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Initial Treatment of Peripheral T-cell Lymphomas "The Rest"

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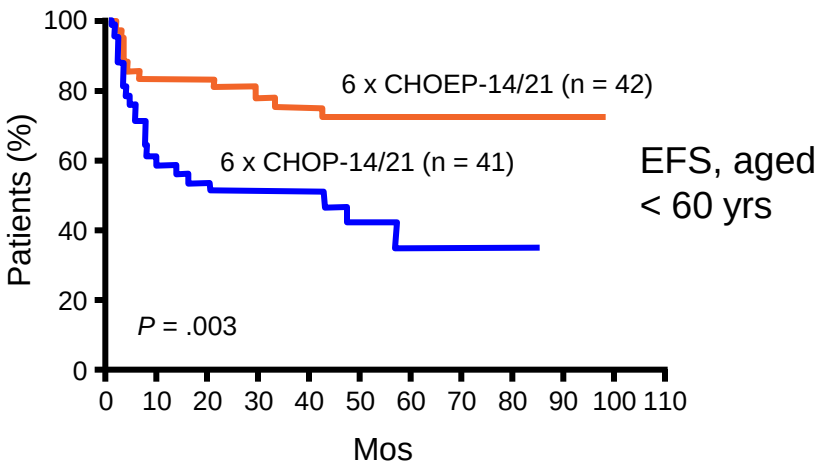
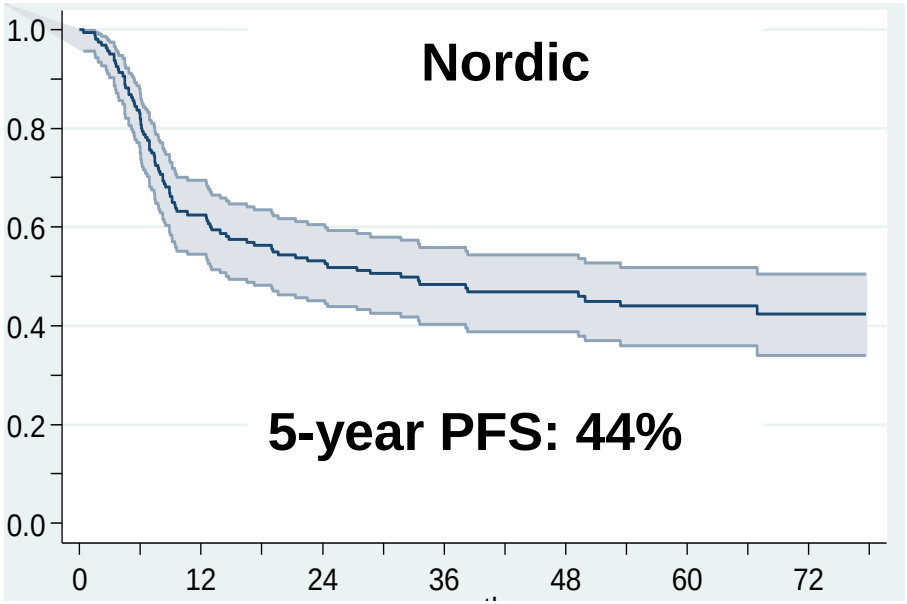
"Standard" Approaches to initial Treatment of PTCL



EFS, aged
< 60 yrs



"Standard" Approaches
CHOP
CHOEP
CHOP/CHOEP-ASCT

Schmitz N, et al. Blood. 2010;116:3418-3425. D'Amore, et al. *J Clin Oncol.* 2012;30(25):3093-3099

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Proportion of T-cell Lymphoma Subtypes

Subtype	% North America	% Europe	% Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Primary cutaneous gamma-delta T-cell			
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell			

International T-Cell Lymphoma Project JCO 2008;26:4124-4130

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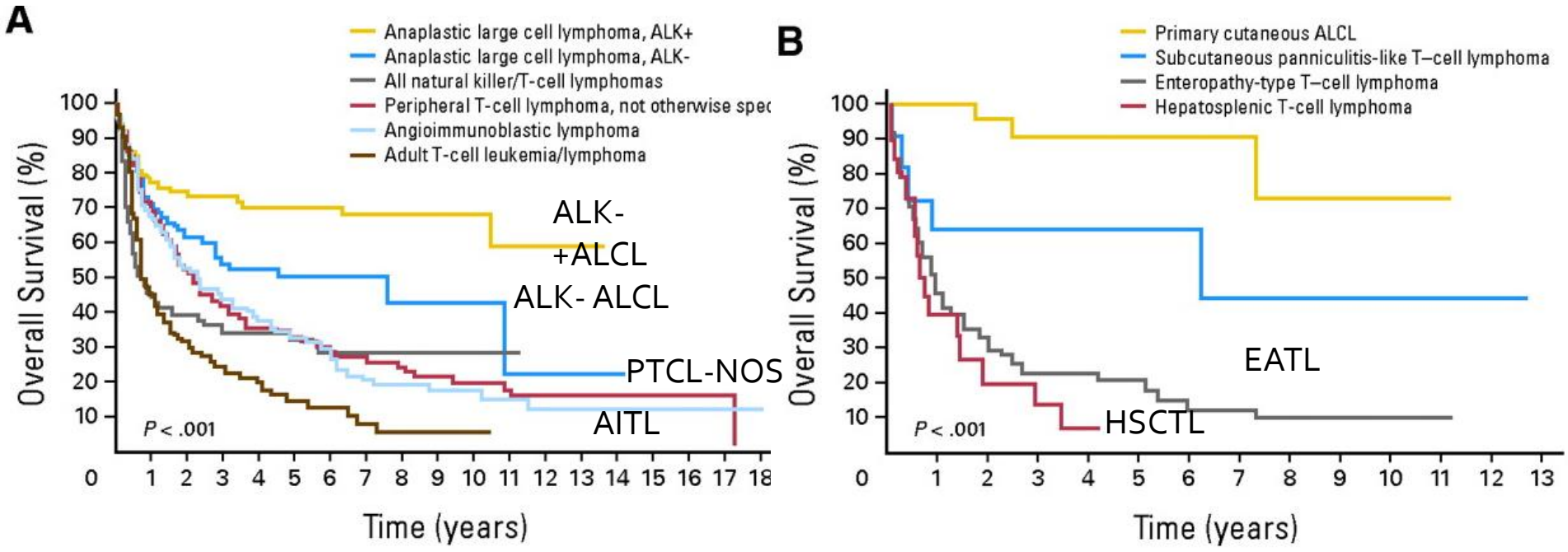
Overall survival of patients by subtype of PTCL



International T-Cell Lymphoma Project JCO 2008;26:4124-4130

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Enteropathy-Associated T-cell Lymphoma

EATL: Clinical Features

Sex	
Total number with data	57
Male	41 (72%)
Female	16 (28%)
Age (years)	
Total number with data	57
Median (range)	58 (23–83)
Presenting Feature	
Total number with data	40
Weight loss	11 (28%)
Abdominal pain	24 (59%)
Diarrhoea	11 (28%)
Bowel perforation	16 (39%)
Distension	2 (5%)
Site of GI involvement	
Total number with data	60
Small intestine	48 (80%)
Large intestine	6 (10%)
Small and large intestines	6 (10%)
Stage	
Total number with data	35
I and II	27 (77%)
III and IV	8 (23%)
Treatment	
Total number with data	42
Surgical resection alone	10 (24%)
Anthracycline-based chemotherapy	21 (50%)
Non-anthracycline-based chemotherapy	9 (21%)
Upfront high dose chemotherapy as consolidation	2 (5%)
Overall survival (months)	
Total number with data	39
Median (range)	7 (0.5–85)

Tan SY, Chuang SS, Tang T, et al. *Leukemia.* 2013; 27(8):1688-1696.

