Primary Cutaneous B Cell Lymphoma

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University of Texas MD Anderson Cancer Canter

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Disclosures

Research supports

- Seattle Genetics
- Kite

- Advisory to ONO-Pharma

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Primary Cutaneous B cell Lymphoma

- Primary Cutaneous Marginal Zone Lymphoma
- Primary Cutaneous Follicle Center Lymphoma
- Primary Cutaneous LBCL-Leg Type

Table 1. Relative frequency and prognosis of primary cutaneous lymphomas included in the 2018 update of the WHO-EORTC classification

WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30⁺ LPDs		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous γ/δ T-cell lymphoma	<1	11
CD8⁺ AECTCL (provisional)	<1	31
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8⁺ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15
CBCL		
PCMZL	9	99
PCFCL	12	95
PCDLBLC, LT	4	56
EBV⁺ mucocutaneous ulcer (provisional)	<1	100
Intravascular large B-cell lymphoma	<1	72

CD8⁺ AECTCL, primary cutaneous aggressive epidermotropic CD8⁺ cytotoxic T-cell lymphoma; DSS, disease-specific survival; NDA, no data available; NOS, not otherwise specified.

*Based on data included in Dutch and Austrian cutaneous lymphoma registries between 2002 and 2017.

Why are they a distinct entity?

- PCBCLs 20% to 25%
- completely different clinical behavior and prognosis compared with morphologically similar nodal lymphomas that may involve the skin secondarily
- Recent molecular studies better defined the prognostic outcome

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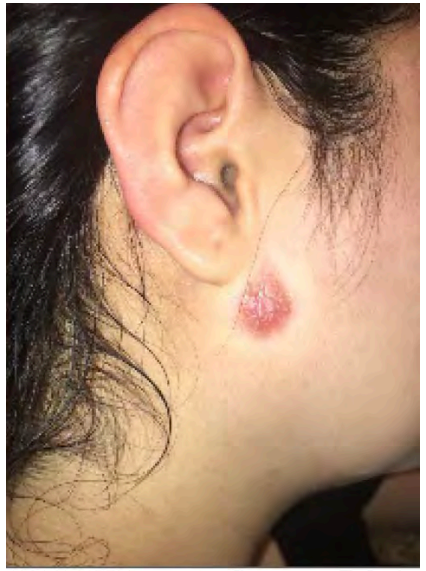
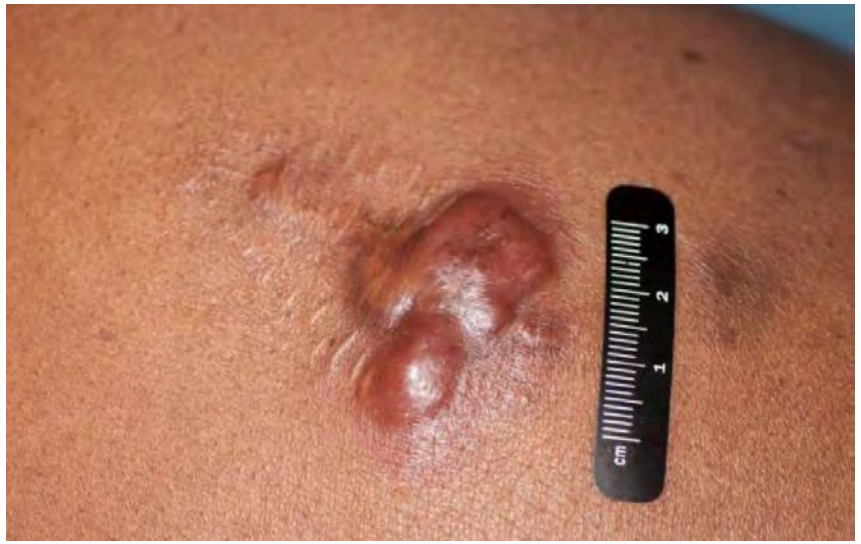
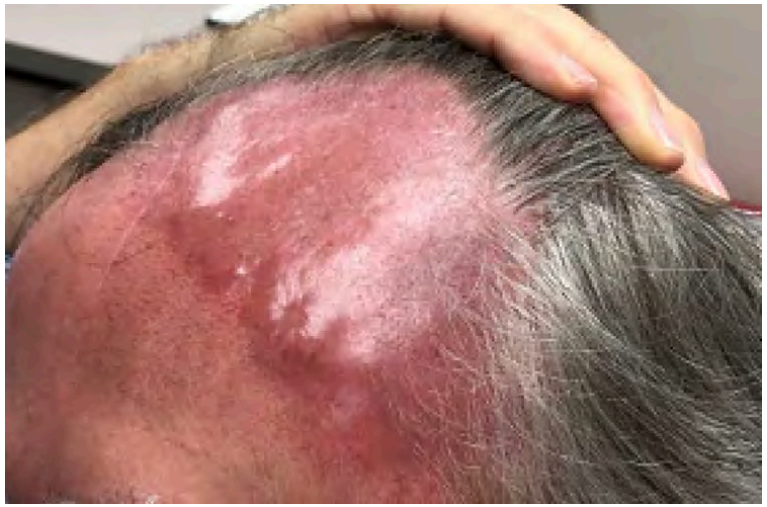
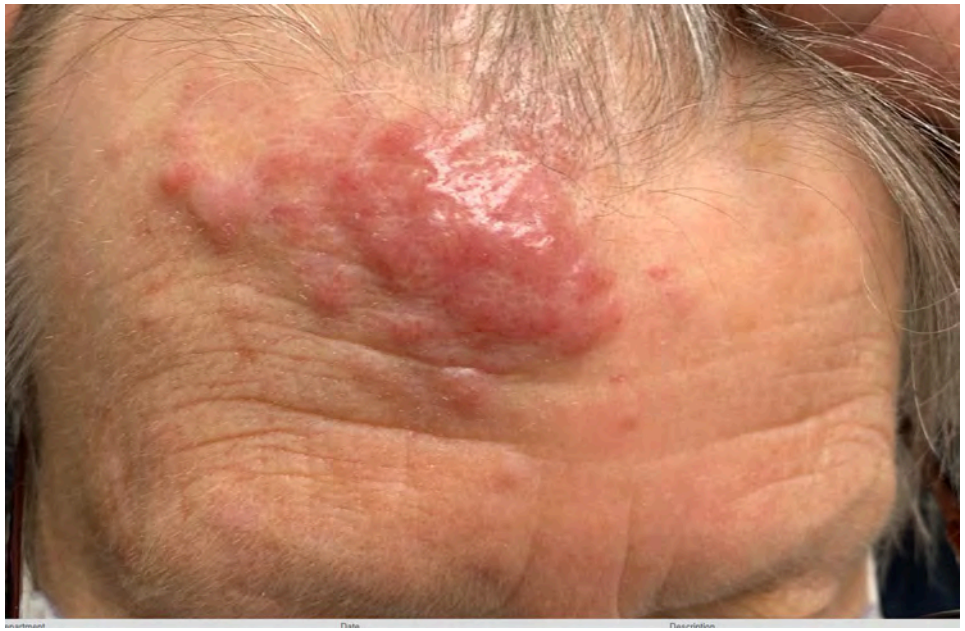
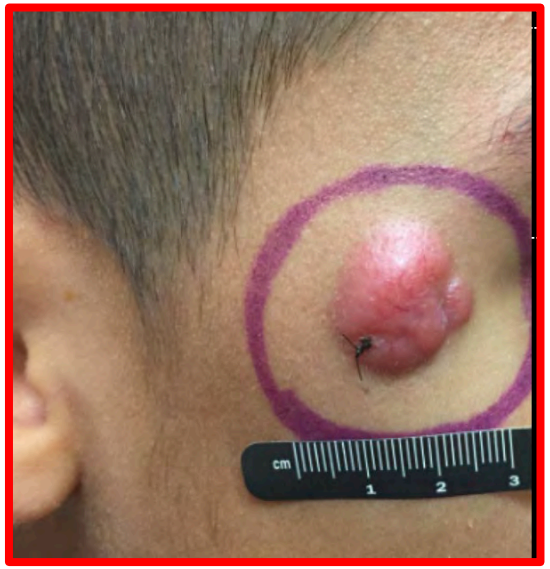
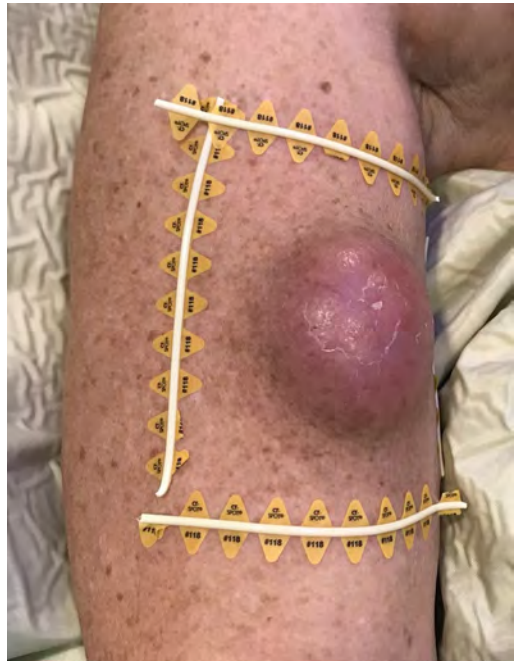



