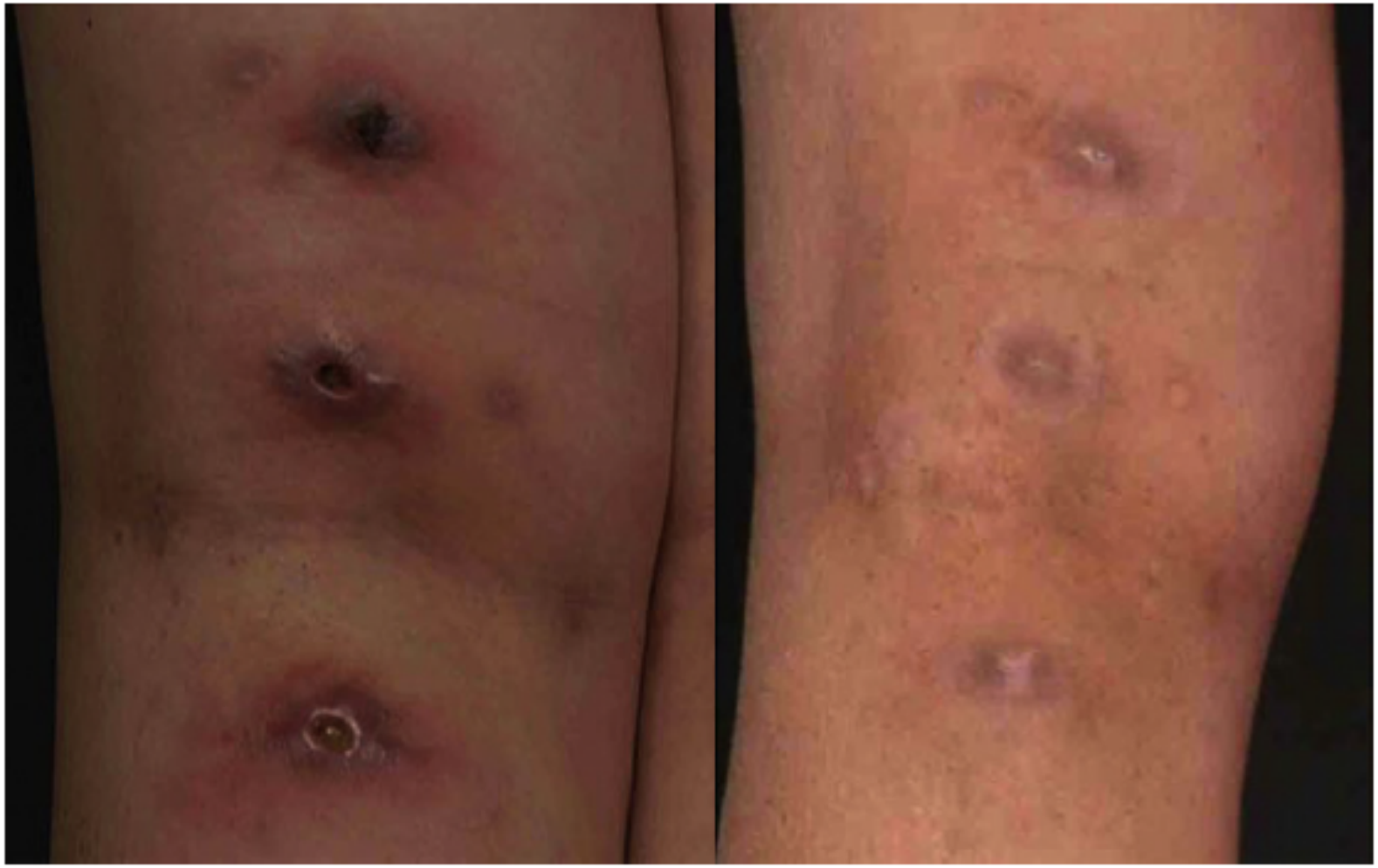
Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas

Table 2. Treatment of mycosis fungoides/Sézary syndrome

Stage	First line	Second line	Experimental	Not suitable
IA	SDT or no therapy	SDT or no therapy	Bexarotene gel	Chemotherapy
IB	SDT	α-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy
IIA	SDT	α-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy
IIB	Radiotherapy or TSEB, chemotherapy	α-interferon, denileukin diftitox, bexarotene	Autologous PBSCT mini-allograft	Cyclosporin
III	PUVA ± α-interferon, ECP ± α-interferon, methotrexate	TSEB, bexarotene, denileukin diftitox,* chemotherapy, alemtuzumab	Autologous PBSCT, mini-allograft	Cyclosporin
IVA	Radiotherapy or TSEB, chemotherapy	α-interferon, denileukin diftitox,* alemtuzumab bexarotene	Autologous PBSCT, mini-allograft	Cyclosporin
IVB	Radiotherapy, chemotherapy	Palliative therapy	Mini-allograft	

The current recommended doses in the UK are 8 Gy in 2 fractions to 12 Gy in 3 fractions for patches, plaques and tumours

Whittaker et al., BJD, 2003



Complete response of mycosis fungoides tumours to low-dose radiotherapy (12 Gy in three fractions).

