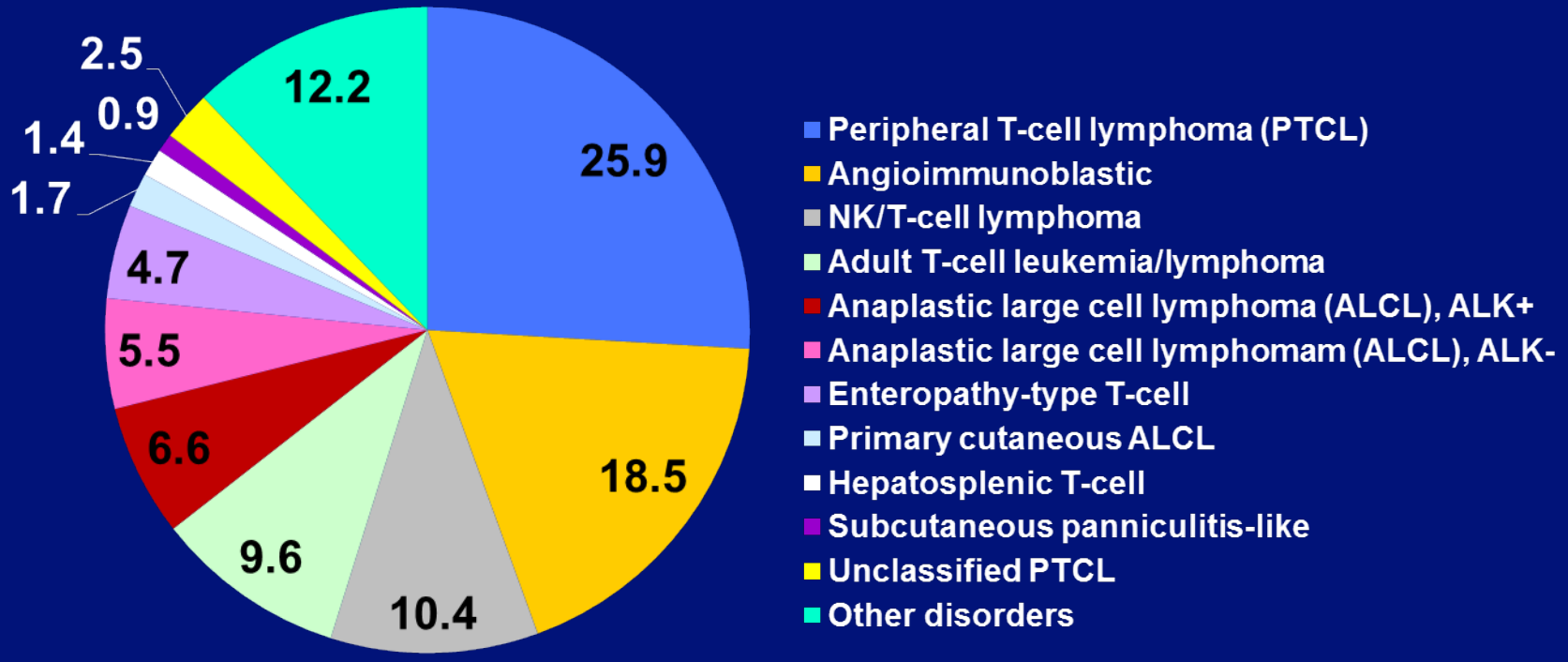
Prognostic Factors for PTCL

Julie M. Vose, M.D., M.B.A.