cm
1
2
3

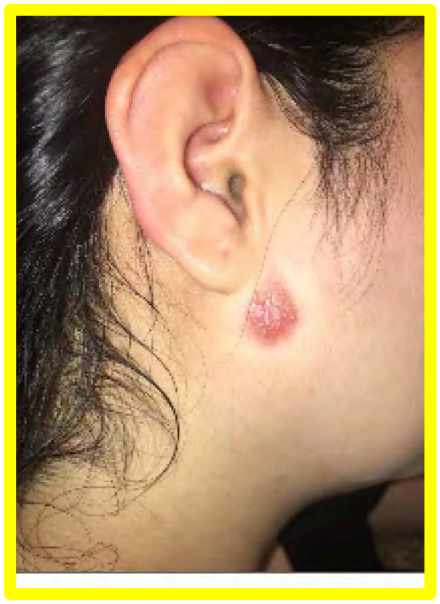




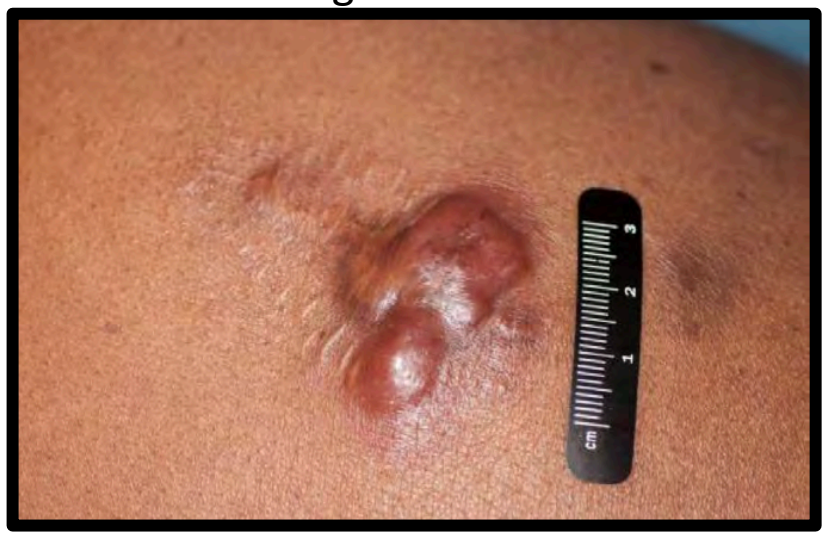

cm
1
2
3



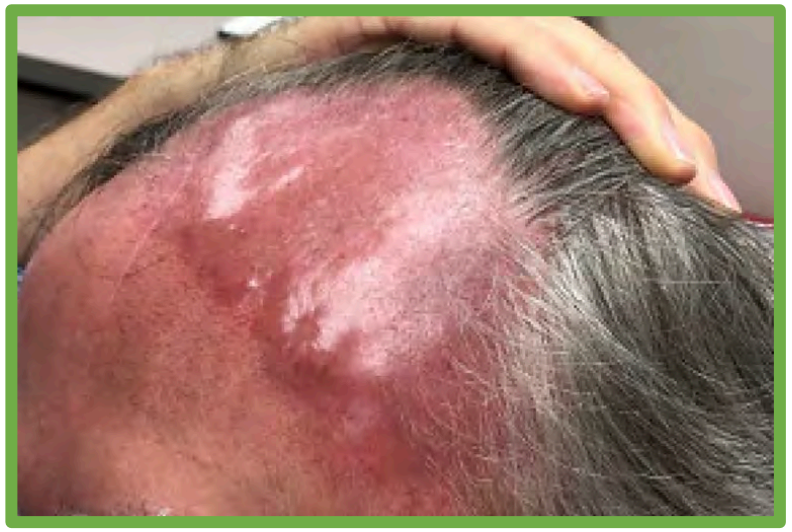
Follicle center



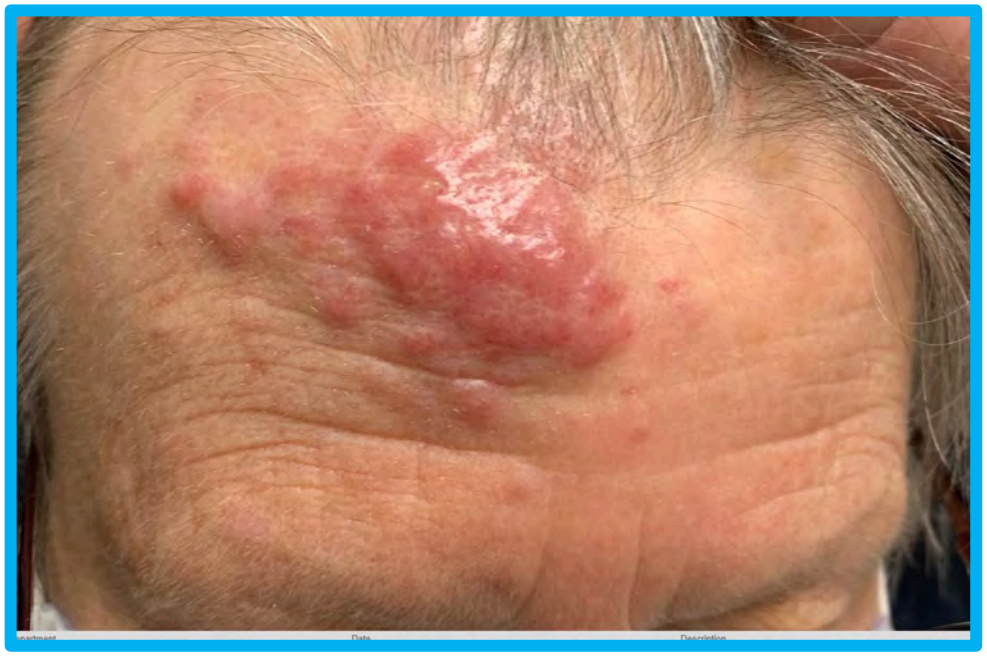
Marginal Zone



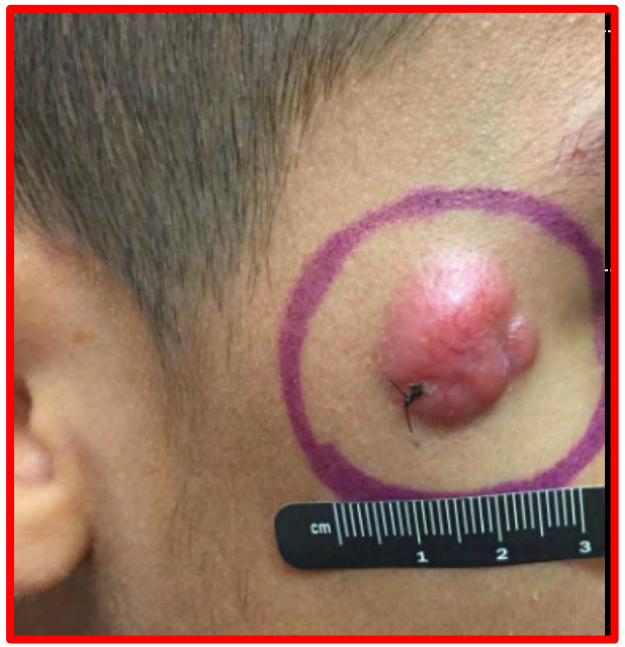
Follicular



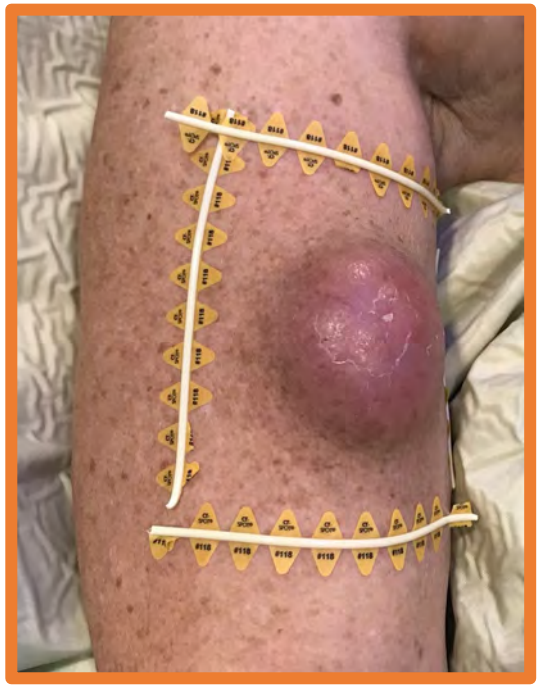
Chloroma

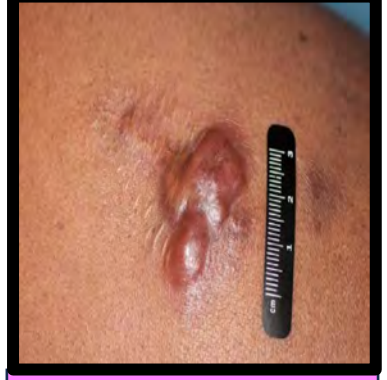


CD4+ small medium

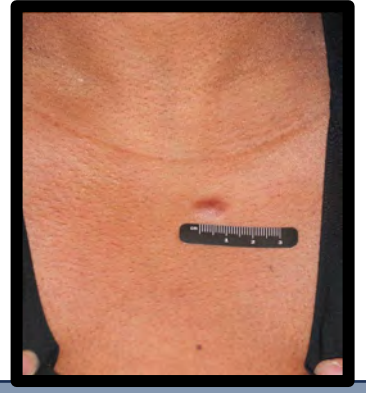


Mantle cell

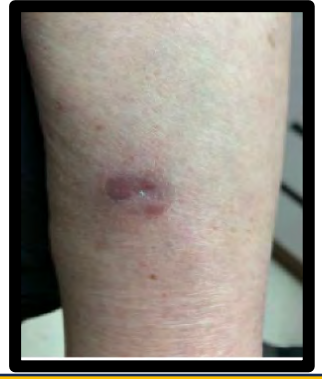




PCMZL



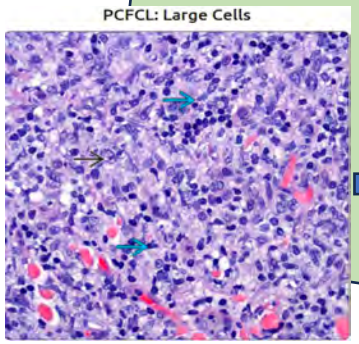
PCFCL



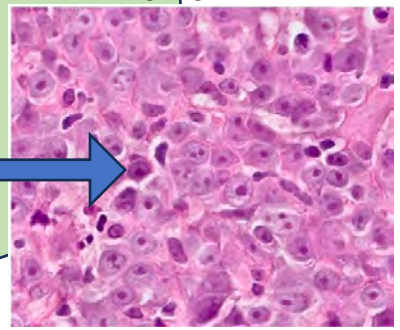
PCLBCL-LT

Small lymphocytes

Large cells



PCLBCL-LT



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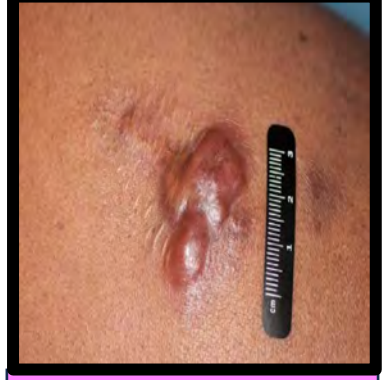
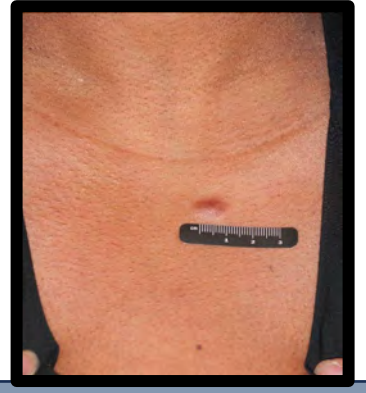
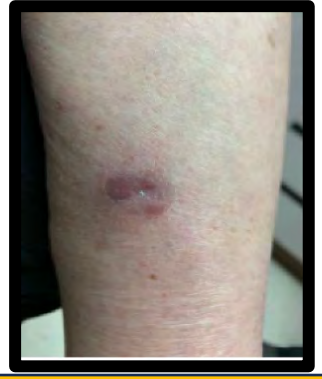


PCMZL



PCFCL



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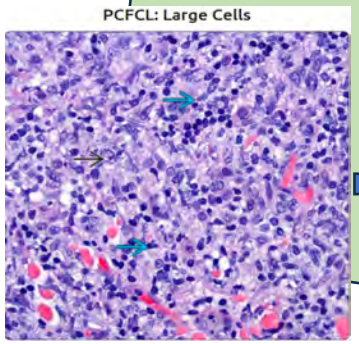
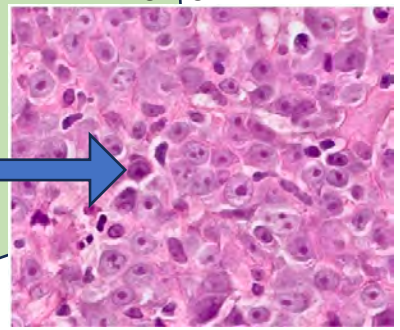


PCLBCL-LT



Local Radiation

Excellent Outcome
95-99%

Chemotherapy
+Radiation

Outcome
50%

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The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

Rein Willemze,[1] Lorenzo Cerroni,[2] Werner Kempf,[3] Emilio Berti,[4] Fabio Facchetti,[5] Steven H. Swerdlow,[6] and Elaine S. Jaffe[7]

	PCFCL, diffuse large cell	PCDLBCL, LT
Clinical presentation	Localized skin lesions on head or trunk; multifocal lesions in rare cases	Skin tumors on (lower) leg(s); uncommonly, lesions at other sites than the leg (15%)
Histopathology		
Morphology tumor cells	Predominance of large centrocytes; centroblasts may be present, but not in confluent sheets	Predominance or confluent sheets of centroblasts and/or immunoblasts
Admixed T cells	Often abundant	Sparse, mainly perivascular
Immunohistochemistry		
B-cell lineage markers	$CD20^+$, $CD79a^+$, $PAX5^+$, IgM^-, IgD^-	$CD20^+$, $CD79a^+$, $PAX5^+$, IgM^+, $IgD^{+/-}$; monotypic light chain expression
Germinal center markers	$BCL6^+$, $BCL2^-$, $CD10^-$	$BCL6^{+/-}$, $BCL2^+$, $CD10^-$
Postgerminal center markers	$IRF4/MUM1^-$, $FOXP1^-$	$IRF4/MUM1^+$, $FOXP1^+$
MYC expression	Negative	Positive (65%-80%)
CD21/CD35: (remnants) of FDC networks	Sometimes present	Absent
Molecular genetics		
Gene expression profile	GCB-type DLBCL	ABC-type DLBCL
Translocations *BCL6*, *MYC*, *IgH*	Absent	*BCL6* (30%), *MYC* (35%), *IgH* (50%)
Array-based CGH; FISH	Amplification 2p16.1	Deletion 6q arm (*BLIMP1*:60%)
	Deletion 1p36	Deletion 9p21.3 (*CDKN2A*:67%)
	Deletion 14q11.2-q12	
NF-κB pathway mutations	No *MYD88* mutation	*MYD88* (60%), *CD79B* (20%), *CARD11* (10%), *TNFAIP3/A20* (40%),
Treatment and clinical course		
First line of therapy	Radiotherapy	R-CHOP
Relapse rate	30%	70%
Extracutaneous dissemination	10%	45%
Prognosis	5-y survival, 95%	5-y survival, 50%-60%

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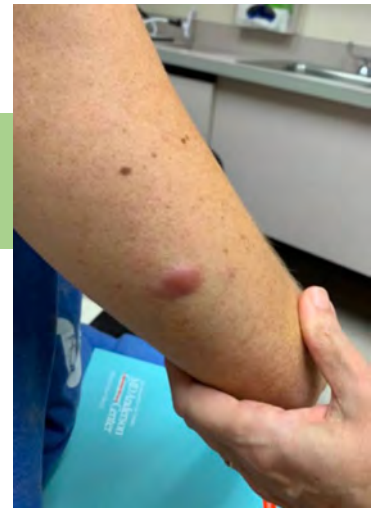
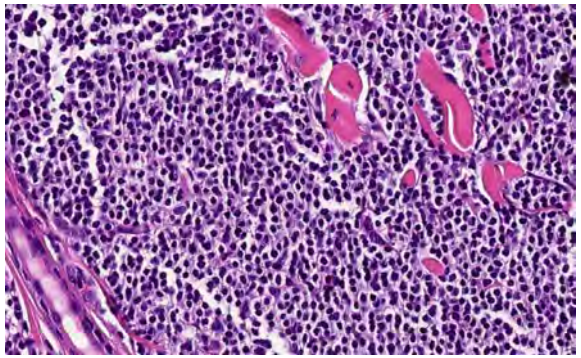
Primary Cutaneous Marginal Zone Cell Lymphoma

Distinct primary cutaneous B-cell lymphomas are currently recognized as a stand-alone entity

- Found on the arms or trunk rather than in the head and neck region
- Bone marrow Limited value with only 2% involved



“**marginal zone” origin**
neoplastic cells largely small lymphocytes, plasma cells



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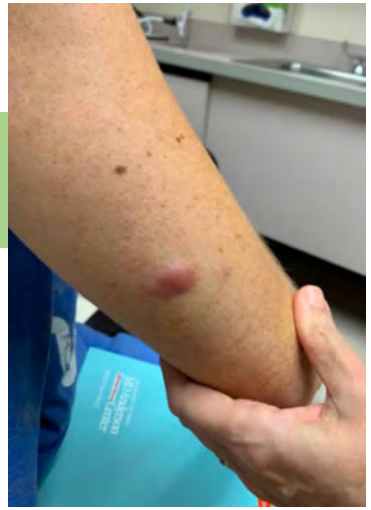