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EATL Type I vs Type II

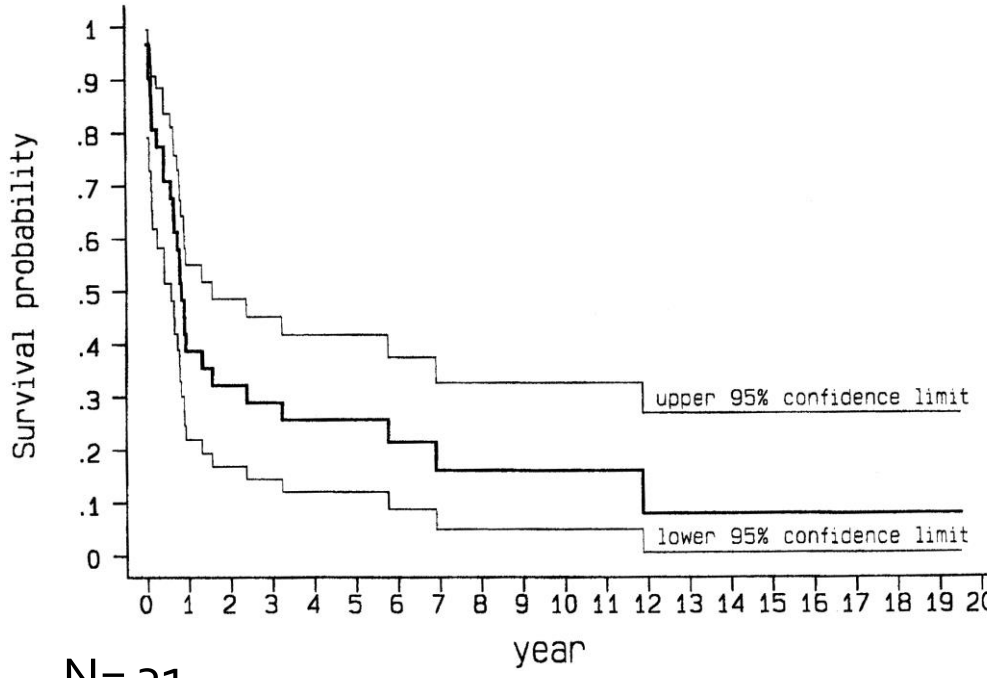
Classic EATL (Type I)	Type II EATL
Frequency	
80-90%	10-20%
Epidemiology	
Complication of celiac disease (1-2%)	Occurs sporadically
Northern Europe	Asia
>90% have celiac disease-associated HLA-DQ2/-DQ8 haplotypes	
Patients with refractory celiac disease at high risk	
Clinical Presentation	
Multifocal involvement of small intestine, intestinal ulcers, stenosis, perforation	Similar but ~20% may involve the large intestine

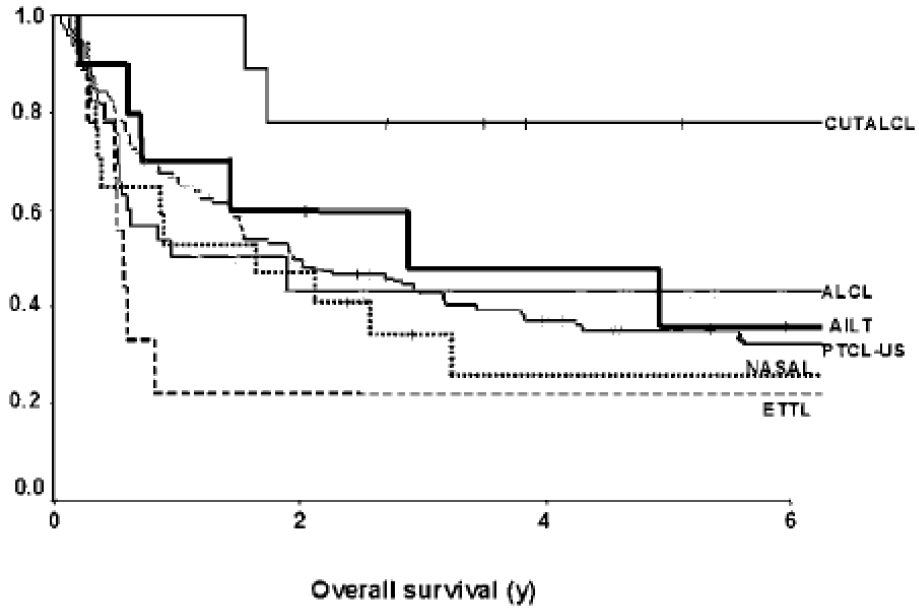
Adapted from:

Ferreri et al, Critical Reviews in Oncology/Hematology 79 (2011) 84–90

Arps DP, et al. *Arch Pathol Lab Med.* 2013;137(9):1227-1231.

EATL: Prognosis with "Standard" Therapy





N= 31

- 25/31 diagnosed at laparotomy
- 42% (13/31) emergency surgery/perf
- PS 2-4 in 73% (19/26)
- 29%, (9/31)died quickly with no treatment or complication of 1 cycle of chemotherapy. Bleeding, infection

N= 9 from BCCA
CHOP in 8/9

Gale J.et al. JCO 2000;18:795; Savage, K.J., et al. Ann Oncol,2004.15(10): 1467-75

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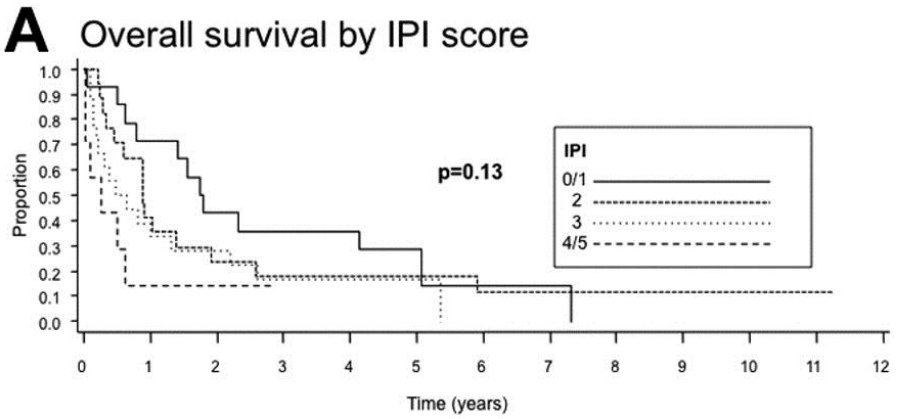
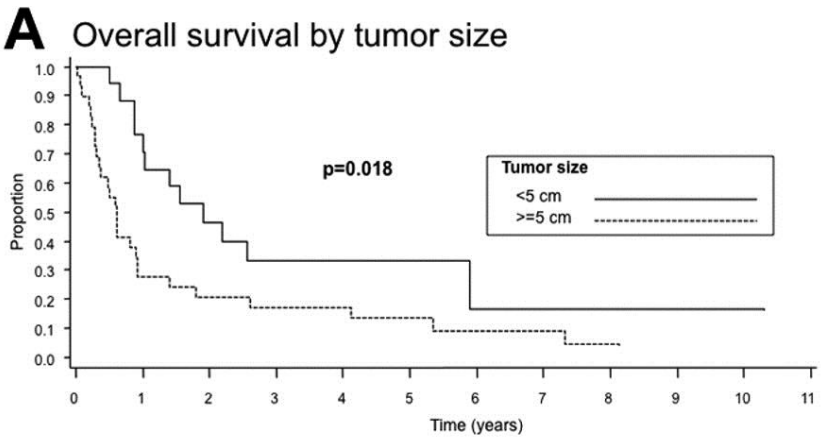
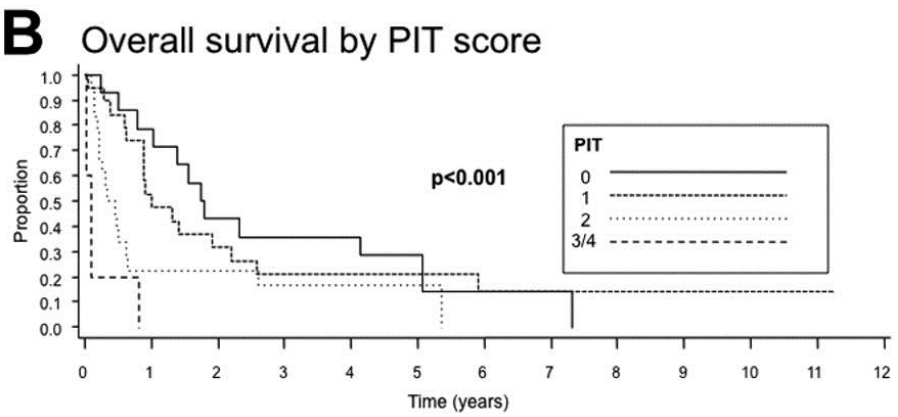
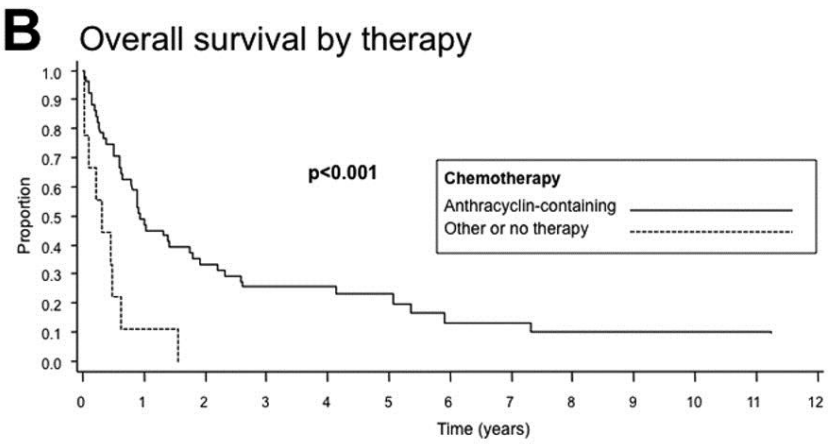
EATL OS according to Prognostic Score, Tumor Size, and Therapy With or Without an Anthracycline: ITCP