University of Nebraska Medical Center

jmvose@unmc.edu

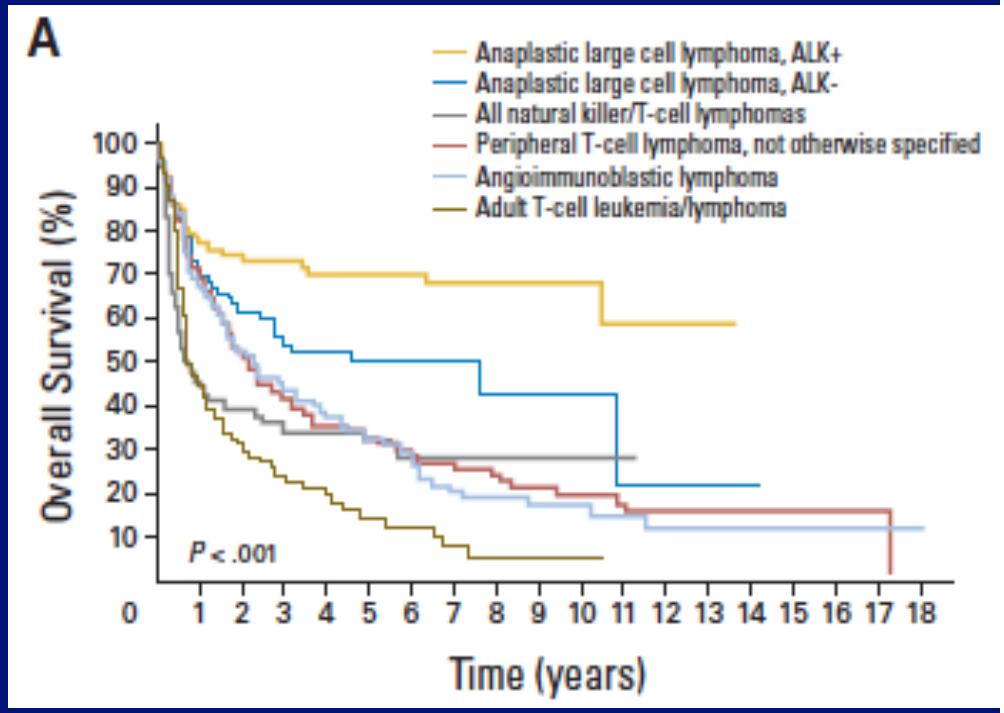
Distribution of 1314 Cases by Consensus Diagnosis

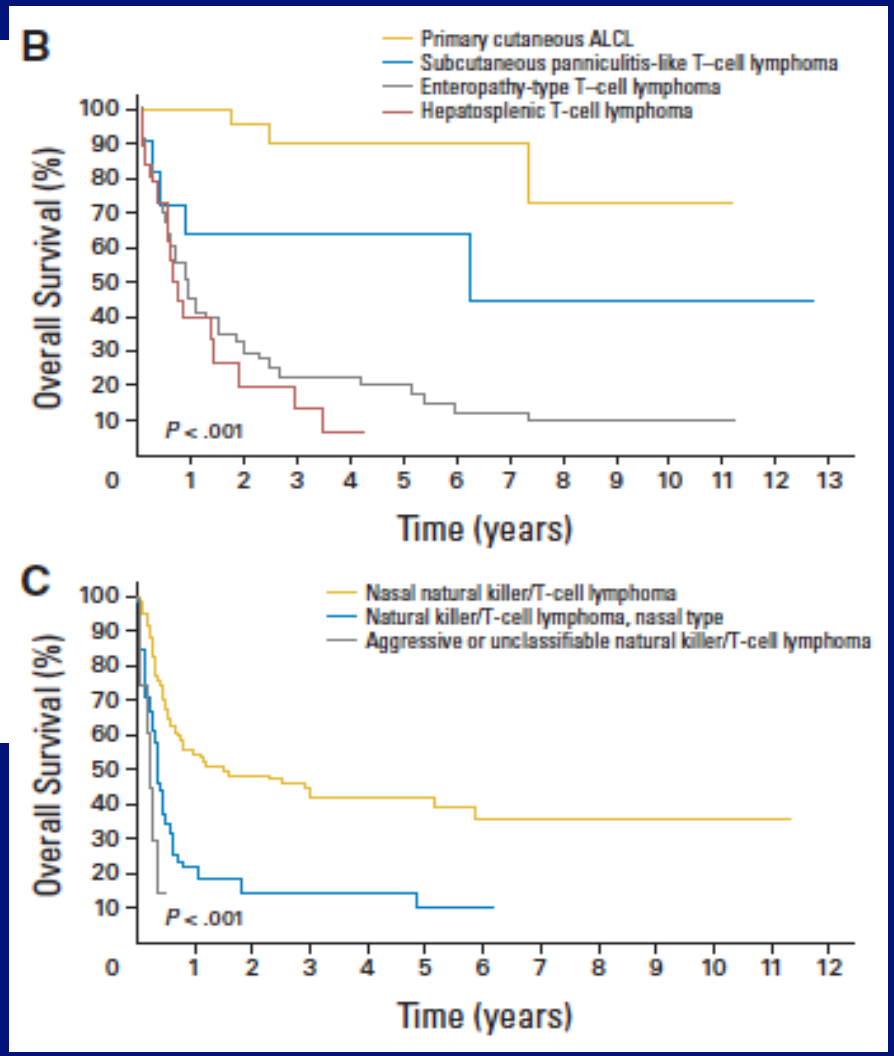


International T-Cell Lymphoma Project

Vose J, et al. *J Clin Oncol.* 2008;26(25):4124-4130.