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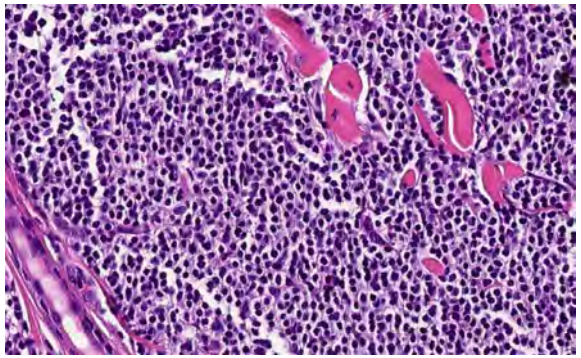

•**Non class switched** resembles extracutaneous MZL
arises in the setting of chronic Th1 type inflammation associated cytokines including IFNγ and IL2
Blood 2008;112:3355

•**Heavy chain class switched** Majority of cutaneous MZL, histologically distinct from extracutaneous MZL
chronic Th2 type inflammation, arise in individuals with an allergic or atopic diathesis
Am J Surg Pathol 2010;34:1830

Primary Cutaneous Marginal Zone Cell Lymphoma

CD5 negative,
CD10 negative,
BCL6 negative,
cyclin D1 negative

T(14;18) t (11:18) trisomy 3, 8 can be found

Primary Cutaneous Marginal Zone Cell Lymphoma

CD5 negative,
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T(14;18) t (11:18) trisomy 3, 8 can be found

BCL2 positive,
CD20 positive B-cells.
Follicles can be BCL6 can be positive
CD21 highlights follicular dendritic cell meshwork
in most but not all cases which most frequently include at least some which are disrupted.
A predominance of T cells is present in many cases

Primary Cutaneous Marginal Zone Cell Lymphoma

Etiology

- *Borrelia burgdorferi*
- positive *H. pylori* serology compared to a control group
- influenza vaccination site
- Tattoos have also been implicated on rare occasion
- higher incidence of autoimmunity and a variety of gastrointestinal tract disorders,
- Sjögren syndrome, rheumatoid arthritis, Hashimoto thyroiditis and ulcerative colitis

Outcome

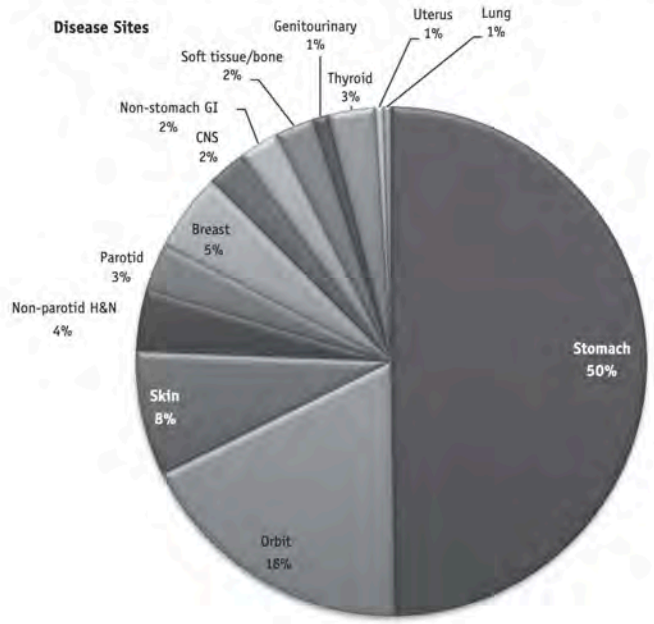
99–100% 5-year disease specific survival
93% overall survival at 10 years

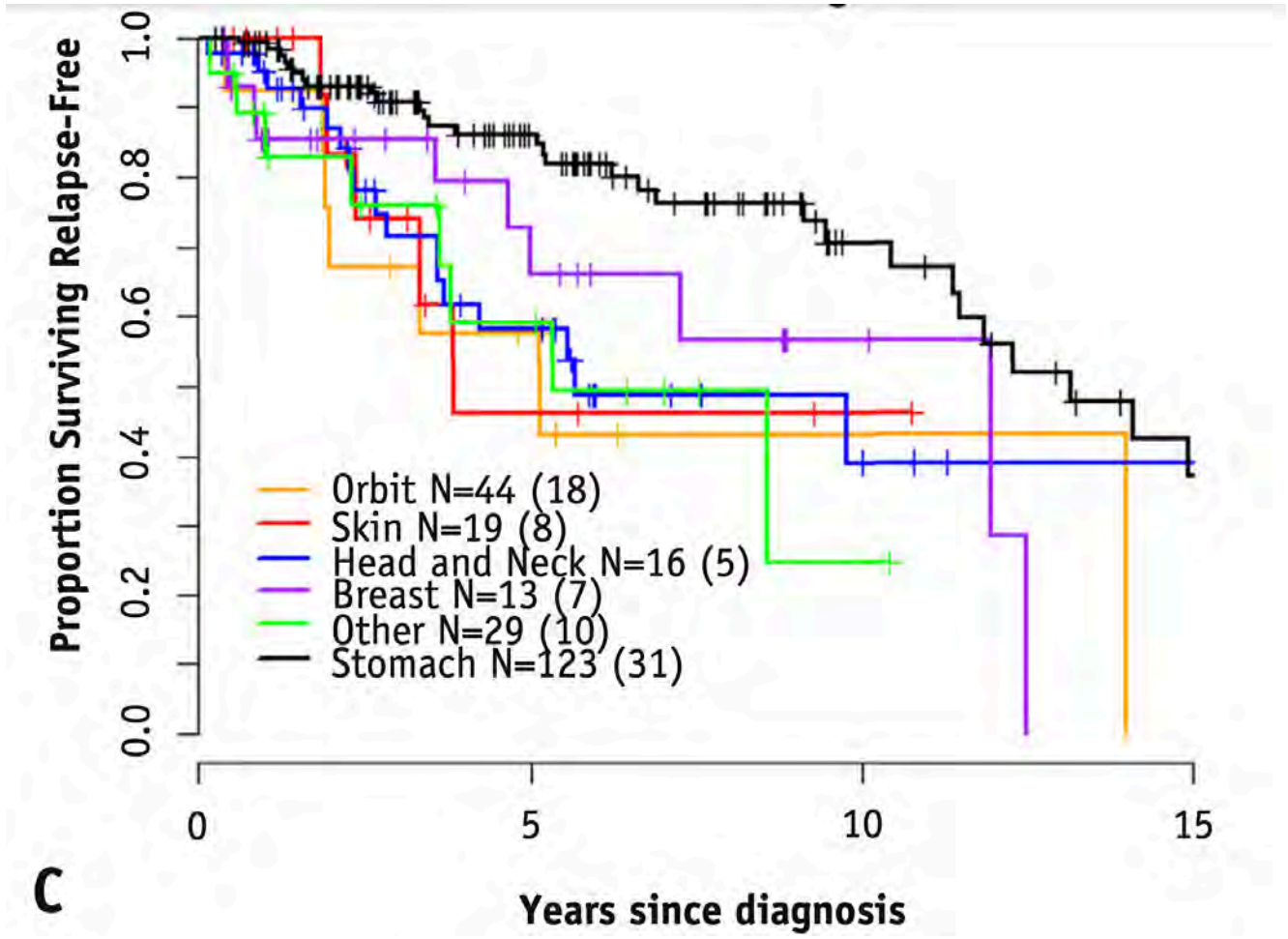
Servitje O. J Am Acad Dermatol 2013;69:357–365
Haverkos B, 2015;20:1161–1166.
Hallermann. Acta Derm Venereol 2011;91:521–525.

Treatment: Local Radiation therapy

Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,* Scott Navarrett, BS,† Meier Hsu, MS,§ Ariela Noy, MD,‖ Carol Portlock, MD,‖ and Joachim Yahalom, MD*





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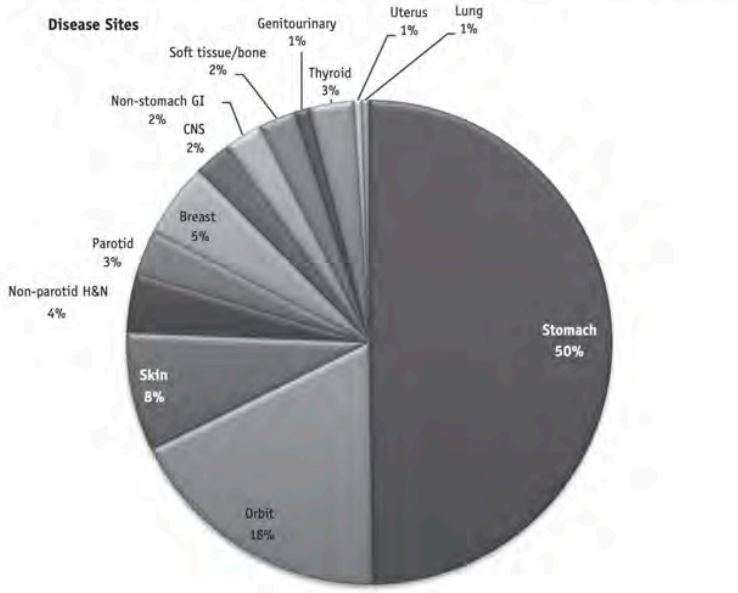
Volume 92 • Number 1 • 2015 Marginal zone lymphoma long-term RT outcomes



Aggressive therapy does not improve the relapse rate
Relapse does not decrease survival

Higher dose control local disease but relapse still happen

Primary cutaneous B-cell lymphoma (non-leg type) has excellent outcomes even after very low dose radiation as single-modality therapy

Mani Akhtari[1,2], Jay Paul Reddy[1], Chelsea C. Pinnix[1], Pamela K. Allen[1], Eleanor M. Osborne[1], Jillian R. Gunther[1], Sarah A. Milgrom[1], Grace L. Smith[1], Christine F. Wogan[1], Nathan Fowler[3], Maria Alma Rodriguez[3] & Bouthaina Dabaja[1]

[1]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*Department of*

- 39 patients with 42 lesions (including 16 with PCFCL)
- Received radiation as the only treatment
- all lesions achieved complete remission, no in-field relapse
- 7/42 patients had an out-of-field relapse.
- 12 Gy (including 4 Gy) are equally effective as doses of > 12 Gy

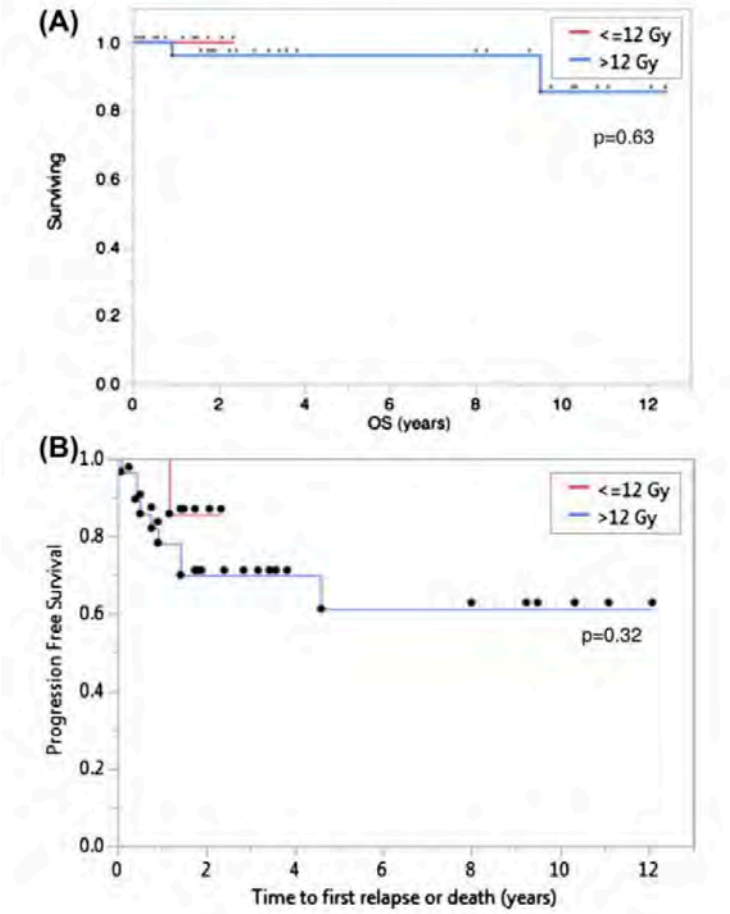
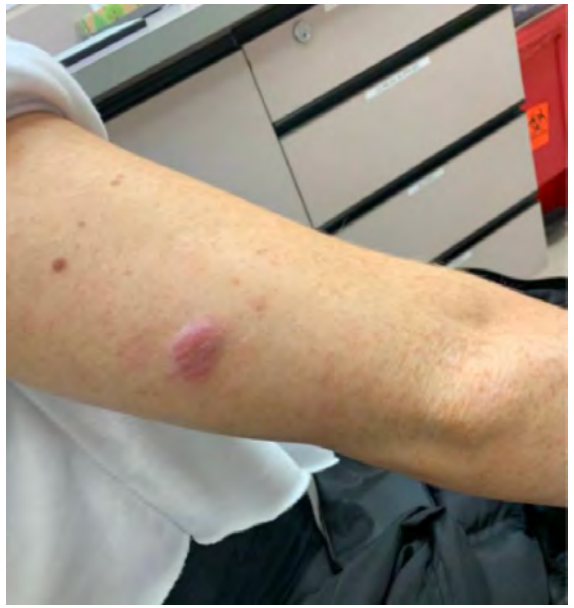


Figure 1. (A) Overall survival for patients treated with ≤ 12 Gy (red line) and > 12 Gy (blue line); $p = 0.63$. (B) Progression-free survival for lesions treated with ≤ 12 Gy (red line) and > 12 Gy (blue line); $p = 0.32$.