93 % (52/56) Combination chemotherapy

Non ambulatory PS, elevated LDH= worse OS and FFS

Jan Delabie et al. Blood 2011;118:148-155

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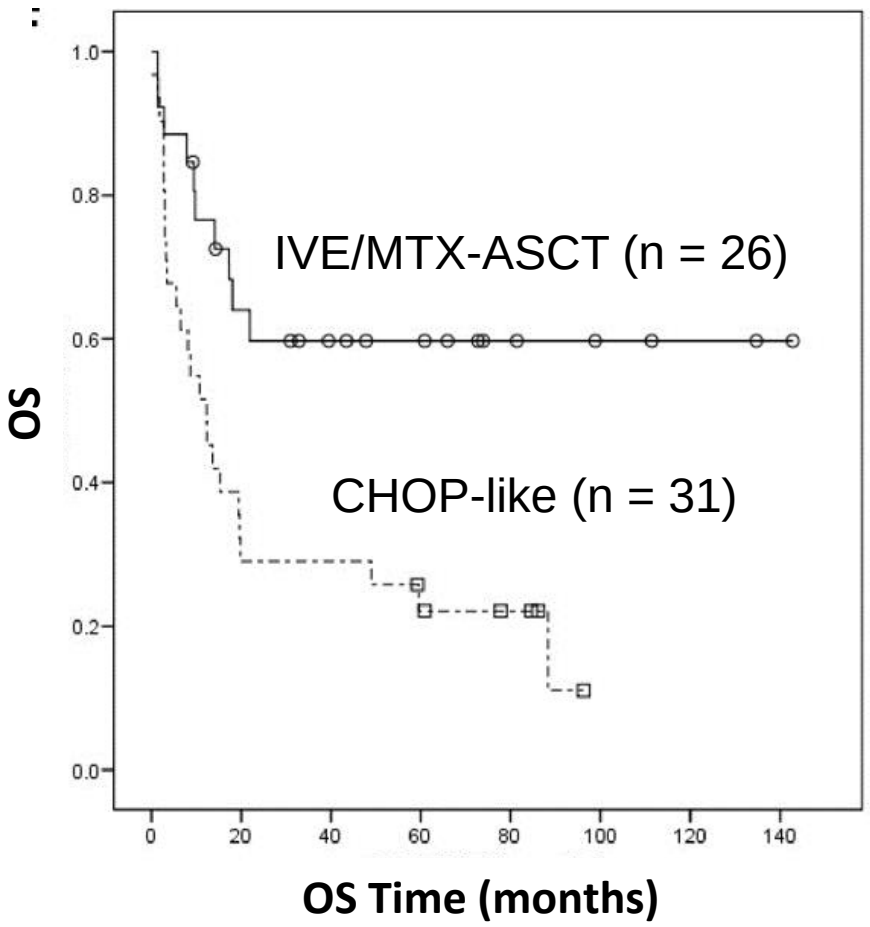
EATL: Apparent Benefit of More Intensive Approaches



- CHOP x 1
- IVE
  - Ifosfamide 3000 mg/m2 d 1–3
  - Epirubicin 50 mg/m2 on d 1,
  - Etoposide 200 mg/m2 on d 1–3

  alternating with

- Methotrexate 1,500 mg/m2

- BEAM or TBI-ASCT

Sieniawski M, et al. *Blood.* 2010;115(18):3664-3670.

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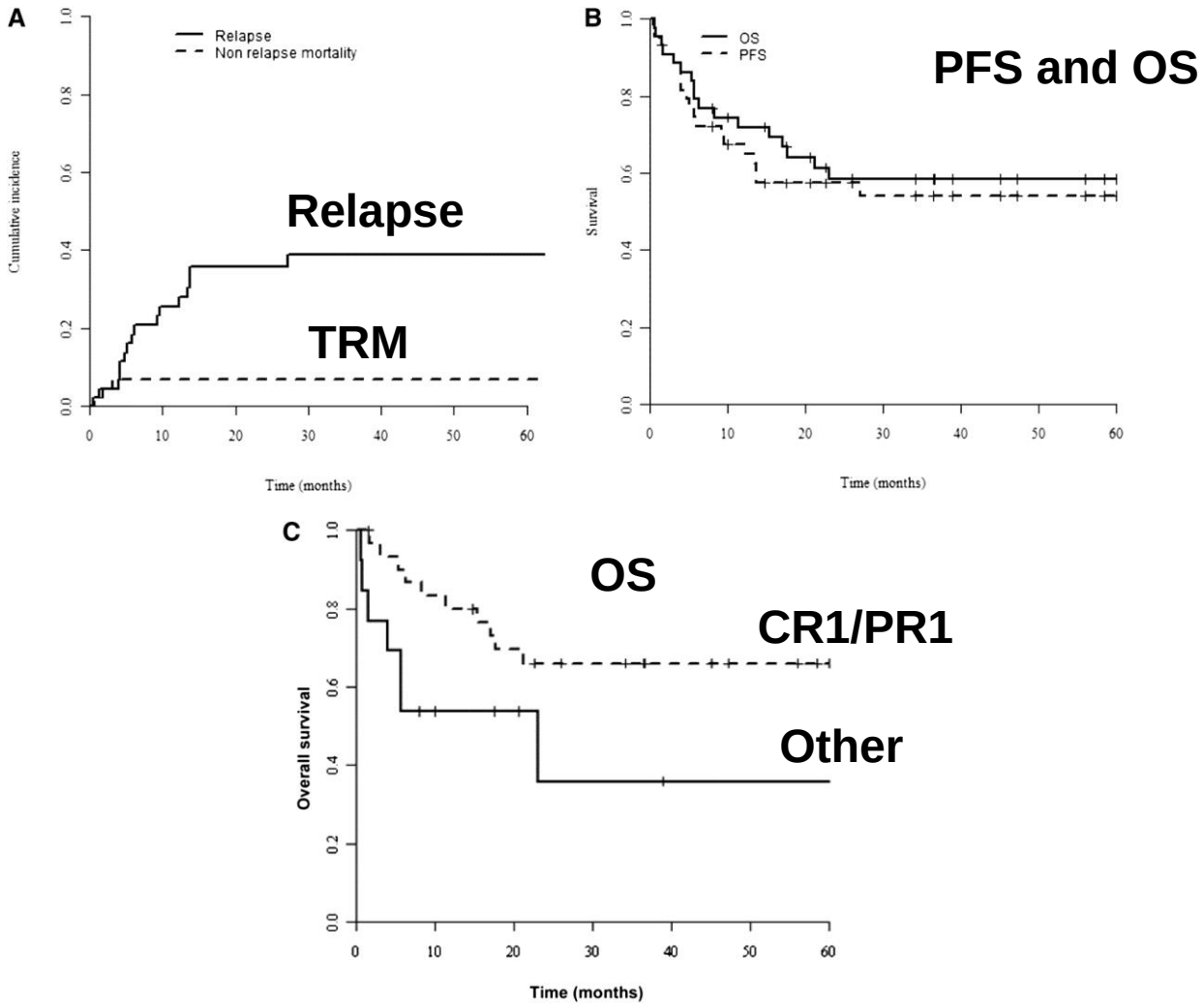
ASCT for EATL: EBMT



Jantunen et al. Blood 2013;121:2529-2532

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CHOEP-ASCT Nordic Lymphoma Group: OS