MYCOSIS FUNGOIDES
Variants and subtypes

CD30$^+$ cutaneous lymphoproliferative disorders: The Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma

- **56 pts**
  - → **25 pts PC-ALCL**
  - → **31 pts LyP**

PC-ALCL are very responsive to RT

- **Relapse rates: 42%**
- **Standard recommended doses:**

30-36 Gy in 2 Gy fx

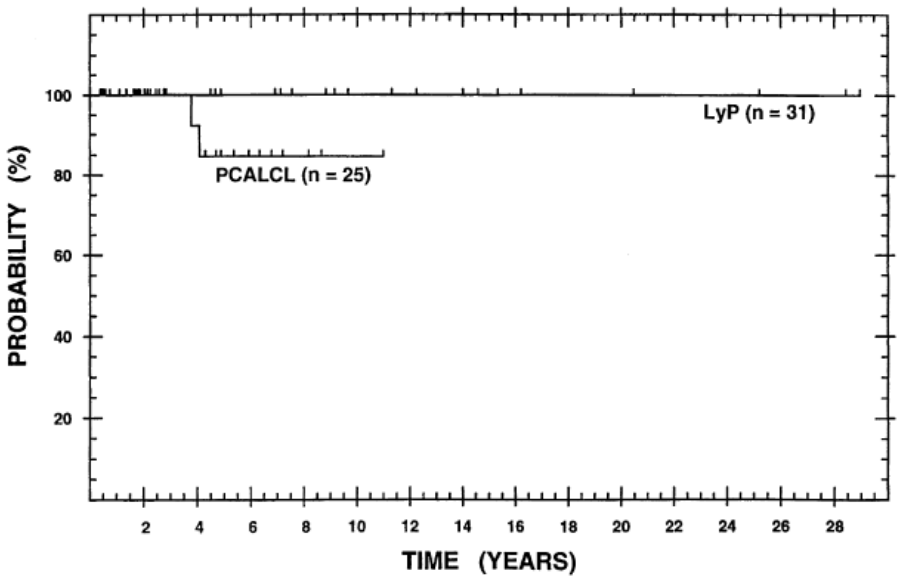
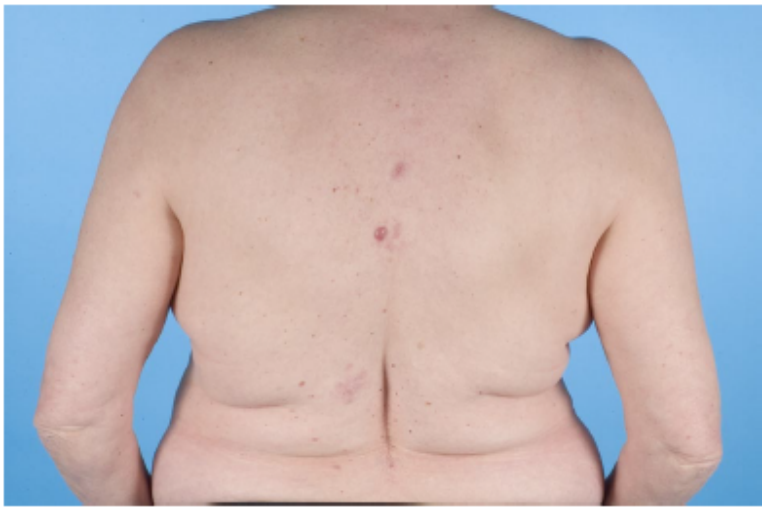


Fig 3. Actuarial disease-specific survival of 31 patients with lymphomatoid papulosis (*LyP*) and 25 patients with primary cutaneous anaplastic large cell lymphoma (*PCALCL*) (LyP vs PCALCL, $P = .08$).

Liu et al., J Am Acad Dermatol, 2003

PRIMARY CUTANEOUS B-CELL LYMPHOMA

PCMZL



132 PCMZL patients treated with RT

130 pts (99%) → CR

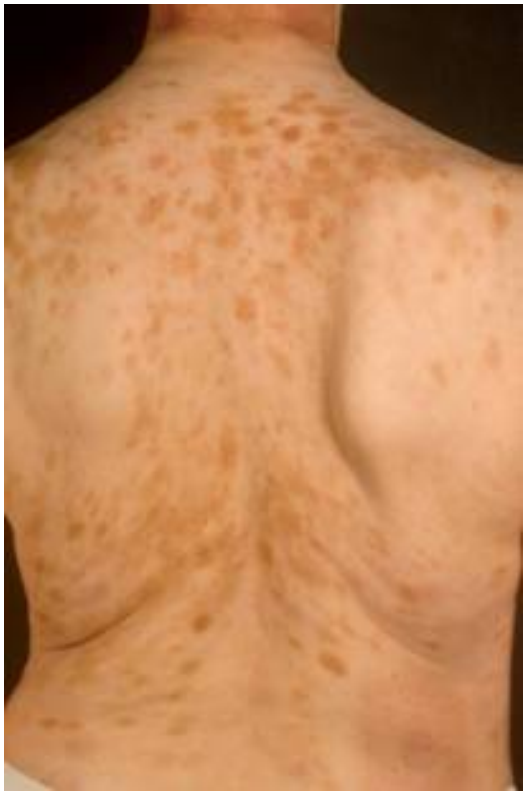
60 pts (46%) → one or more relapses

3 pts → extracutaneous progression

Reported cumulative RT doses:
30-45 Gy

Margin of clinically normal skin: 1-5 cm

Senff et al., Blood, 2008



PCFCL

460 PCFCL patients treated with RT

Local RT = the first choice of treatment
DFT: 30 Gy (range 20-54 Gy)