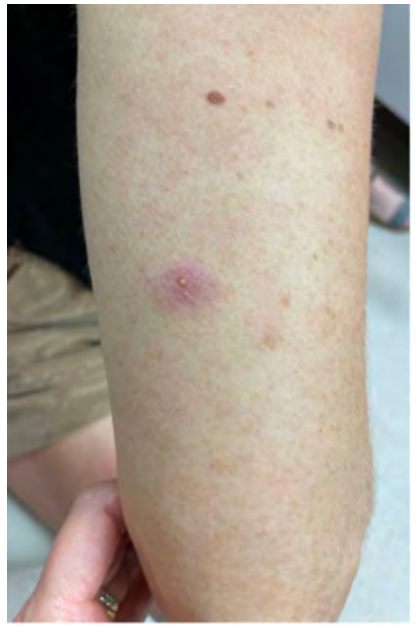
Primary Cutaneous Marginal Zone Cell Lymphoma

23 year old female
Presented with right arm
Red papule
PC-Marginal zone lymphoma

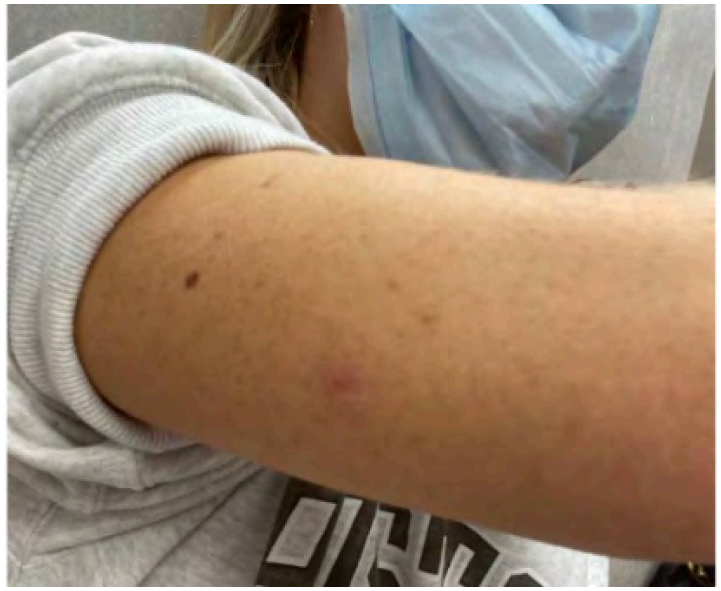


2 Gy x 2 fractions

3 months later



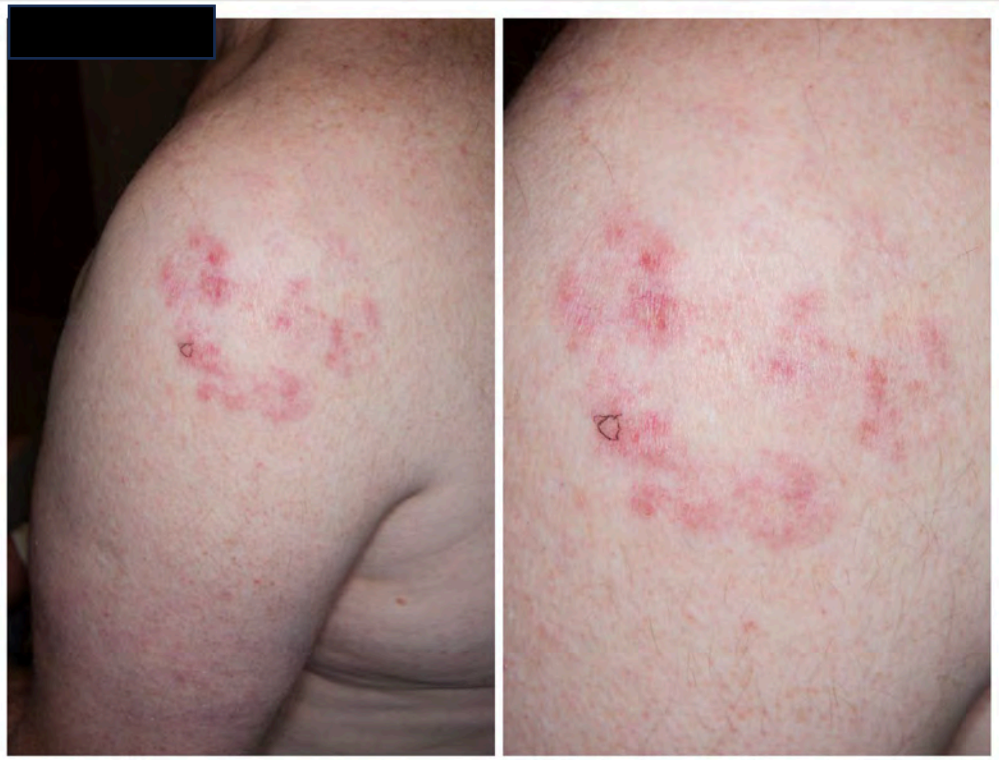
One year later



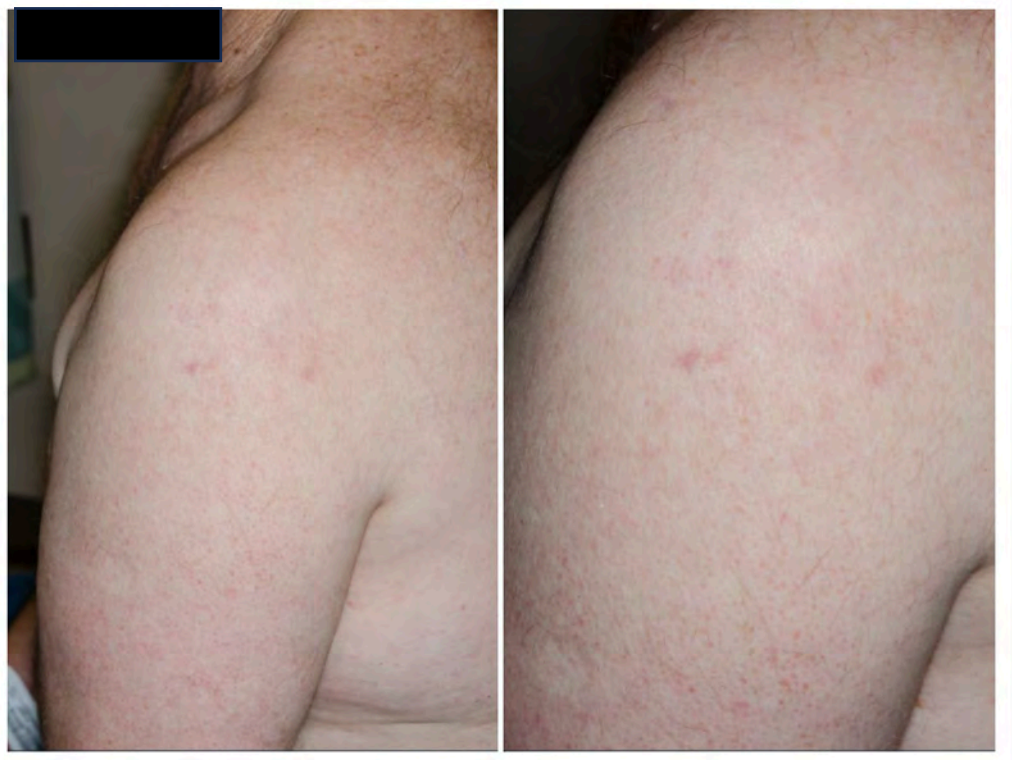
History of IBD ? Ulcerative colitis
Polycystic ovary disease