Overall Survival of PTCL



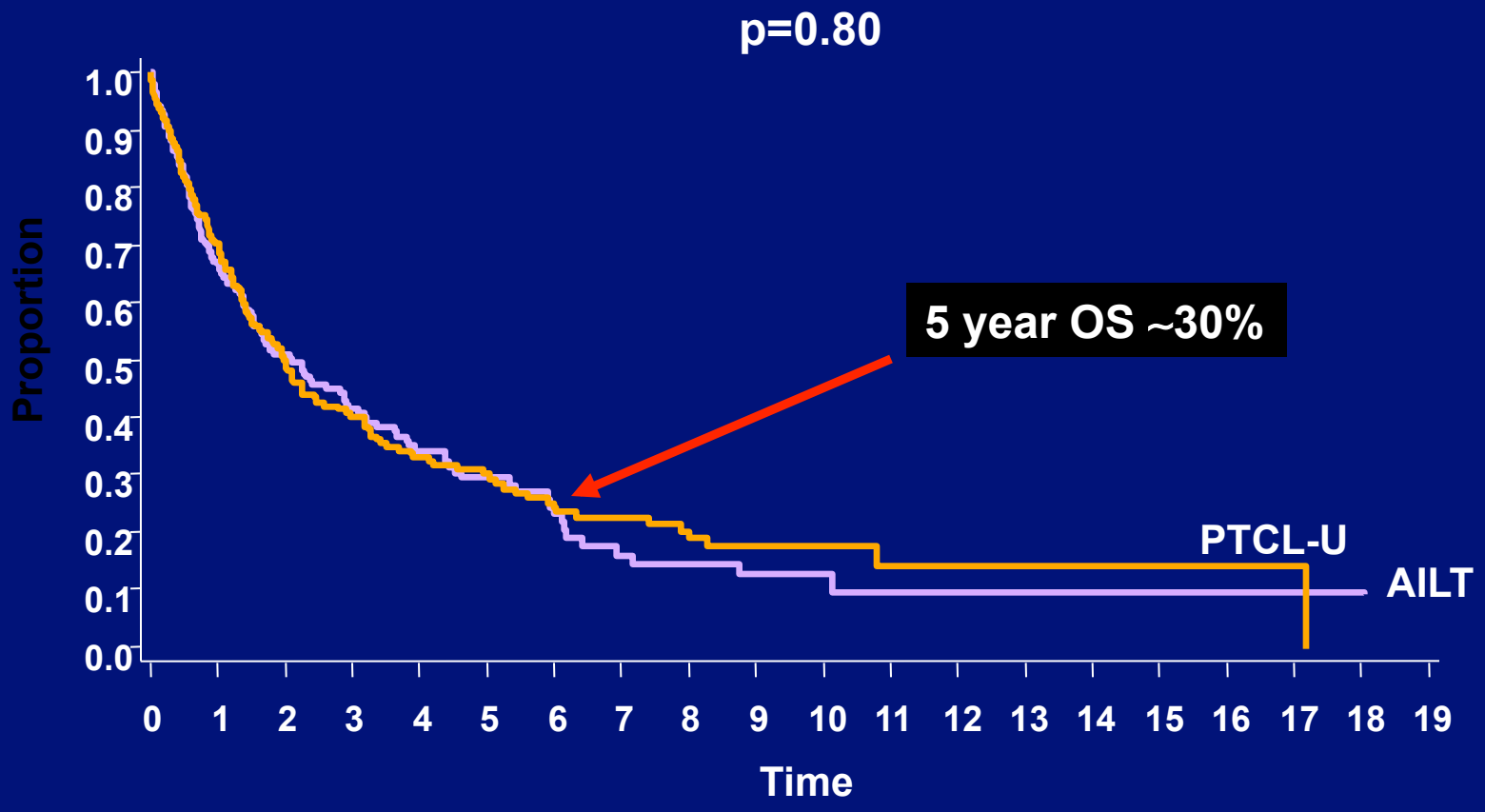


1314 cases
From 22 centers worldwide
All reviewed by a panel of experts
Treated between 1990 and 2002