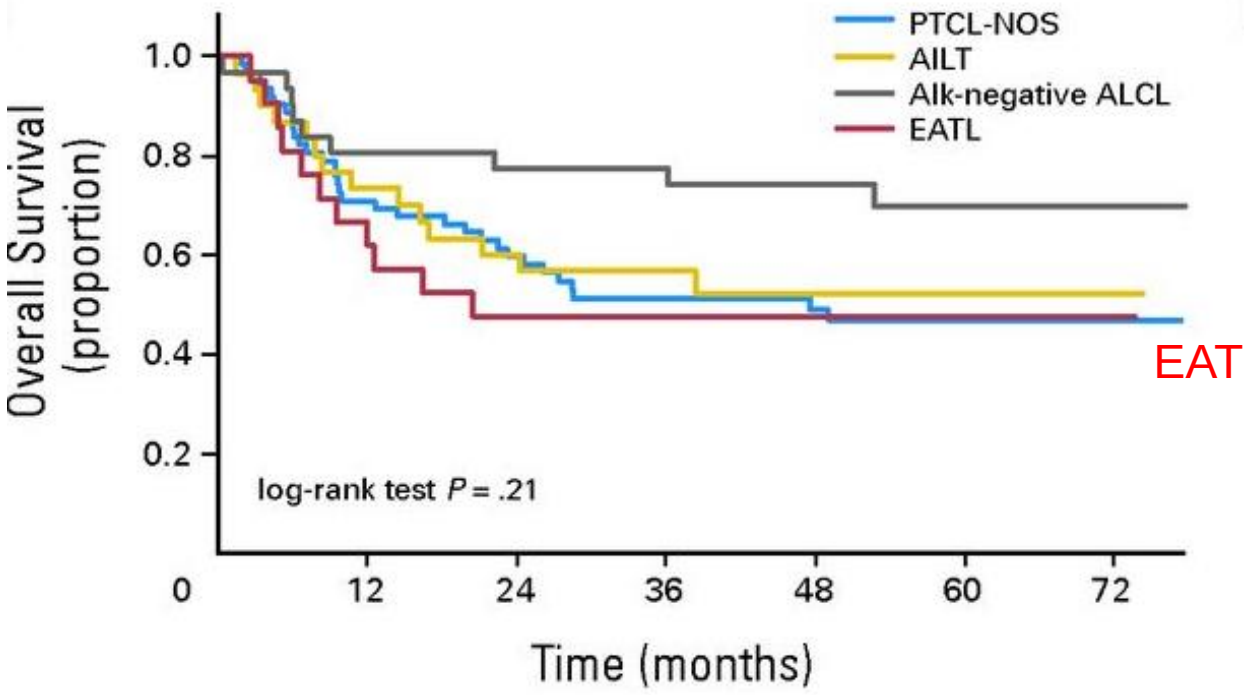
ND PTCL, N = 166
Med Age-57 years
ALK+ / ALCL+ excluded

→ CHOEP*
6 cycles
biweekly

→ CR
PR

→ HDT / ASCT
N = 115
90 CR 3-month post

*Patients > 60 years received CHOP not CHOEP.



EATL (N= 21)

Francesco d'Amore et al. JCO 2012;30:3093-3099

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Differential Diagnostic Considerations for EATL

- Peripheral T-cell lymphoma, NOS
  - More common than EATL
  - Broad morphologic spectrum and typically presents as nodal involvement, but any site may be affected
  - Involvement of small intestine should always raise suspicion for EATL
- Indolent T-cell lymphoproliferative disease of the gastrointestinal tract
  - Dense small, non-destructive lymphoid infiltrate
  - Little or no involvement of the crypt or surface epithelium
  - CD3+, CD8+, CD5+, CD56-, TIA-1+, TCR-BF1+
- NK Enteropathy
  - CD56(+)/TIA-1(+)/Granzyme B(+)/cCD3(+)
  - Does not invade the glandular epithelium.

Perry et al, Blood, 2013: 122 (22)
Malamut et al. Clinical Gastroenterology and Hepatology 2014;12:599–608
Mansoor et. Al. Blood. 2011 Feb 3;117(5):1447-52

Initial Treatment of EATL

- Many series contain subjects to ill to safely tolerate therapy
- Series with more aggressive strategies do not appear to include these patients
- Maybe treat like other PTCL, depends on how you treat them?
- CHOP alone results in few long term survivors
- More intensive therapy appears to have better results
  - Possible selection bias-responders/better PS
  - ASCT in CR1/PR1
  - CHOEP-ASCT
  - IVE/MTX-ASCT

EATL Phenotype and Significance of TCR Lineage

Classic EATL	Type II EATL
Phenotype	
CD3+, CD5-, CD7+	CD3+, CD5-, CD7+
CD8- (80%)	CD8+ (80%)
CD56- (>90%)	CD56+ (>90%)
MATK-	MATK+
Granzyme B+,TIA-1+	Granzyme B+/-, TIA-1+
TCR$\gamma\delta$ or TCR-βF1	TCR$\gamma\delta$ or TCR-βF1
EBV/EBER-	EBV/EBER-

What is the TCR lineage of type II EATL?

- Conflicting reports regarding TCR lineage in type II EATL
- S.Y. Tan et al. report in their series of 60 cases 41% TCR$\alpha\beta$+, 26% TCR$\gamma\delta$+, and 33% TCR-silent cases
- TCR lineage is not a defining feature and not associated with specific clinical implications

Chan JK, Chan AC, Cheuk W, et al. *Am J Surg Pathol.* 2011;35(10):1557-1569.

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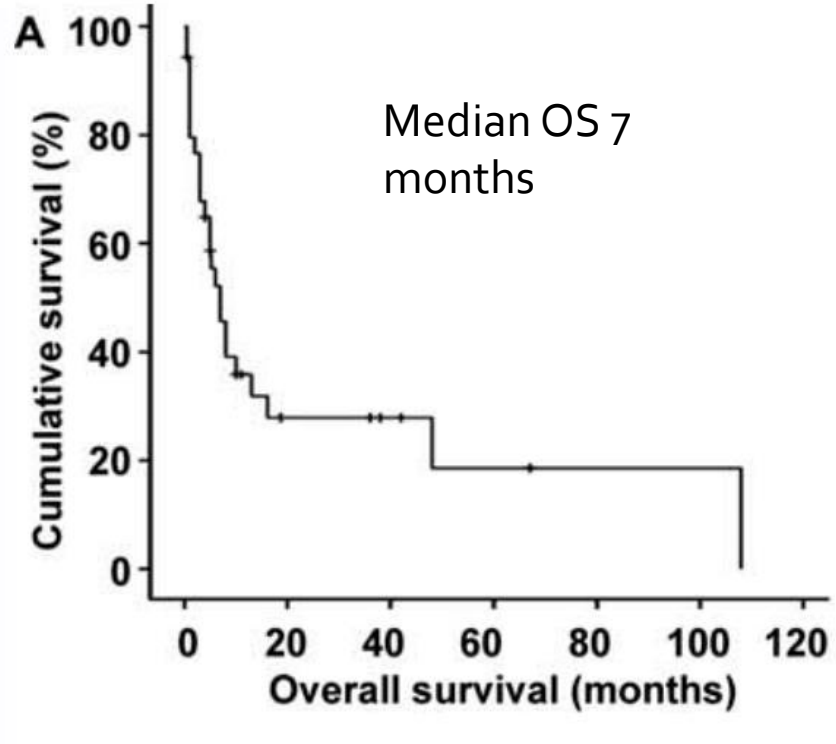
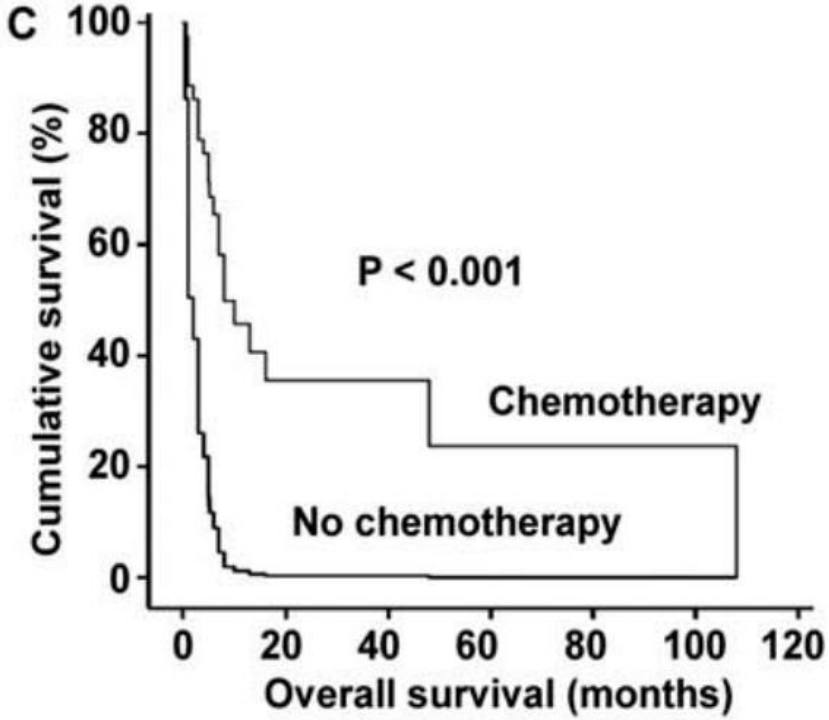
Prognosis in Type II Enteropathy-Associated T-cell Lymphoma: A Multicenter Analysis from the Asia Lymphoma Study Group



Median OS 7 months



Chemotherapy
CHOP 20 ORR 45% , CR 35%
SMILE 5 ORR 60%, CR 60%
ASCT 4, Allo 1-ALL pts alive

Tse E, et al. *Am J Hematol.* 2012;87(7):663-668.