Primary Cutaneous Marginal Zone Cell Lymphoma

Multiple lesions at presentation

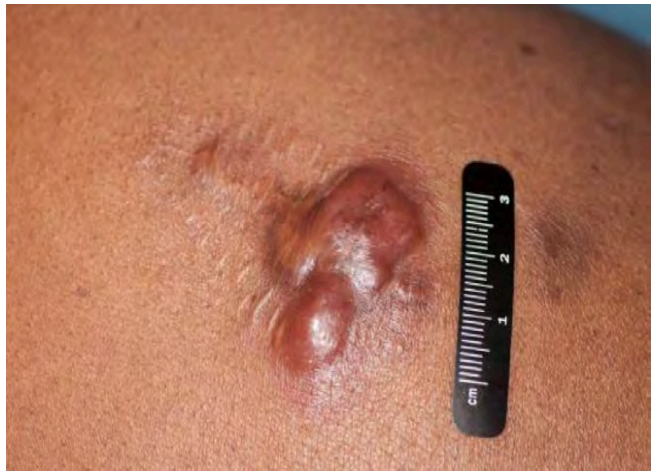


One year after 4 Gy Electron

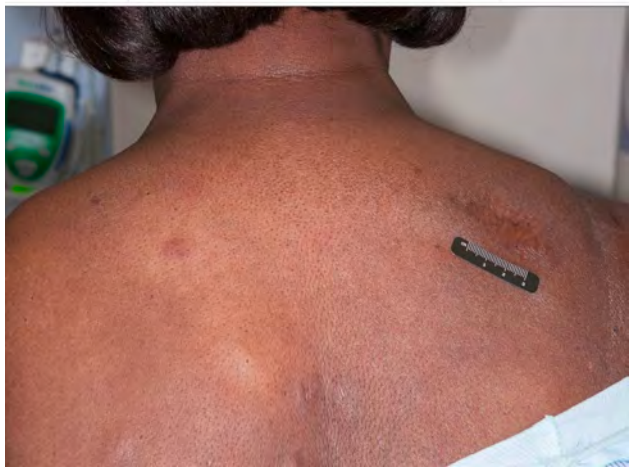


Primary Cutaneous Marginal Zone Cell Lymphoma

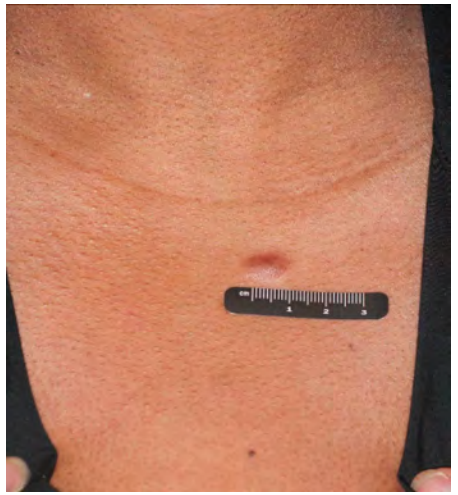
46 year old, PCMZL
Upper back



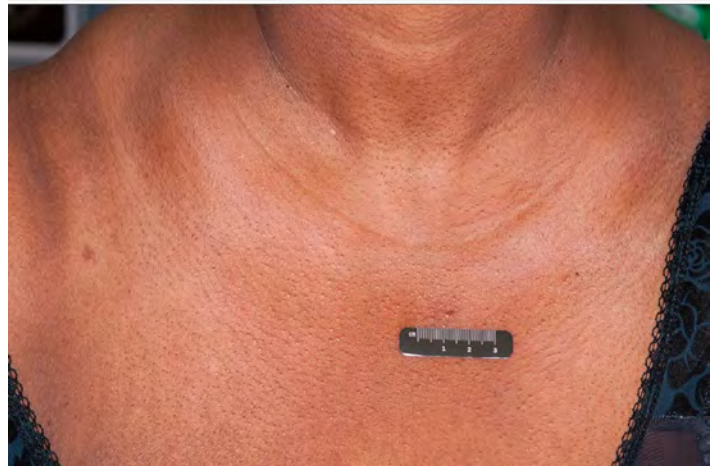
6 months after 4 Gy



3 years later recurrence
Anterior chest

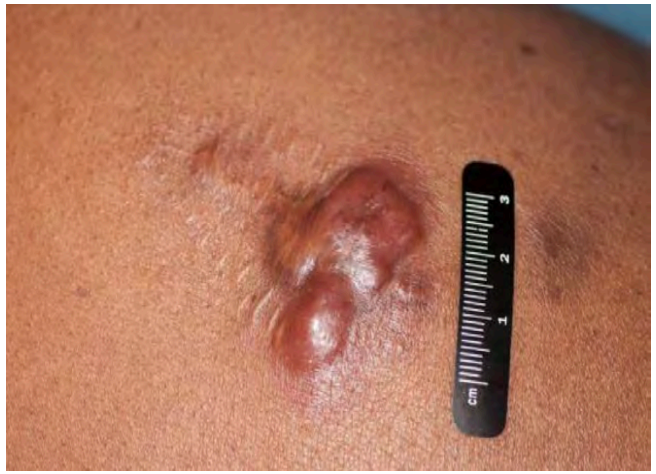


Repeat 4 Gy,
6 years later still in CR

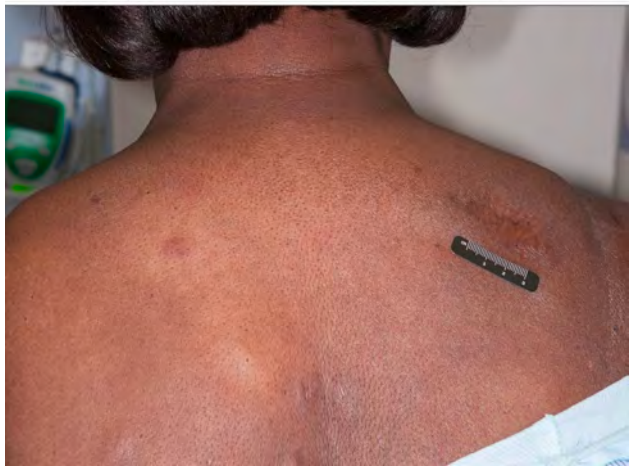


Primary Cutaneous Marginal Zone Cell Lymphoma

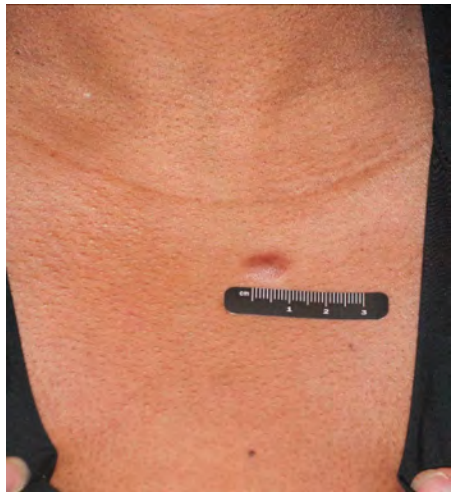
46 year old, PCMZL
Upper back



6 months after 4 Gy



3 years later recurrence
Anterior chest



Repeat 4 Gy,
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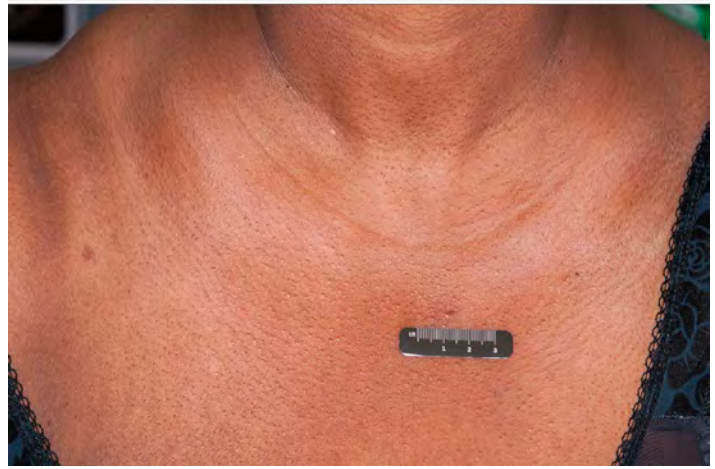
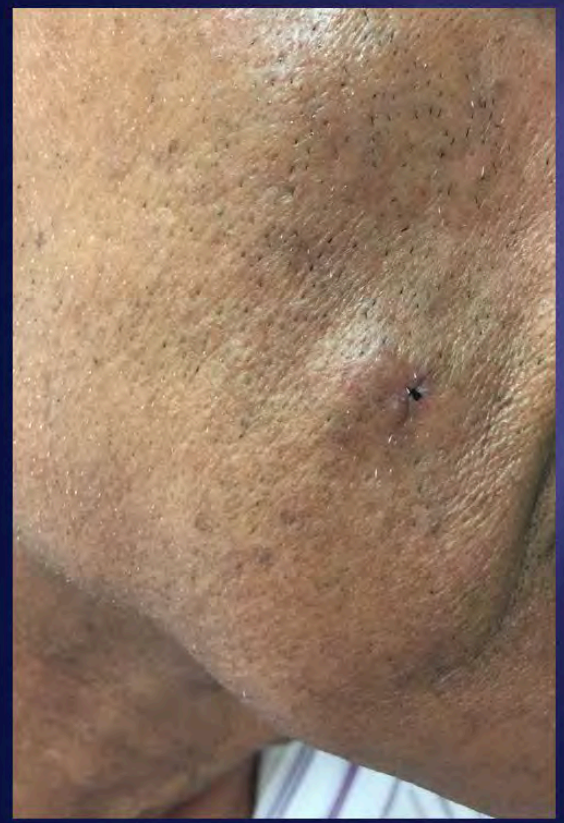
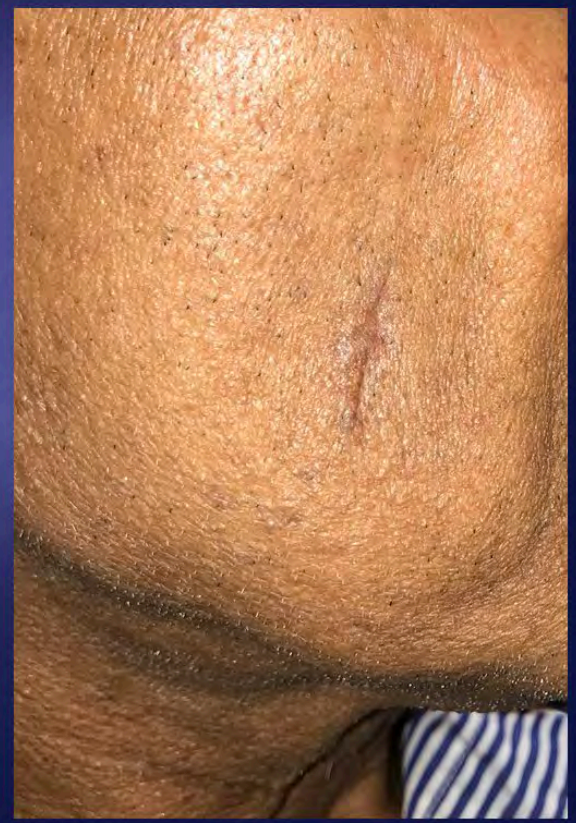


Out of field recurrence is frequent and can be managed with 4 Gy

Spontaneous resolution while thinking if he wants radiation!!



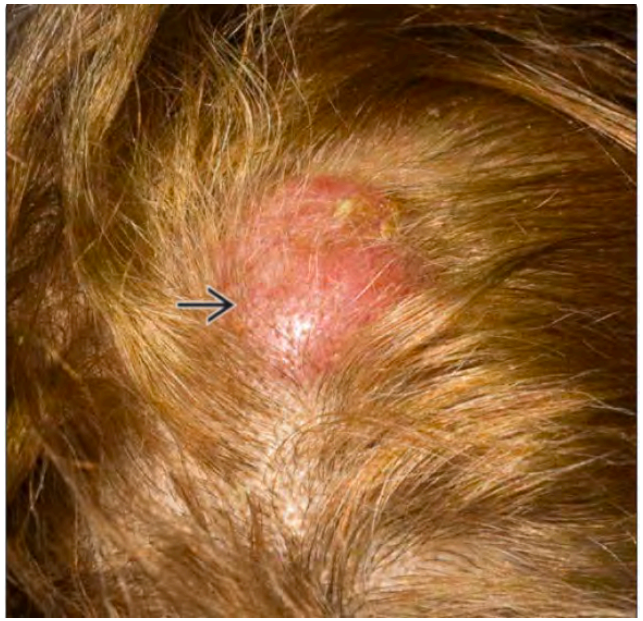


Primary Cutaneous Follicle Center Lymphoma

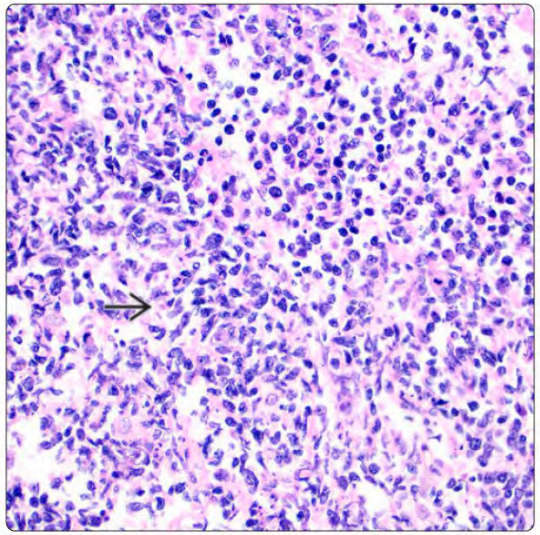
Location: Mostly in head and neck, trunk, back, arms
Some cases of PCFCL can present on legs

- Most primary PCFCL have follicular pattern
  - Confused with follicular lymphoma
  - Absent, negative t (14;18)

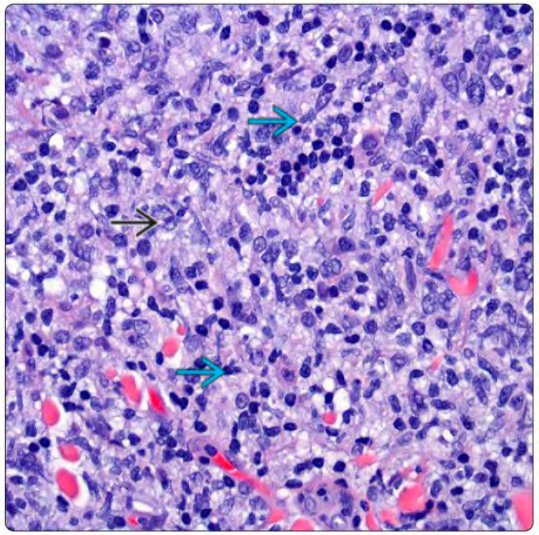
- Large cells can be present at various percentage
  - confused with Large cell



PCFCL: Increased Large Cells



PCFCL: Large Cells



Decrease CD21 follicular dendritic cell meshwork

Decreased predominance of T cells

Primary Cutaneous Follicle Center Lymphoma

Resembling MZL

Tumor **growth** starts in a follicular pattern

cells CD20+, CD79a+, bcl6+,
in a network of CD21+

At an early stage, the abnormal follicles are formed
over time the lesions mature------ the follicular pattern can be erased.

T-cells decrease

At a Later stage large cells become prominent with progression

Rule out DLBCL
/Leg type

The key pathologic feature, the presence, especially in the later stages, of a monotonous population of **large follicle center cells.**

• *Immunophenotype*

CD10(+), Bcl-6(+) Bcl-2 Neg
IRF-4/MUM1(-), FOXP1(-), MYC - p63(-/+)

Primary Cutaneous Follicle Center Lymphoma	Immunohistochemistry	Primary Cutaneous Large B Cell Lymphoma-Leg Type
Positive	Bcl-6	Mostly positive
Often negative	Bcl-2	Positive ~ 90%
Positive in follicular areas	CD10	Negative
Negative	MUM1	Positive, 50-80%
Negative	FOXP1 and MYC	Positive
Negative	Bcl-2(+)/MYC(+)	Common

	Molecular Genetics	
Different from nodal follicular lymphoma		Similar to systemic DLBCL; *MYD88* L265P activating mutation
Negative	*MYC*, *BCL6* rearrangement by FISH	Can be present
Absent	Deletions of chr 9p21.3 (containing *CDKN2A* and *CDKN2B*)	Reported in 67% of cases
Uncommon	Amplification of *BCL2* and *MALT1* genes	Common
~ 10-40% of cases	t(14;18)(q32;q21)	Absent

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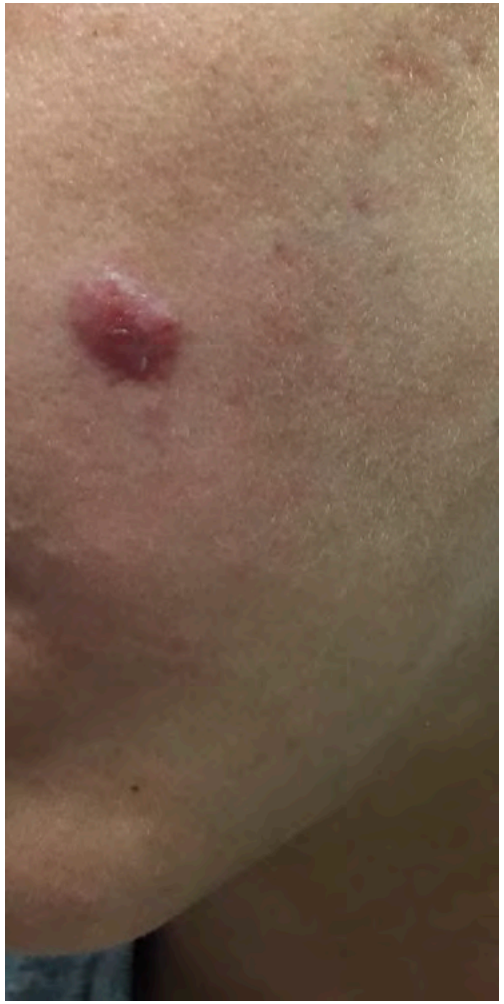
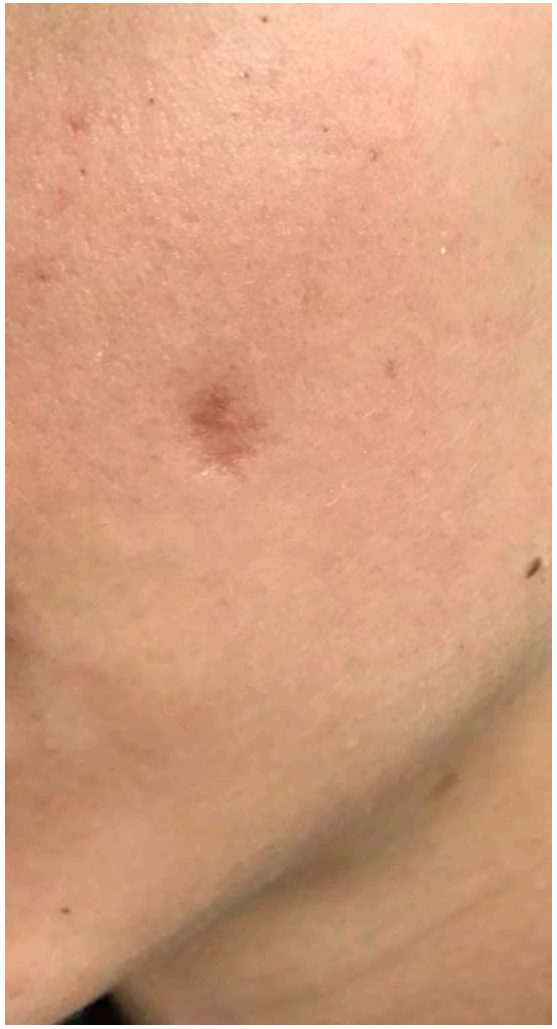


Electron
Therapy
With 4 Gy

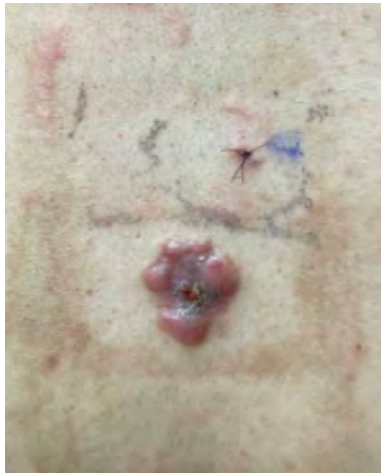
One year later



Primary Cutaneous Follicle Center Lymphoma

Presentation

37 year old woman presented with 2 years history of growing mass in the upper back.