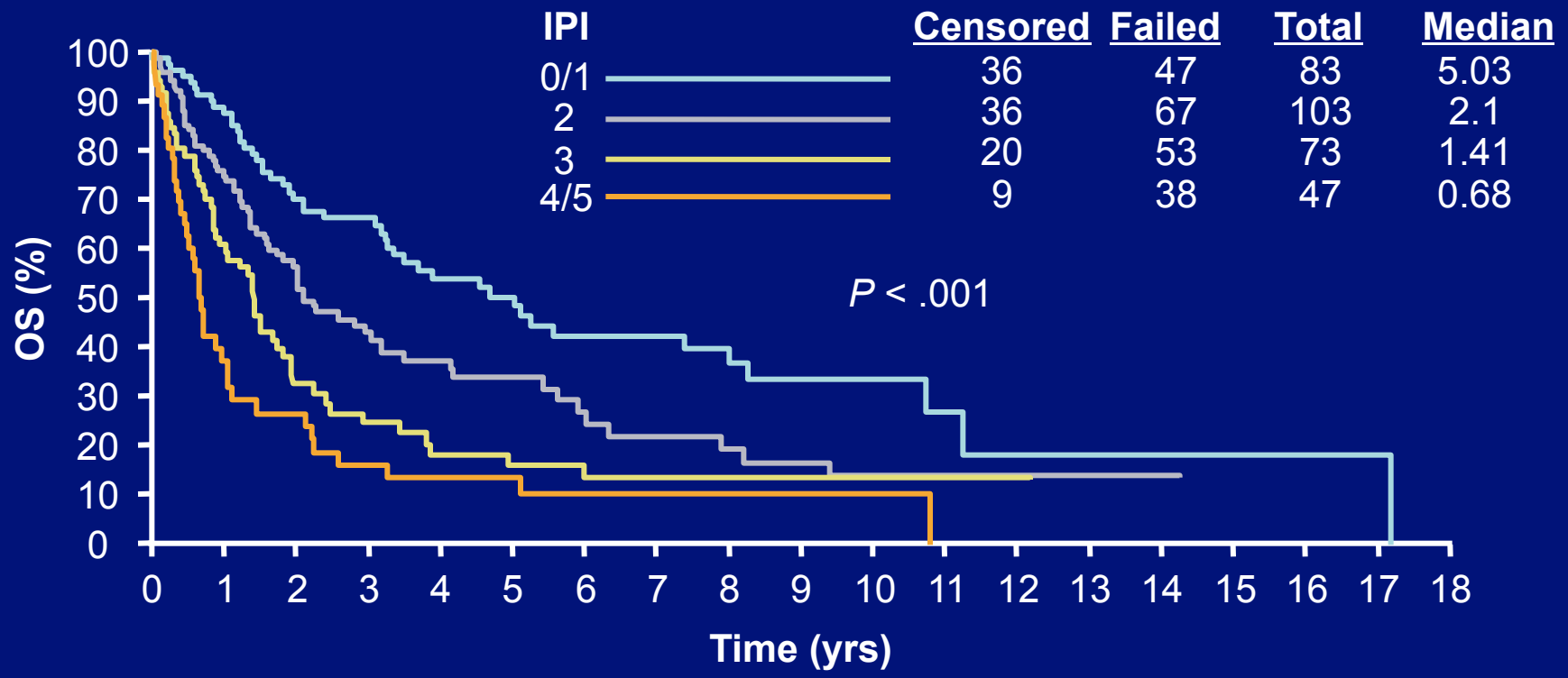
Vose J, et al. *J Clin Oncol.* 2008;26(25):4124-4130.