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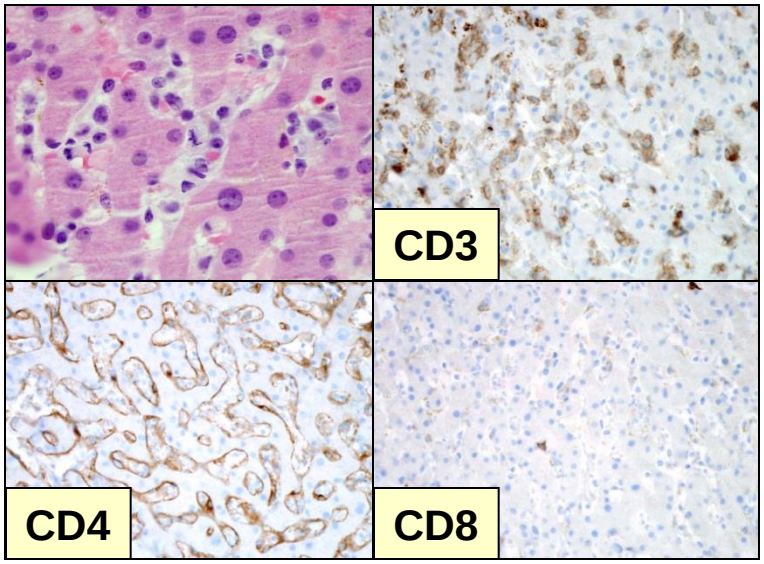
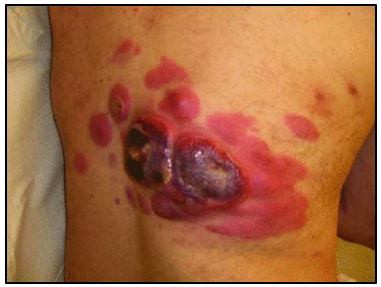
Initial Treatment of Type II EATL

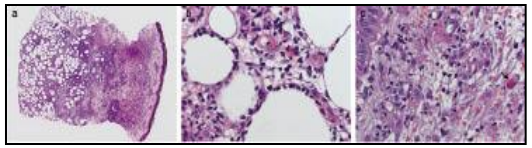
- Appears to have a worse prognosis than Type I ?
- Should EATL Type II be treated differently?
- Unclear if approaches toward NK/T more effective
  - Limited data on SMILE, Gemcitabine based approaches
- Consolidation of responders with transplant characterizes the few long term survivors in literature.

Other T-cell Lymphomas Derived from γδ T-Lymphocytes

Hepatosplenic T-Cell Lymphoma (HSTL)	Primary Cutaneous γδ T-Cell Lymphoma (PCγδTCL)
Setting of chronic immune suppression (solid organ transplantation) or treatment with azathioprine and infiliximab for Crohn's disease	Impaired immune function associated with chronic antigen stimulation
Marked hepatosplenomegaly, no lymphadenopathy	Variable: Epidermotropic (patches/plaques) to deep dermal or subcutaneous nodules with or without epidermal ulceration
CD3+, TCRδ1+, TCR-BF1-, CD56+/-, CD4-, CD8-/+, CD5-, TIA-1+, granzyme B-/+	







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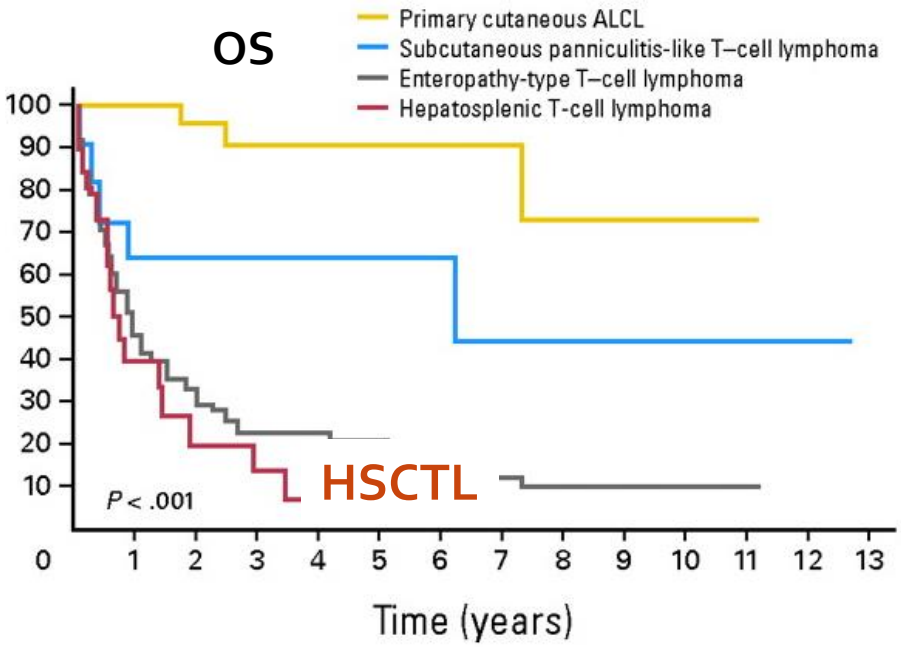
Hepatosplenic T-cell lymphoma

- Very rare
- Young age, usually male
- Associated withy immunosuppression-IBD
- Anti-TNF > other immunosuppressive?
- Often very aggressive course
- Clinical Features
  - Splenomegaly ~100%,
  - Hepatomegaly 80-90%
  - Elevated LFTs 50%,
  - LDH markedly elevated
  - Bone marrow ~100%
  - Peripheral blood in 50–80%
  - Lymphadenopathy usually absent
  - Cytopenia due to hypersplenism and/or HLH ,



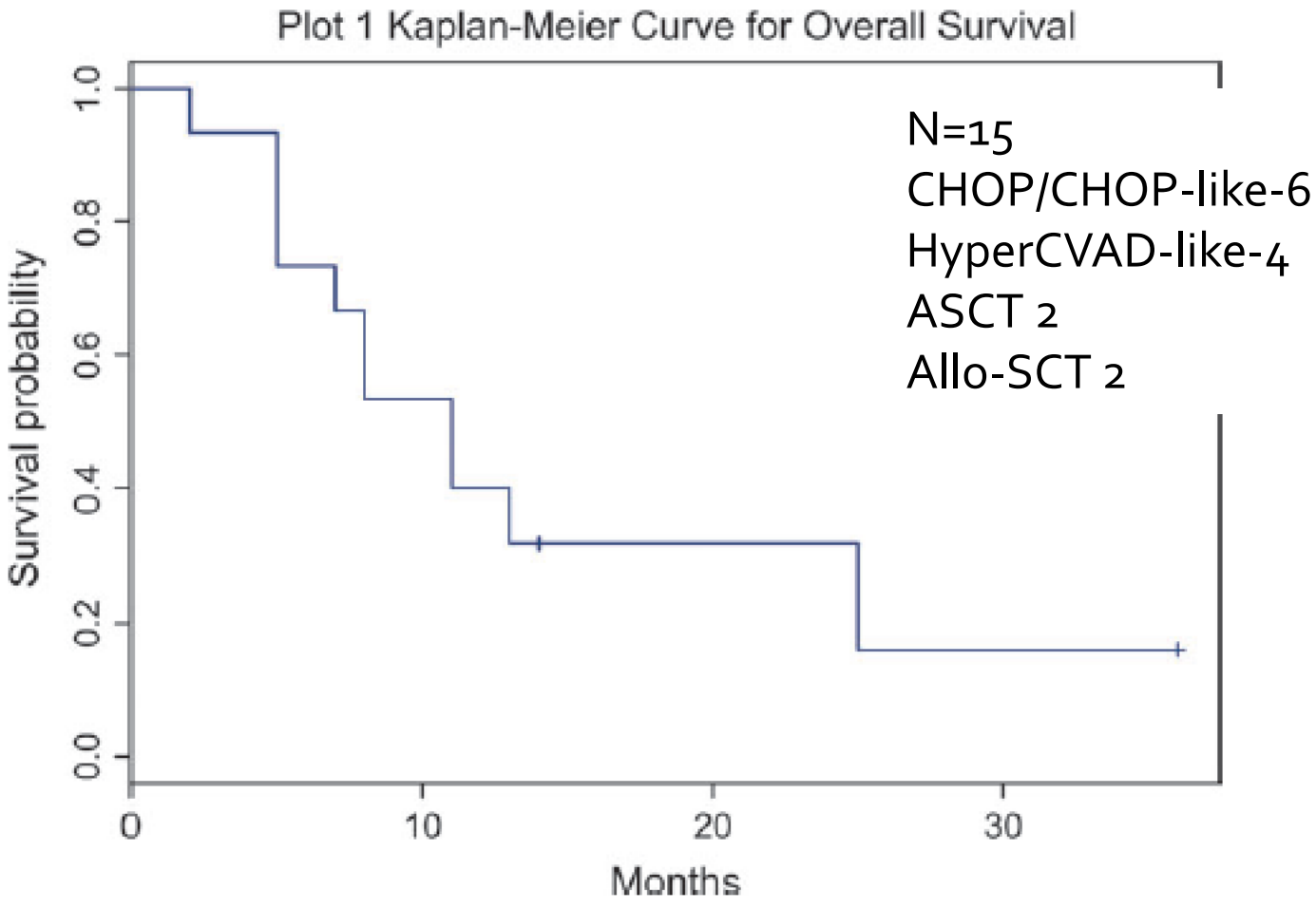
Ferreri, Govi, Pileri; Critical Reviews in Oncology/Hematology 83 (2012) 283–292
Voss et al, Clin Lymphoma Myeloma Leuk. Feb 2013; 13(1): 8–14.