Pathology:

suggestive of Marginal zone but the large cells led
To suspect a primary DLBCL, and she was about to start chemotherapy

Staging work up negative, PET scan SUV of 4.1.

Pathology reviewed again and suggested a **Primary Cutaneous follicle center**

Treated with 2 Gy x 2 fractions

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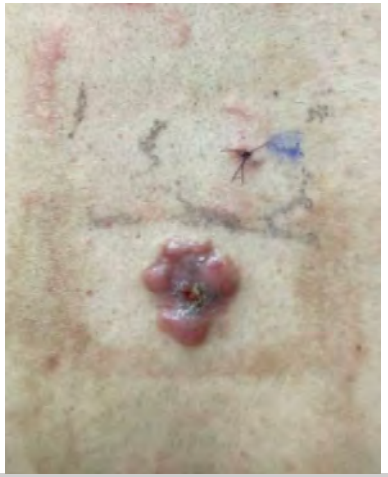
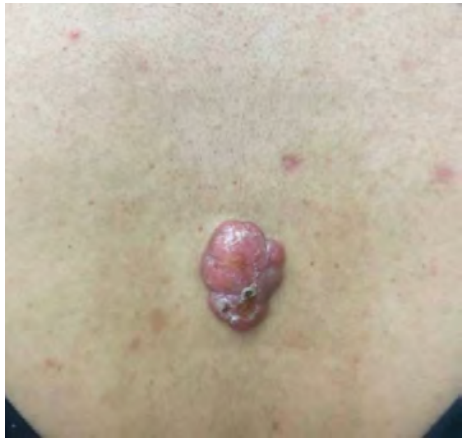


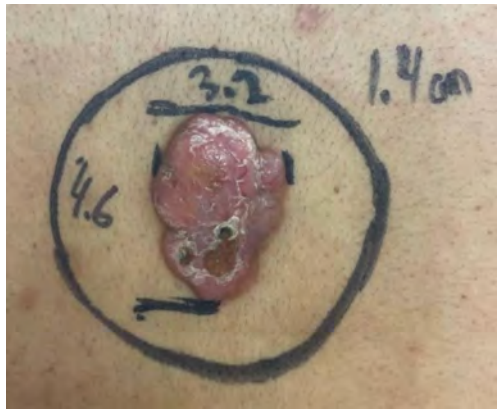
Treated with 2 Gy x 2 fractions

Four months later the lesion

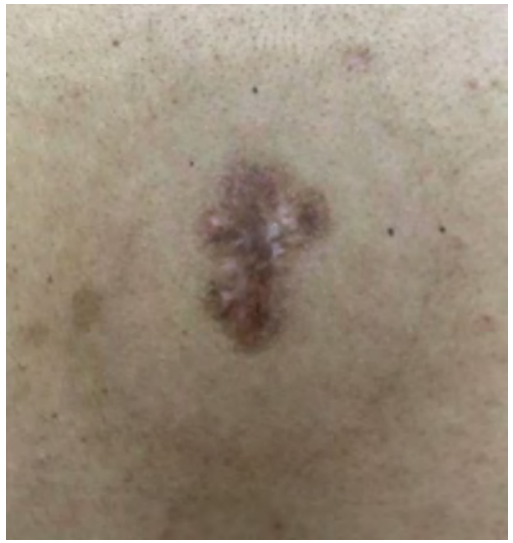
Lesion came back



Completed the dose to 20 Gy at 2 Gy



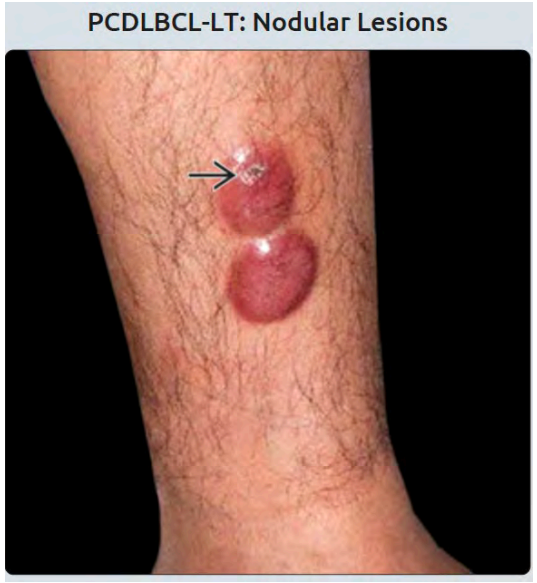
15 months later



Primary Cutaneous Large B Cell Lymphoma-Leg Type

20% of Primary Cutaneous Lymphoma

Most (~ 85%) cases arise in the skin of the lower leg(s)
○ Subset (~ 15%) arises in skin of the trunk, arms, head, and Neck
• Single or multiple lesions at the time of presentation



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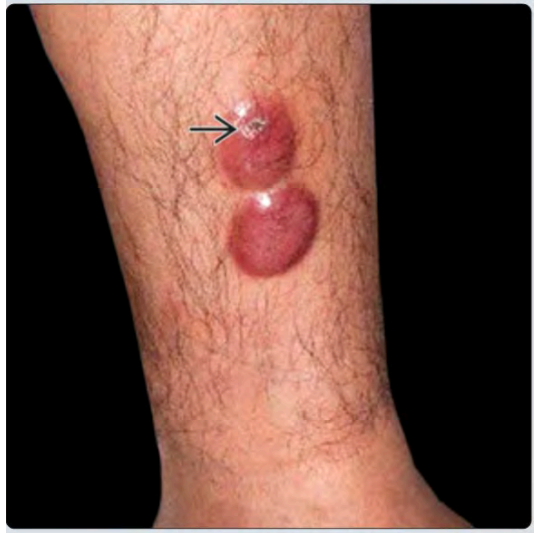
PCDLBCL-LT: Nodular Lesions



Pathologic Interpretation Pearls

MICROSCOPIC

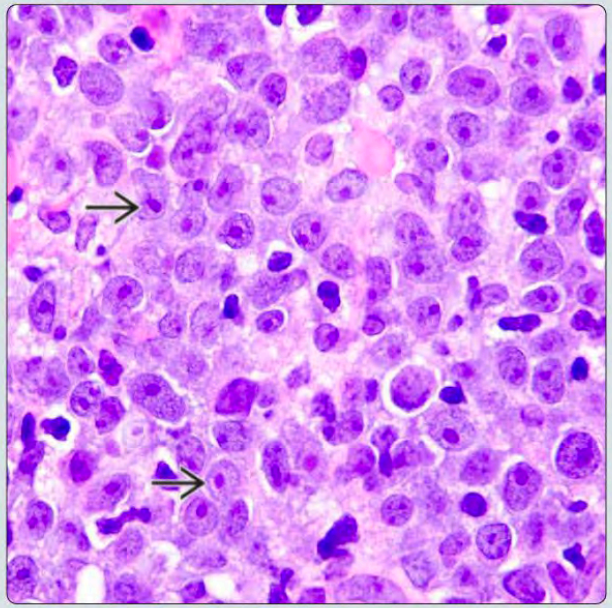
- Diffuse pattern of involvement in dermis
- Monotonous and cohesive large immunoblasts
- Few small reactive T cells in background
- No epidermotropism

ANCILLARY TESTS

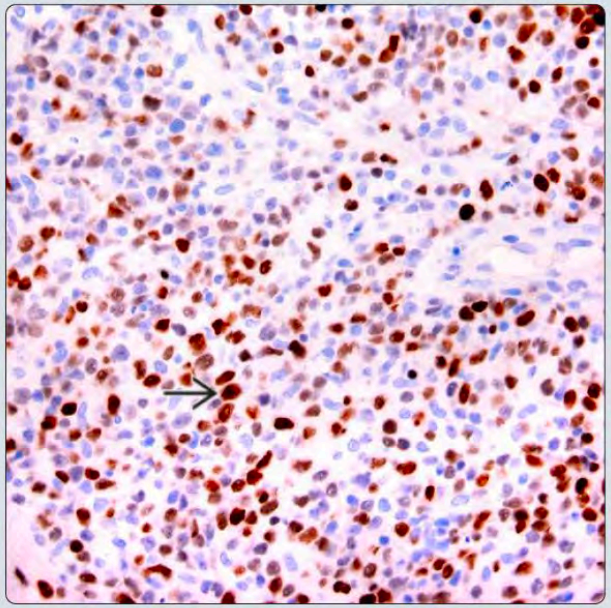
- Pan-B-cell antigens (+), Bcl-2(+), Bcl-6(+)
- MUM1(+), FOXP1(+), IgM(+), CD10(-)
- FISH may show rearrangements of *MYC*, *BCL6*, or *IGH* genes in ~ 10-20% of cases

(Left) *The lymphoma cells in a diffuse , and consist ly round ated i , munoblasts. tely 50-80% CL-LT are , a marker erminal is case, ~ oma cells*

PCDLBCL-LT: Immunoblastic Cells



PCDLBCL-LT: MUM1(+)



Primary Cutaneous Large B Cell Lymphoma-Leg Type

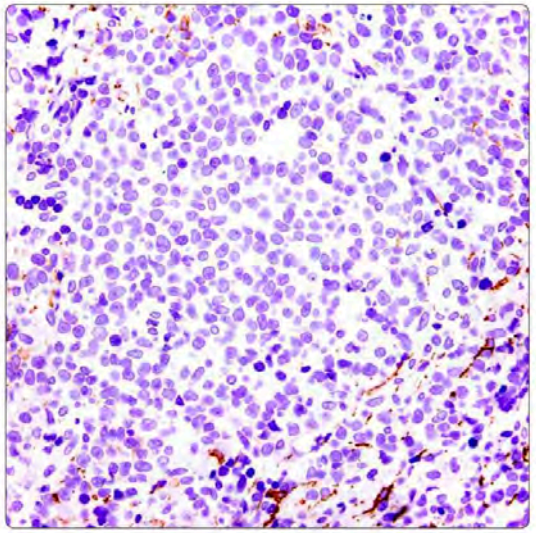
The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

Rein Willemze,[1] Lorenzo Cerroni,[2] Werner Kempf,[3] Emilio Berti,[4] Fabio Facchetti,[5] Steven H. Swerdlow,[6] and Elaine S. Jaffe[7]

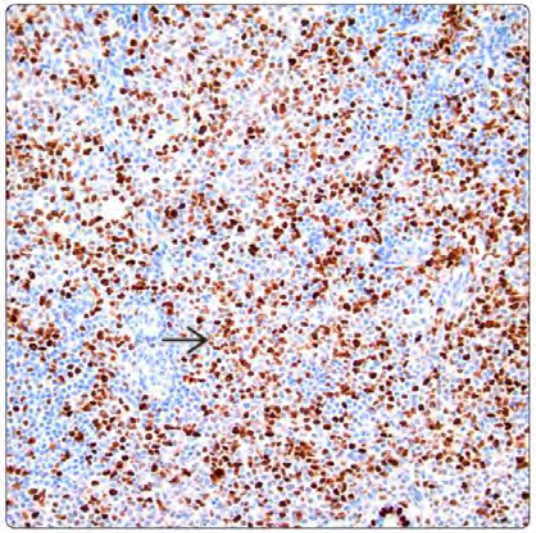
Histopathology	
Morphology tumor cells	Predominance or confluent sheets of centroblasts and/or immunoblasts
Admixed T cells	Sparse, mainly perivascular
Immunohistochemistry	
B-cell lineage markers	$CD20^{+}$, $CD79a^{+}$, $PAX5^{+}$, IgM^{+}, $IgD^{+/-}$; monotypic light chain expression
Germinal center markers	$BCL6^{+/-}$, $BCL2^{+}$, $CD10^{-}$
Postgerminal center markers	$IRF4/MUM1^{+}$, $FOXP1^{+}$
MYC expression	Positive (65%-80%)
CD21/CD35: (remnants) of FDC networks	Absent
Molecular genetics	
Gene expression profile	ABC-type DLBCL
Translocations *BCL6*, *MYC*, *IgH*	*BCL6* (30%), *MYC* (35%), *IgH* (50%)
Array-based CGH; FISH	Deletion 6q arm (*BLIMP1*:60%) Deletion 9p21.3 (*CDKN2A*:67%)
NF-κB pathway mutations	*MYD88* (60%), *CD79B* (20%), *CARD11* (10%), *TNFAIP3/A20* (40%),