International T-cell Lymphoma Project

Overall Survival AITL vs PTCL-NOS

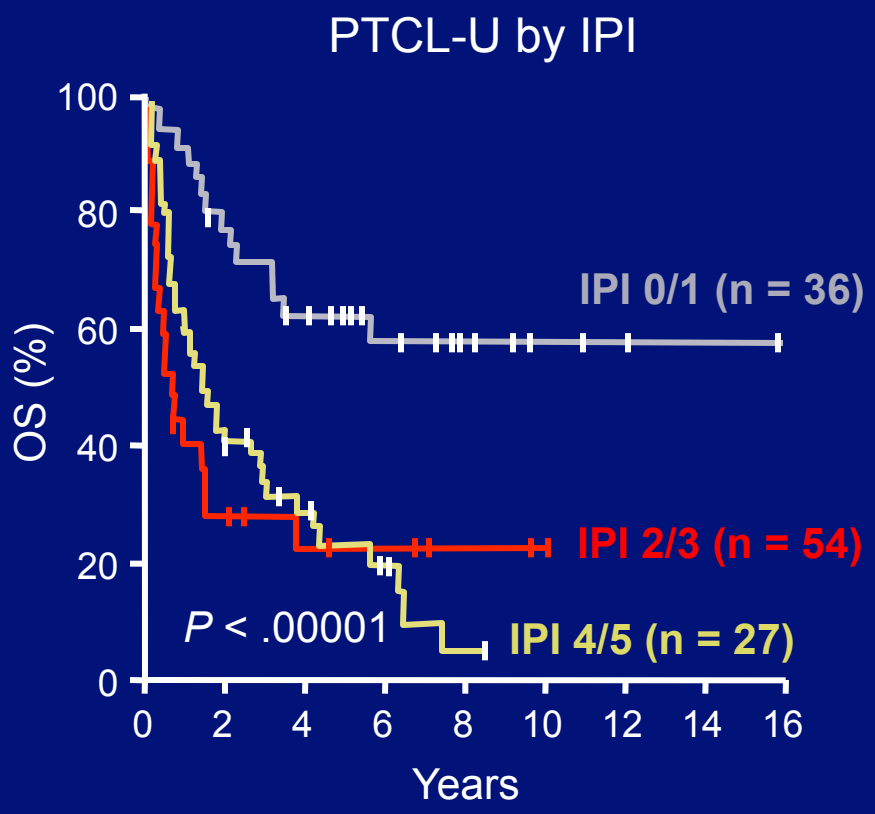


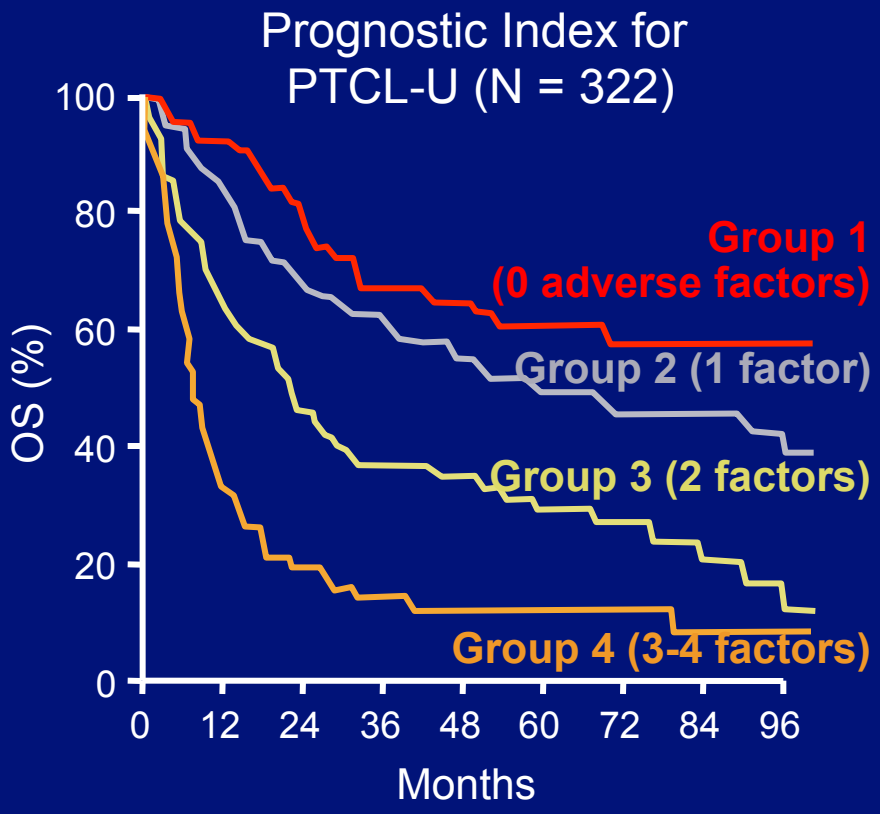
PTCL-NOS: OS by IPI



Weisenburger DD, et al. Blood. 2011;117:3402-3408.

Overall Survival Based on Prognostic Score





Savage KJ, et al. Ann Oncol. 2004;15:1467-1475.

Gallamini A, et al. Blood. 2004;103:2474-2479.