HSTCL

Induction phase		Consolidation phase		
Regimen	Response	Regimen	Response	Status
CHOP	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Auto BMT	CR	DOD
CHOP-like	CR	Auto BMT	CR	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Allo BMT	CR	DOD
CHOP-like	PR	Auto PBSC	CR	DOD
CHOP-like	PR	Auto PBSC	Failure	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	Failure	—	—	DOD
CHOP	Failure	—	—	DOD
CHOP-like	Failure*	—	—	DOD
CHOP-like	CR	Allo BMT	NE	TRD
CHOP	Failure	—	—	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	PR	Allo BMT	NE	TRD
Platinum-Ara-C based	PR	Auto PBSC	CR	Alive
CHOP	Failure	—	—	DOD
Platinum-Ara-C based	PR	Auto PBSC	CR	Alive
CHOP-like	Failure	—	—	DOD
CHOP-like	Failure	—	—	DOD

Belhadj et al BLOOD, 15 DECEMBER 2003, VOLUME 102, NUMBER 13

HSTCL at MDACC



N=15
CHOP/CHOP-like-6
HyperCVAD-like-4
ASCT 2
Allo-SCT 2

Falchook et al, Annals of Oncology 20: 1080–1085, 2009

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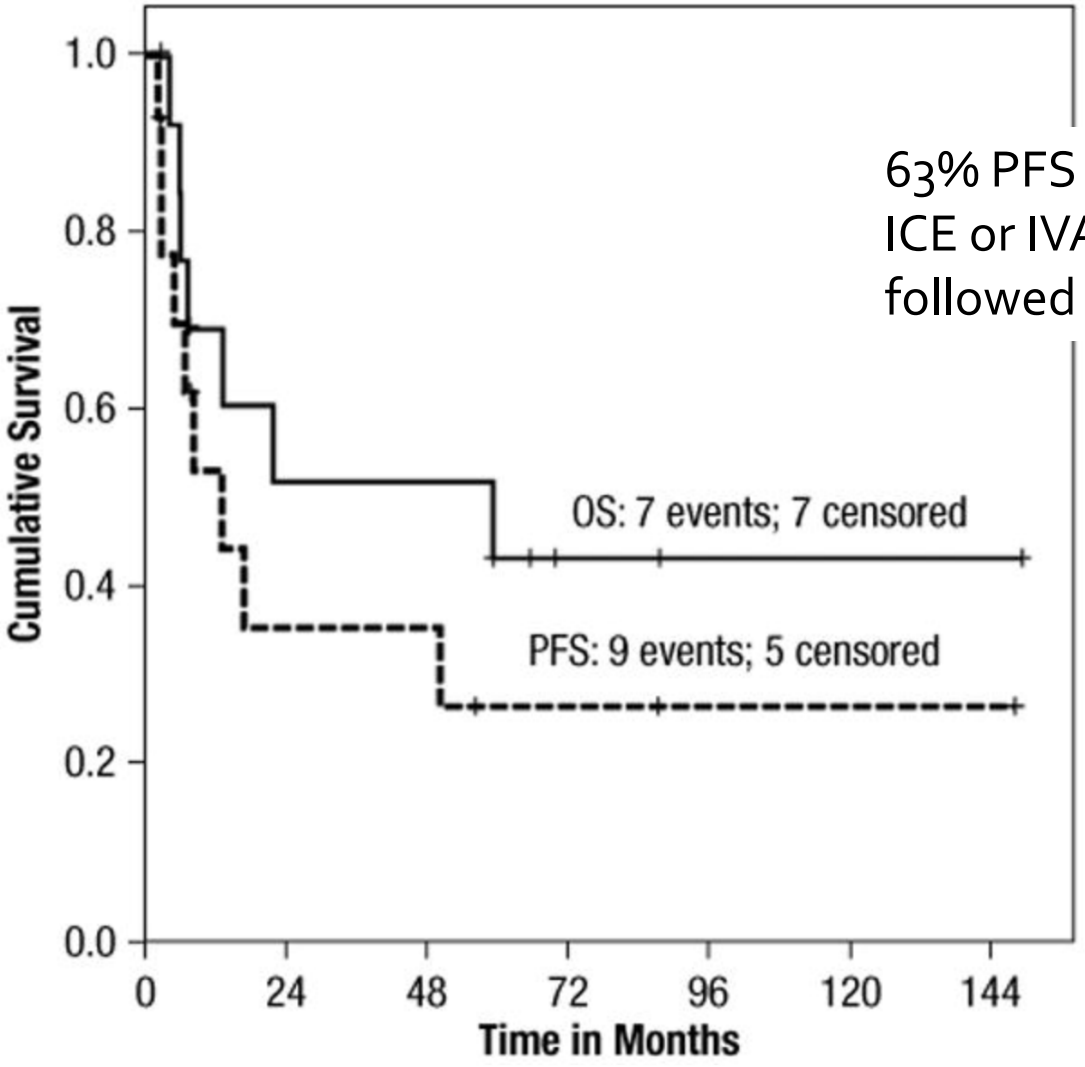
HSTCL at MSKCC



63% PFS when
ICE or IVAC induction
followed by SCT

Voss et al, Clin Lymphoma Myeloma Leuk. Feb 2013; 13(1): 8–14.

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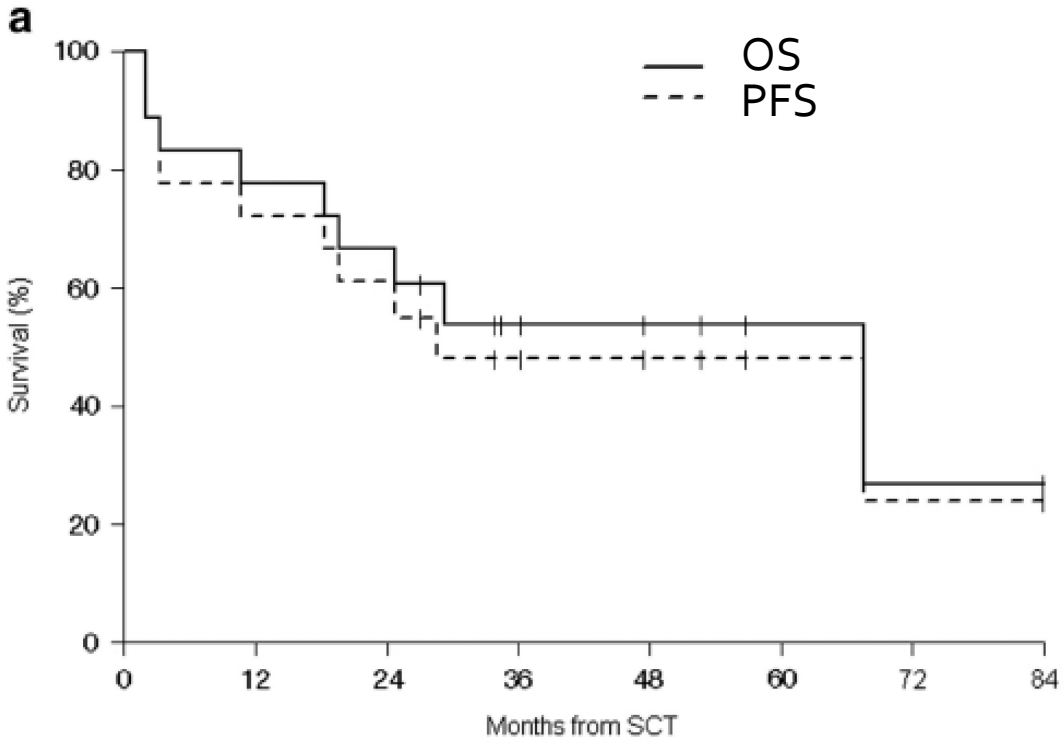
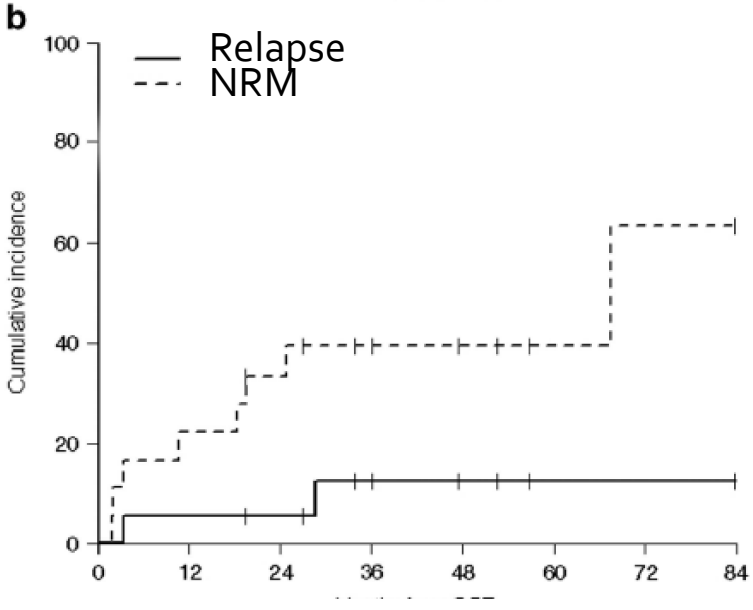
HSCTL
Allo-HSCT: EBMT