Primary Cutaneous Large B Cell Lymphoma-Leg Type

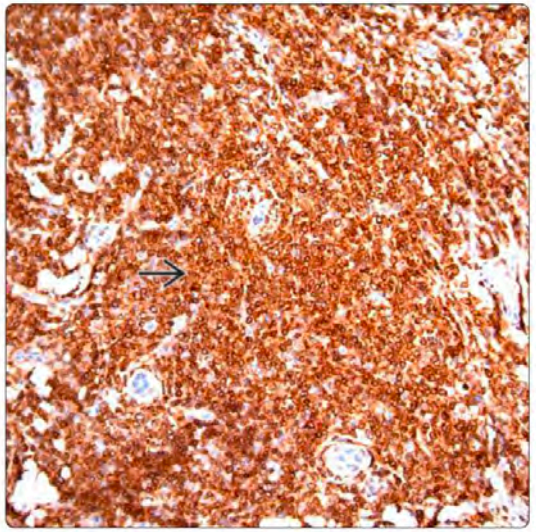
PCDLBCL-LT: CD10(-)



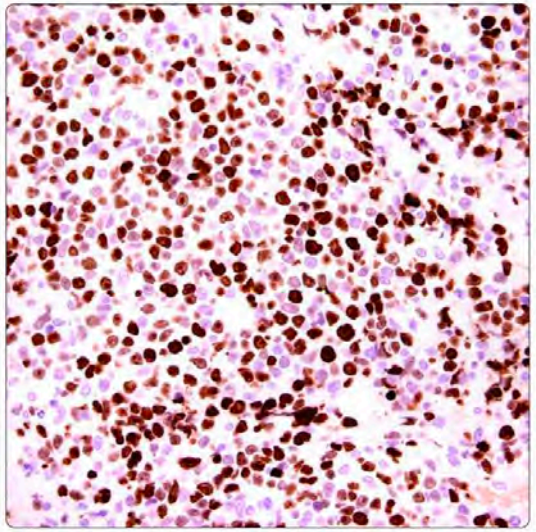
PCDLBCL-LT: Bcl-6(+)



PCDLBCL-LT: BCL-2(+)



PCDLBCL-LT: Ki-67



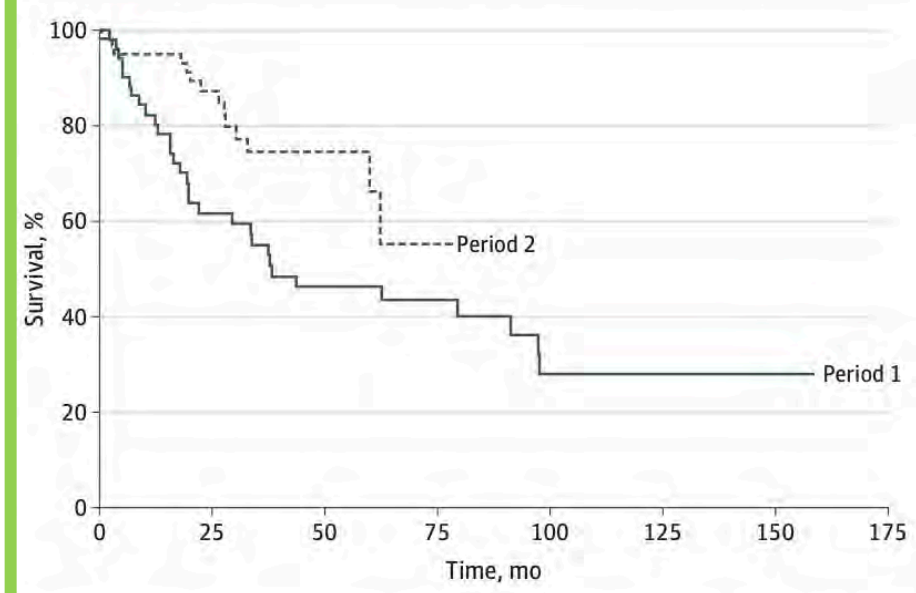
Original Investigation

Improvement of Survival in Patients With Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type, in France

Florent Grange, MD, PhD; Pascal Joly, MD, PhD; Coralie Barbe, MD; Martine Bagot, MD, PhD;

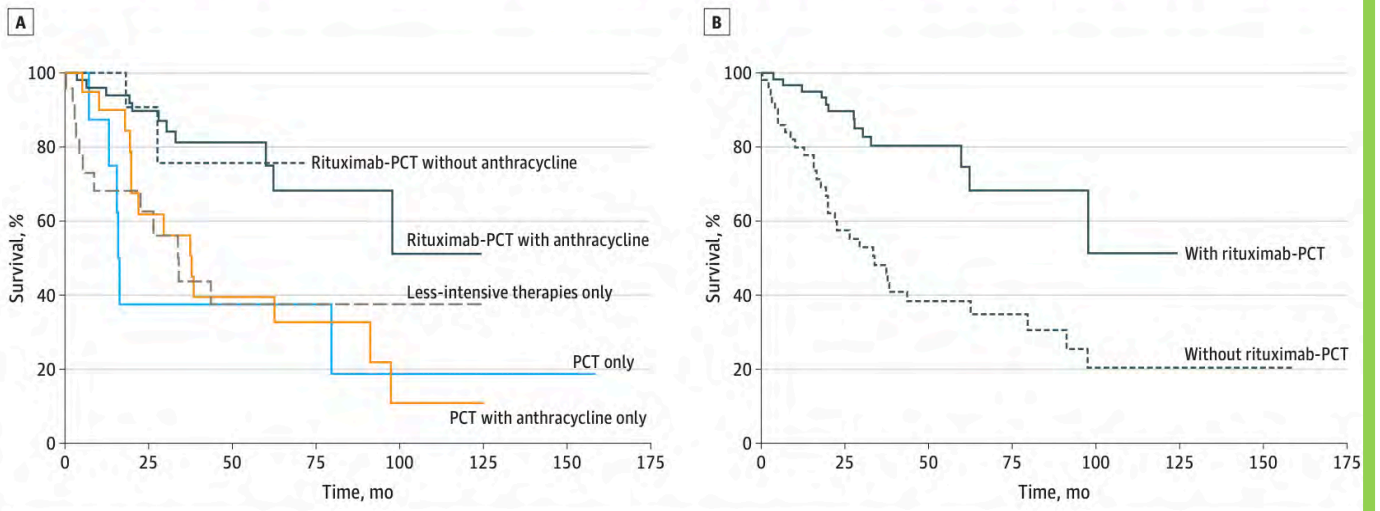
JAMA Dermatology May 2014 Volume 150, Number 5

Figure 1. Specific Survival of 115 Patients With a Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type, According to the Period of Diagnosis



Period 1 included 54 patients; period 2 included 61 patients. The difference in survival was significant ($P = .01$).

Figure 2. Specific Survival of 115 Patients With a Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type, According to Type of Treatment



A, Survival of patients according to the most intensive therapy received. The therapies consisted of a combination of rituximab and polychemotherapy (PCT) with anthracycline, rituximab-PCT without anthracycline, PCT with anthracycline (without rituximab), PCT only (without anthracycline and/or rituximab), and less-intensive therapies only (including single-drug chemotherapy and radiotherapy). The global difference between the curves was significant ($P = .002$). B, Sixty-three patients received treatment at any time with rituximab-PCT; 52 patients only received other treatments (including PCT without rituximab). The difference between rituximab-PCT regimens and other treatments was significant ($P < .001$).

- m January 1, 1988, to December 31, 2003 (period 1), and from January 1, 2004, to December 31, 2010 (period 2)

Clinical Investigation: Lymphoma

Treatment and Outcomes in Patients With Primary Cutaneous B-Cell Lymphoma: The BC Cancer Agency Experience

Sarah N. Hamilton, MD,*,† Elaine S. Wai, MD,‡ King Tan, MBBS,§ Cheryl Alexander,‡ Randy D. Gascoyne, MD,*,§,|| and Joseph M. Connors, MD*,||

Radiation dose of 111 patients
Of the subjects treated with RT

11% received an EQD2 of < 25
67% with EQD2 25-35 Gy
22% received EQD 2 >35 Gy

Local failure 2%

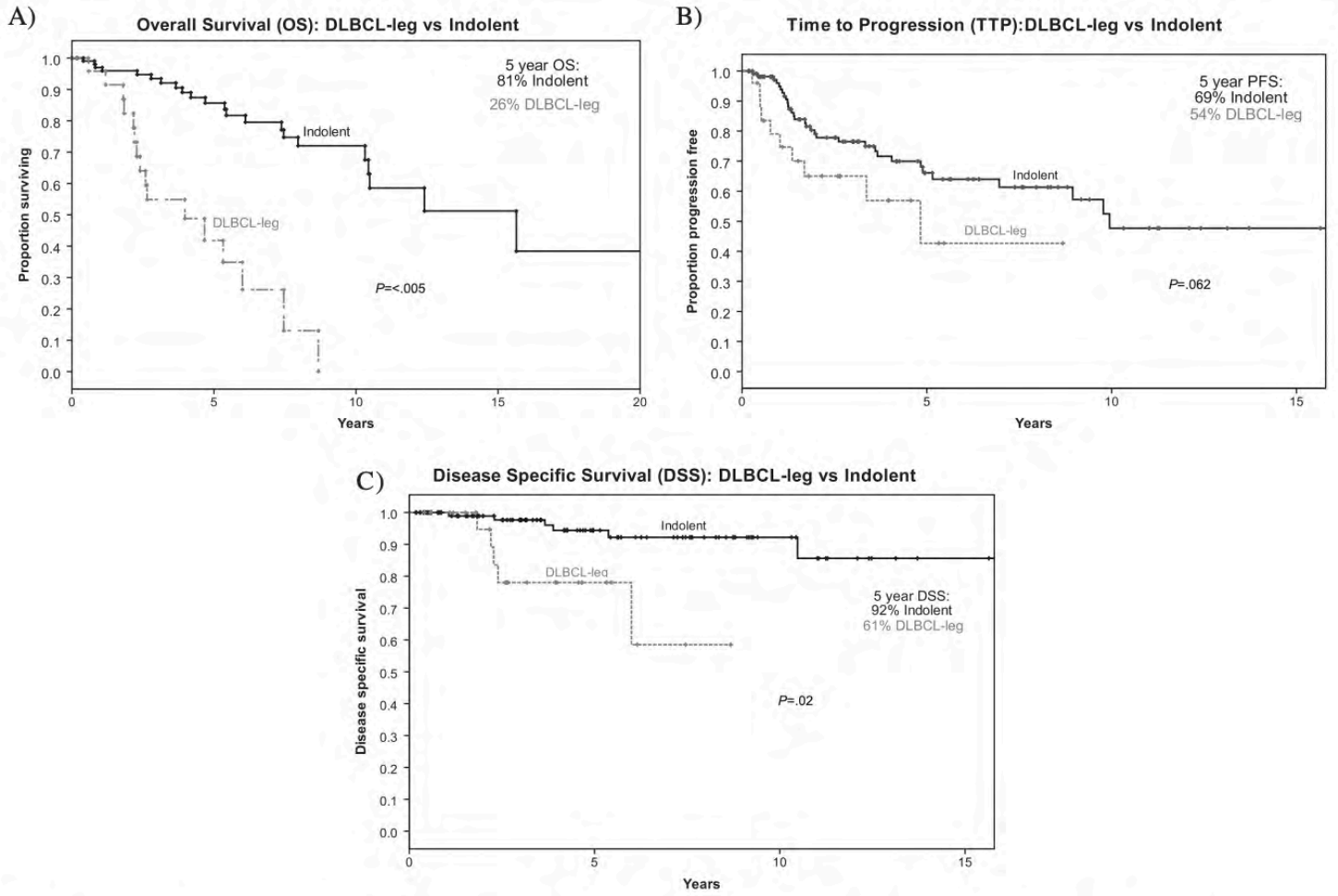
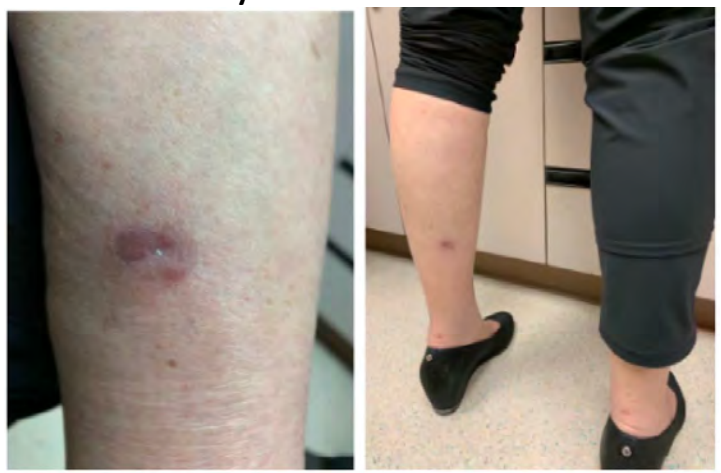
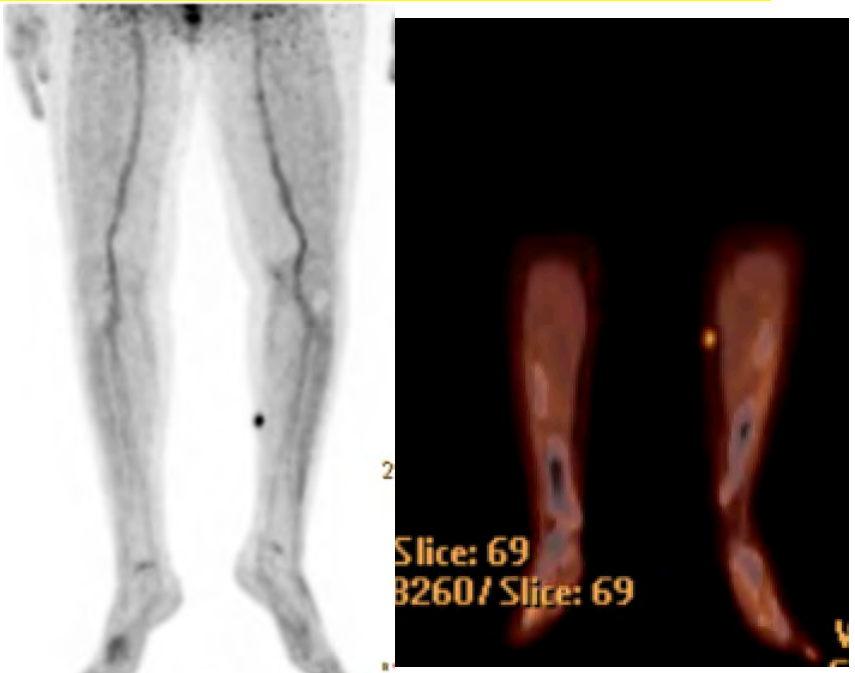


Fig. 1. Kaplan-Meier curves of (A) overall survival: diffuse large B-cell leg-type (DLBCL-leg) versus indolent. (B) Time to progression: DLBCL-leg versus indolent. (C) Disease-specific survival: DLBCL-leg versus indolent.