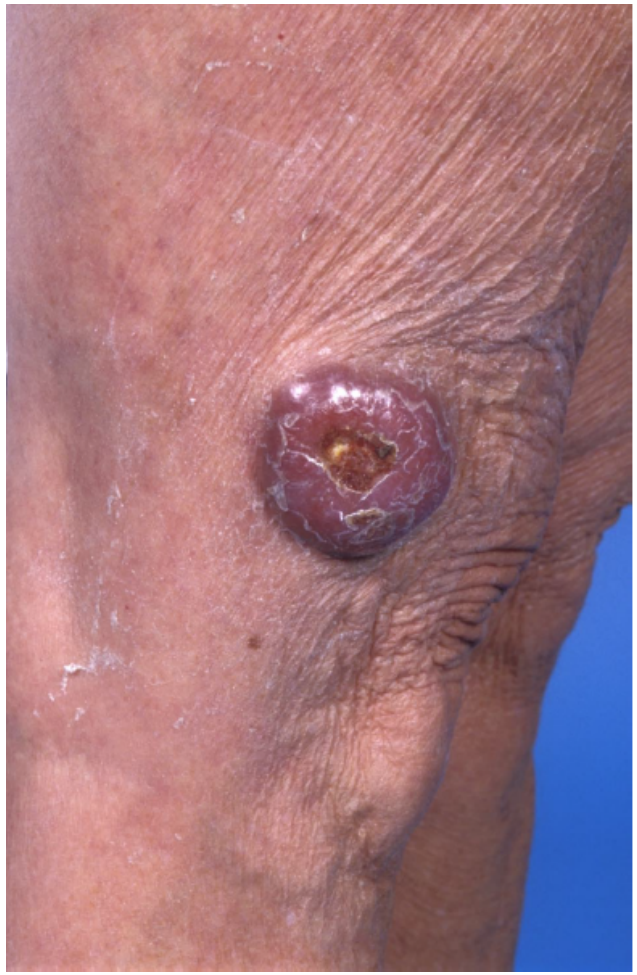
CR in all cases

Three major studies *(Eich et al., IJROBP, 2003 – Senff et al., Arch Dermatol, 2007 – Smith et al., JCO, 2004)* → **relapse rate of 30%**
Italian study *(Piccinno et al., IJROBP, 1993)* → **relapse rate 76%**

Variance in techniques used and in the margins of healthy-looking skin included in the RT field (range, 0.5-5 cm)

Senff et al., Blood, 2008

PCLBCL – LT



Radiotherapy is less effective

101 patients

CR rate 88%

Relapse rate 58%

Extracutaneous progression

30% of patients

Senff et al., Blood, 2008

Table 4. Recommendations for initial management of the 3 main types of CBCL

Disease type and extent	First-line therapy	Alternative therapies
PCMZL		
Solitary/localized	Local radiotherapy Excision Antibiotics*	IFN-α i.l. Rituximab i.l. i.l. steroids
Multifocal	Wait-and-see Local radiotherapy Chlorambucil† Rituximab i.v. Antibiotics*	IFN-α i.l. Rituximab i.l. Topical or i.l. steroids
PCFCL		
Solitary/localized	Local radiotherapy Excision	IFN-α i.l. Rituximab i.l.
Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP‡
PCLBCL, LT		
Solitary/localized	R-CHOP ± IFRT	Local radiotherapy Rituximab i.v.
Multifocal	R-CHOP	Rituximab i.v.

→ **30-36 Gy**

→ **30 Gy**

Senff et al., Blood, 2008

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Table 3
Response assessment at one month for all randomised sites of disease. CR = complete response; PR = partial response; SD = stable disease.

Response	Indolent		Aggressive		Total
	24 Gy	40–45 Gy	30 Gy	40–45 Gy	
CR	145 (82%)	138 (79%)	249 (82%	251 (83%)	783 (82%)
PR	18 (10%)	24 (14%)	29 (9%)	24 (8%)	95 (10%)
SD/ progression	14 (8%)	12 (7%)	25 (8%)	24 (8%	75 (8%)
Death	0 (0%)	0 (0%)	1 (<1%)	3 (1%)	4 (<1%)
Not assessable	2	2	0	3	7
No RT received	1	1	5	3	10
Missing	0	4	10	13	27
Total	180	181	319	321	1001

Lowry et al., Radiother Oncol, 2011

- Very heterogeneous presentations
- Several options
- Complex disease history
- Combination with other therapies

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