N= 25
Allo HSCT 18: 3 yr PFS 48%
Auto HSCT 7: 5 Relapsed



Tanase et al, Leukemia (2015) 29, 686–688

Lymphoma With Features Intermediate Between Aggressive T-Large Granular Lymphocytic Leukemia and Hepatosplenic T-Cell Lymphoma: A Diagnostic Dilemma?

Chi Young Ok,[1] C. Cameron Yin,[1] Mariko Yabe,[2] Carlos E. Bueso-Ramos,[1] Roberto N. Miranda,[1] L. Jeffrey Medeiros,[1] Sergej N. Konoplev[1]

Table 1 Comparison Between Aggressive T-LGLL and HSTCL αβ Type

Variable	Aggressive T-LGLL	HSTCL αβ Type
Median Age, Years	41	35
Sex	No predilection	Female predilection
B Symptoms	Common	Common
Hepatosplenomegaly	Common	Common
Lymphadenopathy	Common	Not common
Anemia	Variable	Variable
Neutropenia	Variable	Variable
Thrombocytopenia	Variable	Variable
Autoimmunity	Associated	Not associated
Clinical Course	Aggressive	Aggressive
Tumor Cells		
PB	Increased LGLs	LGLs can be seen
BM	Interstitial/intrasinusoidal	Interstitial/intrasinusoidal
Spleen	Cords and sinuses	Cords and sinuses
Liver	Sinusoidal	Sinusoidal
Immunophenotype	$CD3^+$, $CD4^-$, $CD8^+$, $CD56^{+/-}$, $CD57^{+/-}$	$CD3^+$, $CD4^-$, $CD8^{+/-}$, $CD56^{+/-}$, $CD57^+$
Cytotoxic Granules	TIA-1^+, granzyme B^+, perforin$^+$	TIA-1^+, granzyme$^{+/-}$, perforin NA
Isochromosome 7q	Absent	Present
TCR Gene Rearrangement	Clonally rearranged	Clonally rearranged

Clinical Lymphoma, Myeloma & Leukemia June 2014

Initial Treatment of HSTCL

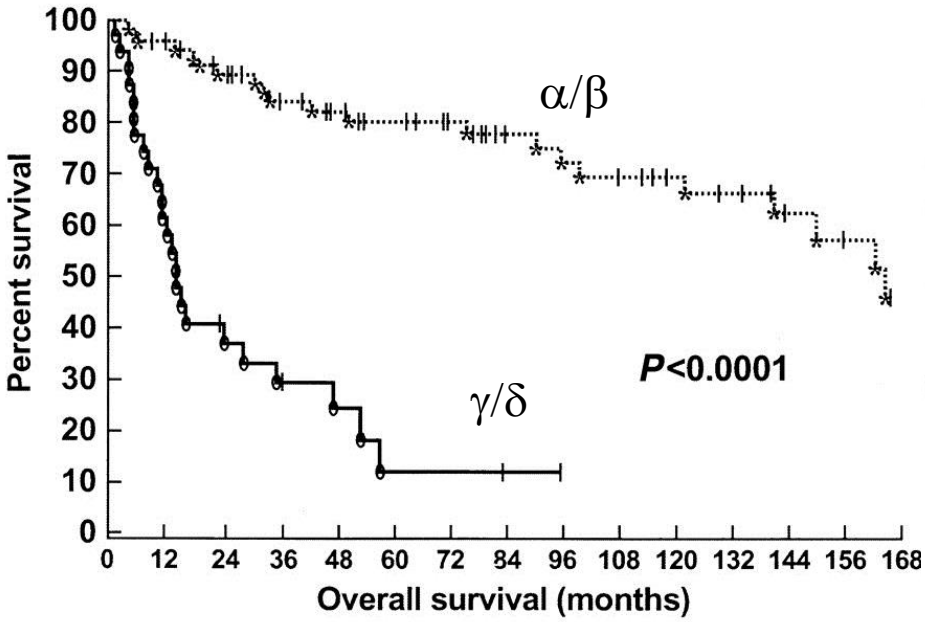
- Probably need a different approach than other PTCL
- CHOP alone results in few long term survivors
- More intensive therapy appears to have better results
  - ICE or IVAC –AlloSCT > Auto-SCT (our approach)
  - Others successfully treated with
    - DHAP/ESHAP
    - Anecdotal reports of
      - EPOCH, Pentostatin, Alemtuzumab and new agents
  - Great majority (if not all) of Long term survivors in literature were consolidated with SCT

Cutaneous g/d T-cell Lymphoma

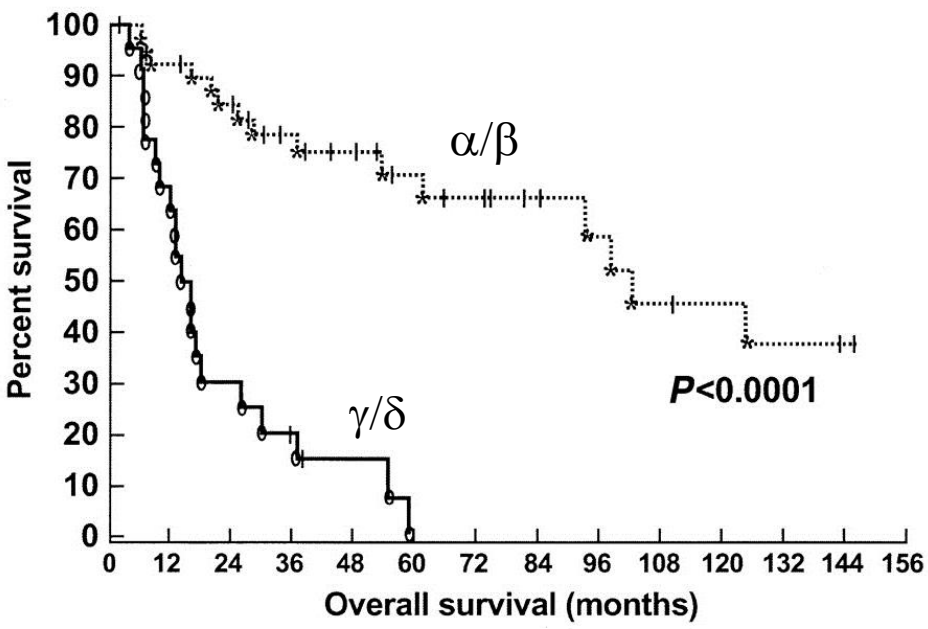
- Clonal proliferation of mature, activated g/d T-cells w/ a cytotoxic phenotype
  - CD2+, CD3+, bF1-, g/d+, CD5-, CD56+, cytotoxic proteins
  - Generally CD4-, CD8-, EBV-
  - Epidermotropic, dermal, and/or subcut. histologic patterns
- Generalized plaques and/or ulceronecrotic nodules or tumors
  - Extremities often involved
  - Mucosal and other extranodal sites frequently involved
  - Involvement of LNs, spleen or BM is uncommon
  - Hemophagocytic syndrome (HPS), *Hemophagocytic lymphohistiocytosis (HLH)*
- Tendency for aggressive clinical course
- CNS

Guitart et al Am J Surg Pathol 36,11, November 2012

Survival of Cutaneous PTCL by Phenotype Alpha/Beta Versus Gamma/Delta



All Cases



Clinical Tumors

Toro JR, et al. *Blood*. 2003. May 1;101(9):3407-3412.