Primary Cutaneous Large B Cell Lymphoma-Leg Type

67 year old female





SUV 4.3

Single lesion

Pathology:

- skin involved by lymphoma with a diffuse pattern.
- The lymphoid cells are predominantly large with features of centroblasts and immunoblasts

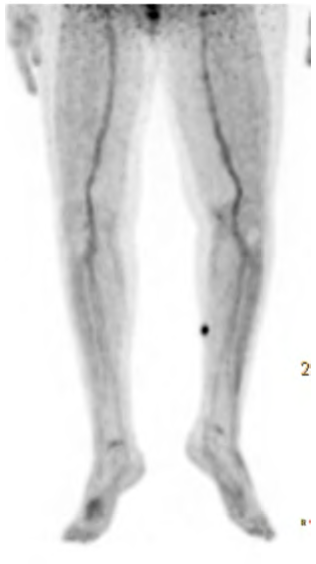
.

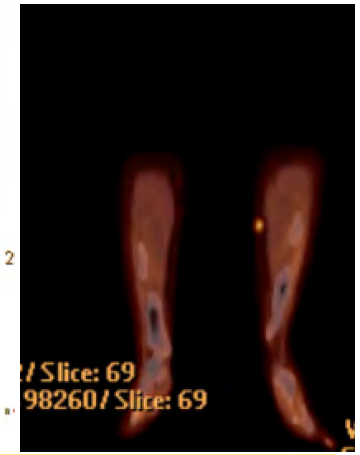
- Numerous mitotic figures are appreciated. No epidermotropism is appreciated.
- The tumor cells are positive for PAX5, MUM-1 (diffuse), and FOXP1 (diffuse), Scattered cells are positive for MYC

- neoplastic cells are positive for CD20, BCL-2, BCL-6 and MUM1/IRF4, negative for CD3, CD5 and CD10. The Ki-67 proliferative index is high (80-90%).

- The neoplastic cells are negative for Epstein-Barr virus encoded small RNA (EBER) is negative.

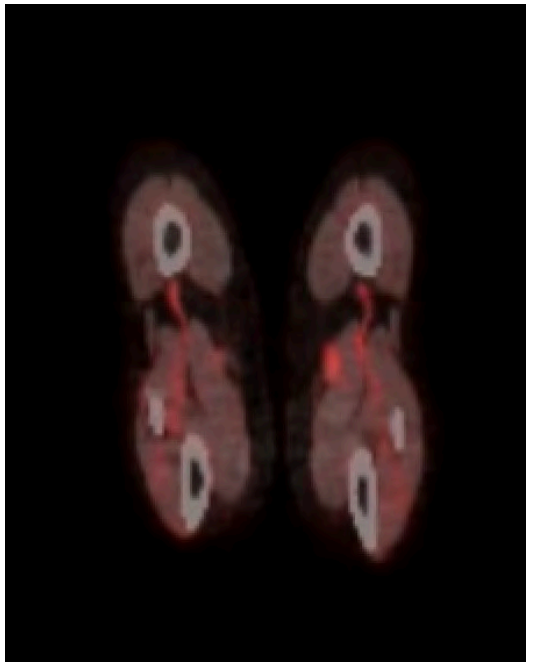
Primary Cutaneous Large B Cell Lymphoma-Leg Type

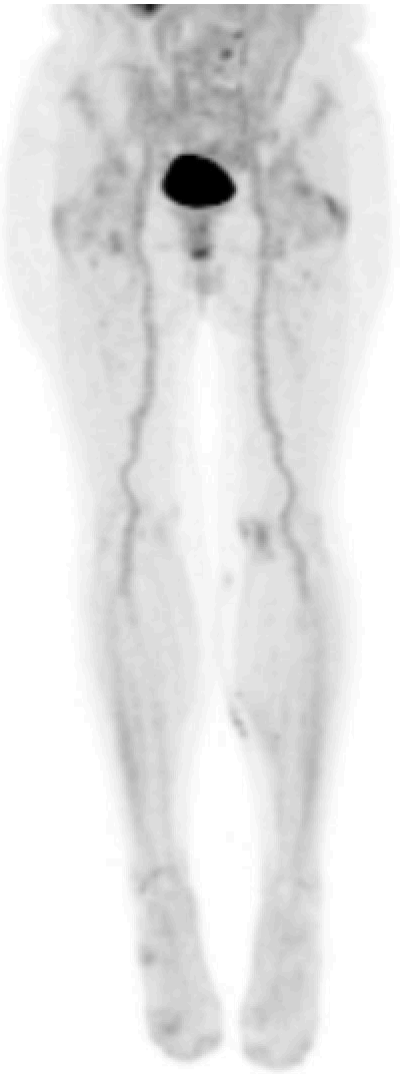


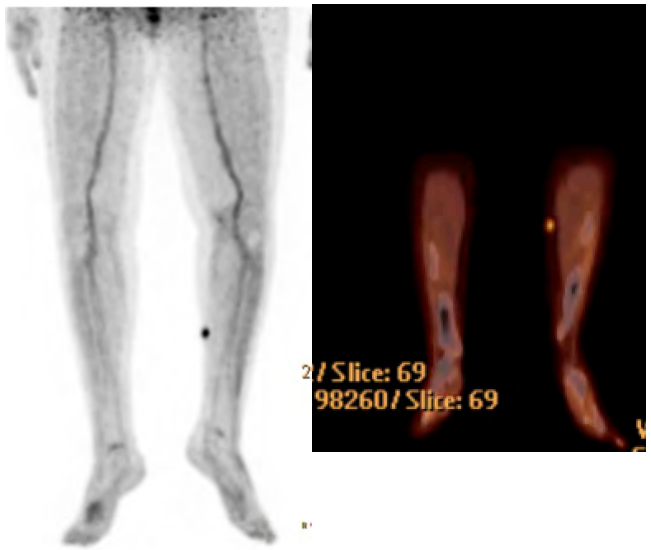


RCHOP x 4 cycles
Followed by ISRT to 30 Gy

14 months later relapsed
In the popliteal fossa
Biopsy proven







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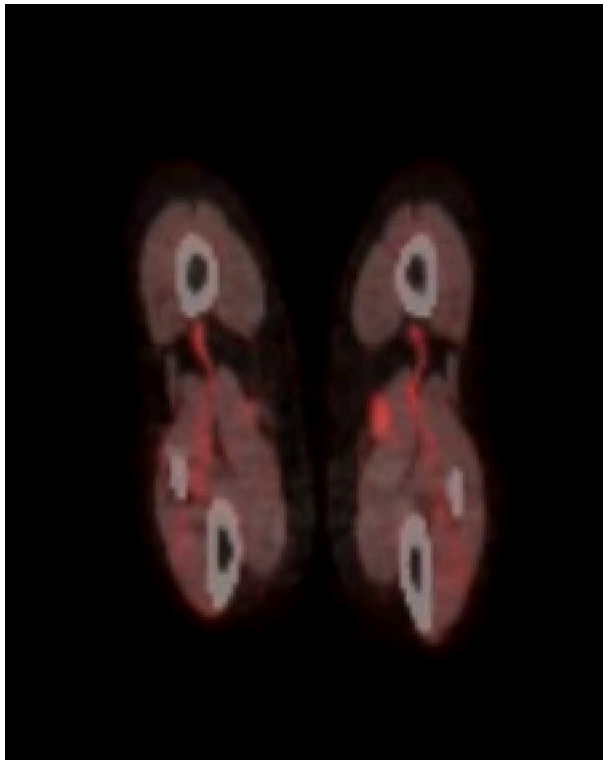
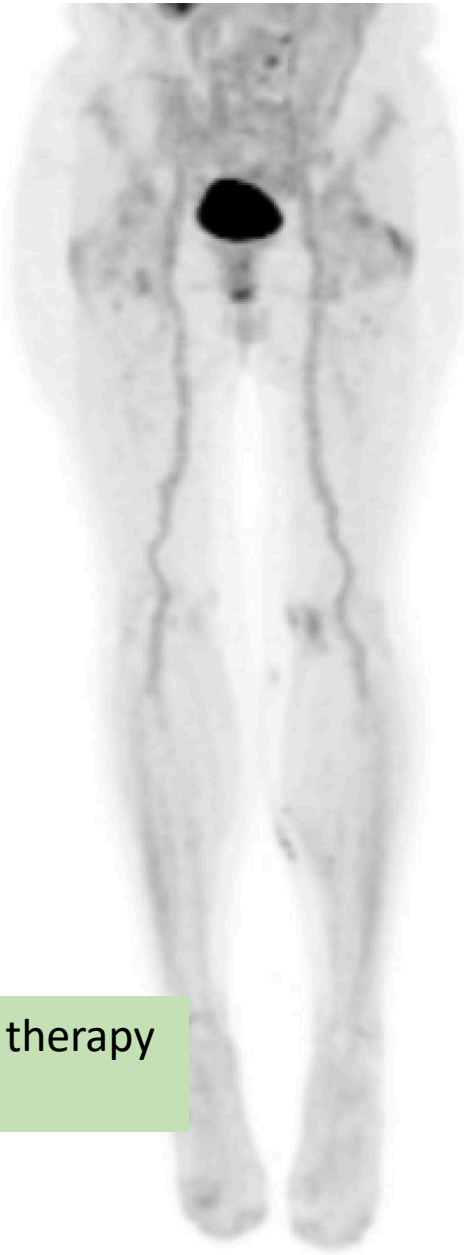
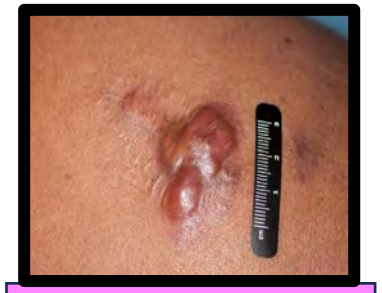


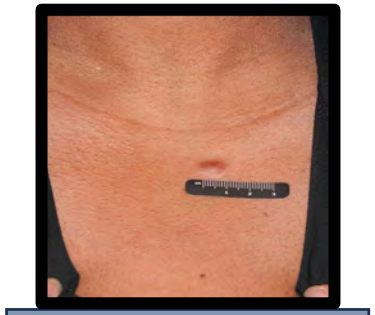


Received Bridging/ Priming radiation prior to CAR T cell therapy
In remission at last follow up 18 months later

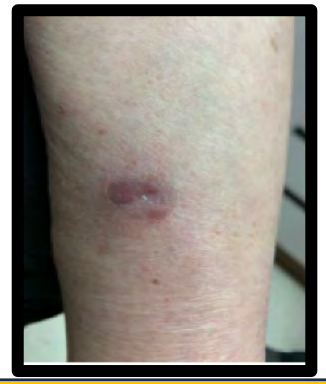
Conclusions on the management of PCBCL



PCMZL



PCFCL



PCLBCL-LT

Small lymphocytes

Large cells

Local Radiation

Chemotherapy +Radiation

Excellent Outcome 95-99%

Outcome 50%

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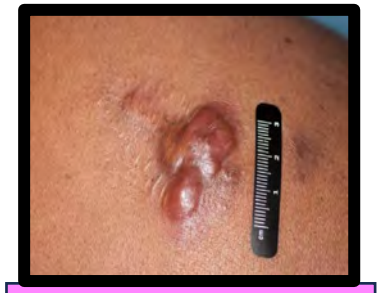
Conclusions on the management of PCBCL



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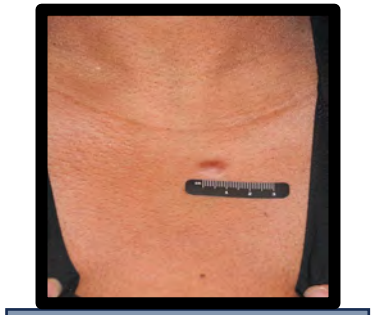

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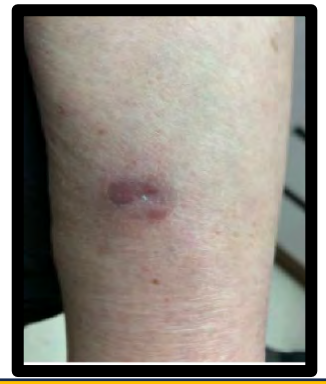

PCLBCL-LT

Small lymphocytes

Large cells

Local Radiation

Start with 4 Gy
90% durable CR
It might not even be a cancer

Excellent Outcome
95-99%

Chemotherapy
+Radiation

Outcome
50%

Radiation dose: 30 Gy

? 36-40 X

Personnel opinion

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