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Indolent Cutaneous g/d T-cell Lymphoma

Indolent Primary Cutaneous γ/δ T-Cell Lymphoma Localized to the Subcutaneous Panniculus and Its Association With Atypical Lymphocytic Lobular Panniculitis

Cynthia M. Magro, MD, and Xuan Wang, MD, PhD

Am J Clin Pathol 2012;138:50-56

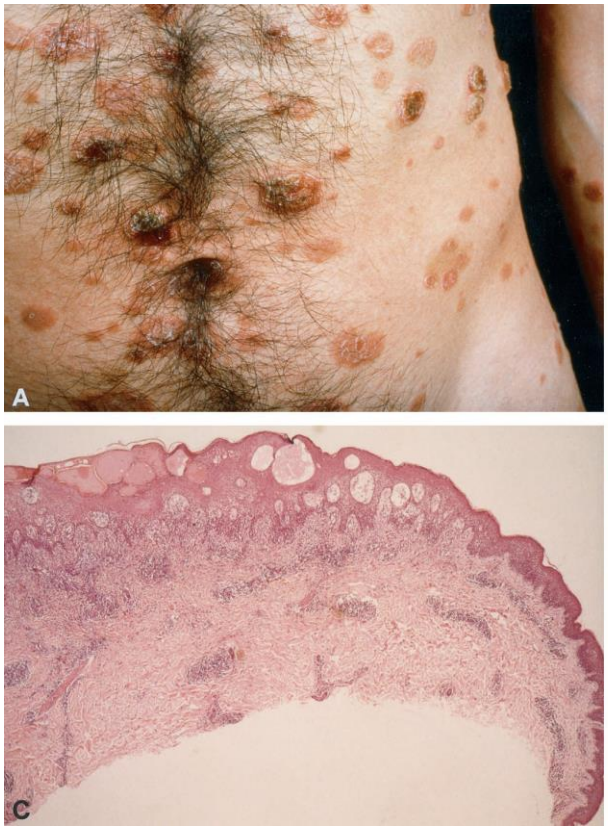
Guitart et al. Am J Surg Pathol 2012; 36,11

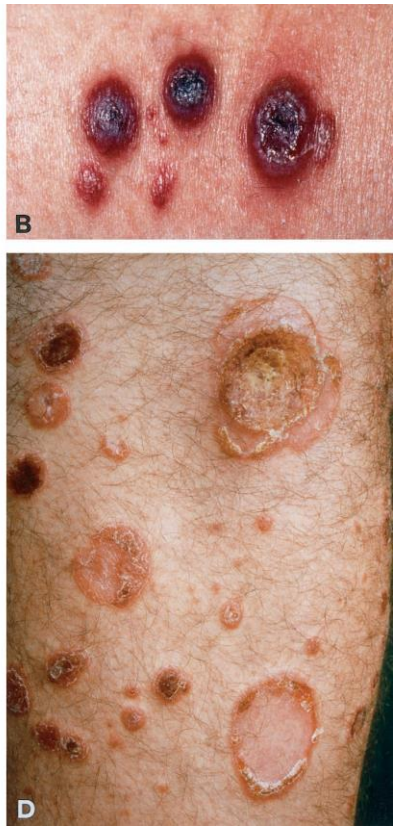
Subset of patients presenting with chronic erythematous and scaly patches resembling MF…some evolved into a more aggressive phase… the overall survival of this group was significantly better, and some patients have remained with indolent patch lesions for several years

Epidermotropic CD8+ T-cell

N=17
Cases 1-8 generalized patches, plaques, and verrucous or hemorrhagic papulonodular and tumoral lesions
Extranodal sites
- oral cavity
- testis
- lung
- central nervous system

Sparing of lymph nodes,
Rapidly fatal course





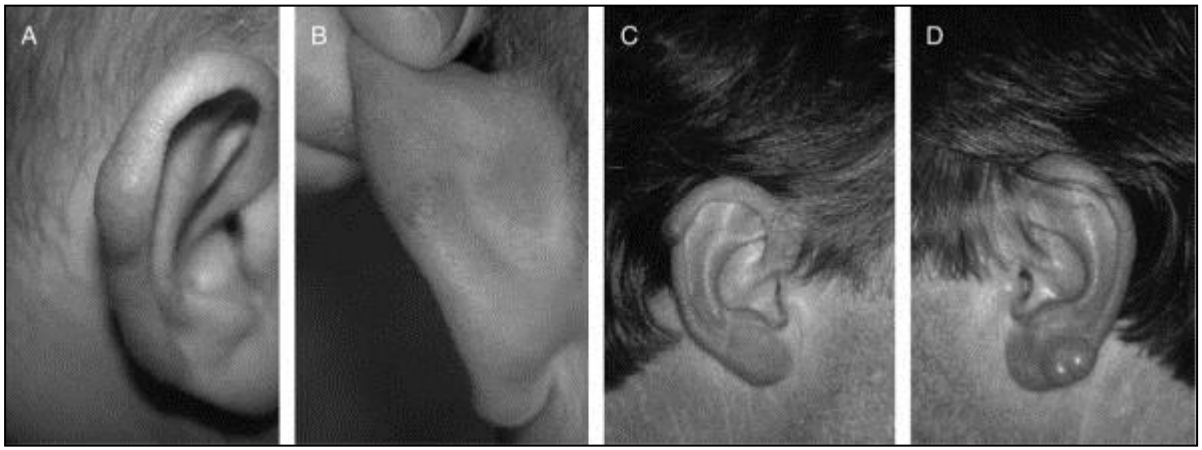
Other cases presented with features characteristic of other subtypes of CTCL, such as and clinical behavior of were similar to that reported for CD4+ cases of similar subtypes.

Berti et al. American Journal of Pathology, Vol. 155, No. 2, August 1999

Indolent CD8-positive Lymphoid Proliferation of the Ear: A Distinct Primary Cutaneous T-cell Lymphoma?

No.	Sex/Age	Lesion/Location	DBD (mo)	Staging	Treatment	Relapse/Location	Follow-up (mo)
1	M/61	Nodule/right ear	12	Normal	Rx	Yes/left ear	AWD/10
2	F/29	Nodule/left ear	4	Normal	Rx	No	CR/4
3	M/60	Nodules/both ears	4	Normal	Surgery	Yes/both ears	CR/168
4	M/51	Thick plaque/left ear	6	ND	SR	No	CR/14

AWD indicates alive with disease; CR, complete remission; DBD, duration before diagnosis; ND, not done; Rx, radiotherapy; SR, spontaneous remission.



Recent case of similar histology on NL fold
“Indolent CD8-positive Lymphoid Proliferation of the Ear-non-Ear type”

Petrella, et al , American Journal of Surgical Pathology. 31(12):1887-1892, December 2007.

Cutaneous γ/δ and Epidermotropic CD8 T-cell Lymphoma: Initial Treatment

- Very little data to guide therapy
- Appears that treating like other PTCL is not an effective strategy.
- Anecdotal therapy with “polychemotherapy” as used for other T-cell lymphomas well as many of the newer agents: pralatrexate, romidepsin, brentuximab, bexarotene.
- Guitart et al-4 pts with Allo-SCT, 3 -died of POD or TRM and 4th relapsed but was alive at time of report.

- Our approach-make sure aggressive form (if not treat as for more indolent CTCL and follow closely)
- If aggressive and fit pt
  - Non-CHOP induction followed but SCT, ?CNS
- If aggressive and not fit pt.
  - Treat as relapsed PTCL-single agents, clinical trials, etc.

Initial Treatment of PTCL: The Rest
Suggested approaches

- EATL Type I
  - Can probably treat like other PTCL-in particular if you treat with CHOP/CHOEP-ASCT
- Should EATL Type II be treated differently?
  - Unclear if approaches toward NK/T more effective
  - Strongly consider consolidation of responders with transplant
- HSTCL-non-CHOP (ICE or IVAC) induction followed by SCT
- Cutaneous cytotoxic lymphomas
  - If aggressive treat like HSTCL
  - If indolent treat like other CTCL-but observe as they can become aggressive