Categories of Prognostic Factors

- **Clinical Characteristics** – Age, stage, ENS, PS, BM+ (IPI, PIT)
- **Laboratory Tests** – LDH, monocytosis, B2M
- **Histology of PTCL** – Subtypes of T-cell NHL
- **Genomics of PTCL** – new models

Biologic Prognostic Markers in PTCL

Prognostic Marker	Outcome
EBV +	Unfavorable
Ki-67% $\geq$ 80	Unfavorable
Cytotoxic granule expression	Unfavorable
T-helper receptor profile – CCR3 or CCR5	Favorable
% transformed cells > 70%	Unfavorable
Proliferative signature	Unfavorable
NFkB signature	Favorable

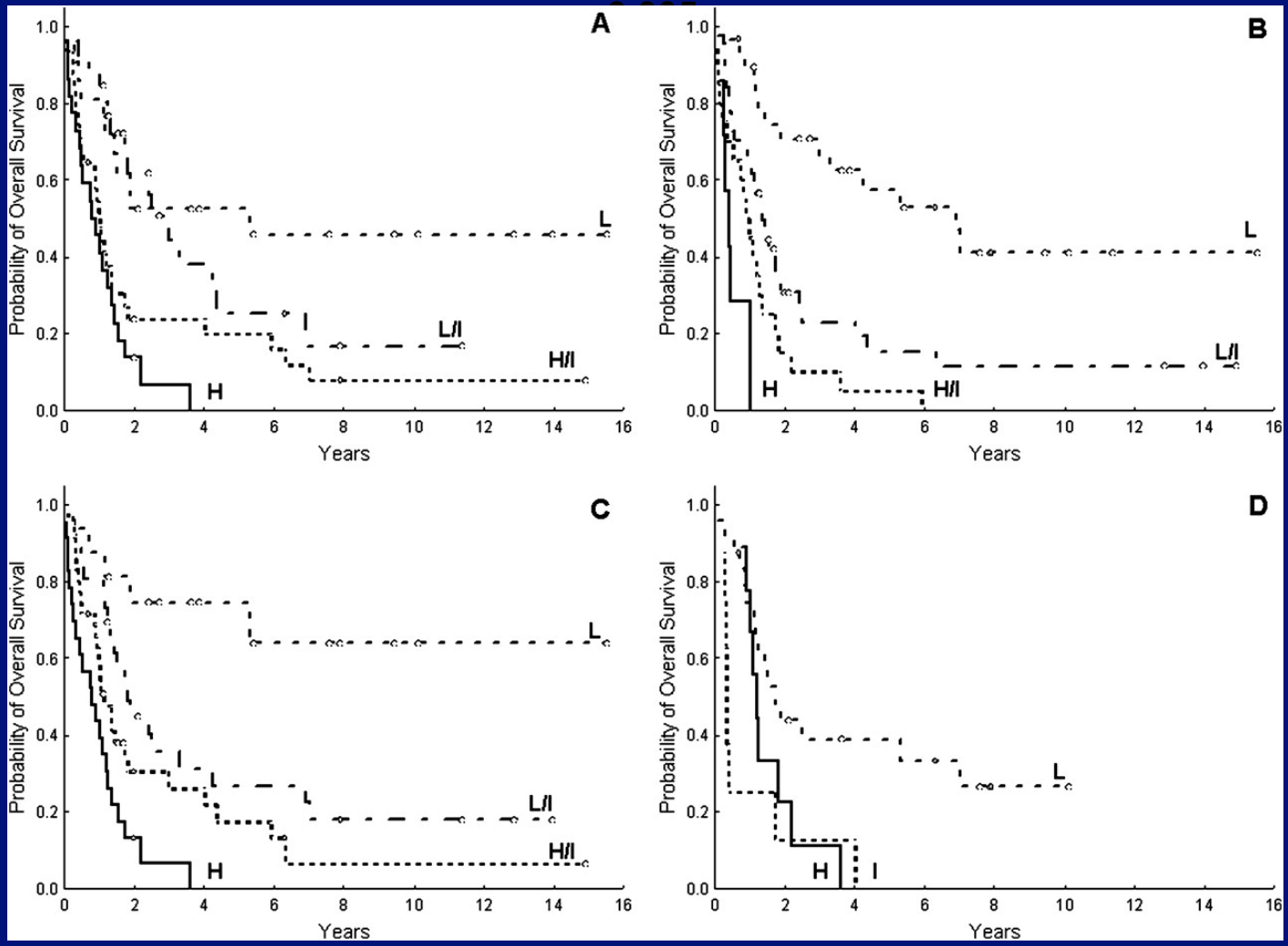
Prognostic Indices for T-cell NHL

- International Prognostic Index (IPI)
- Prognostic Index for T-cell lymphoma (PIT) – uses BM+
- Modified PIT (mPIT) – BM+ changed to Ki-67 %
- International peripheral T-cell lymphoma Project (IPTCLP) – based on PTCL and AITL only

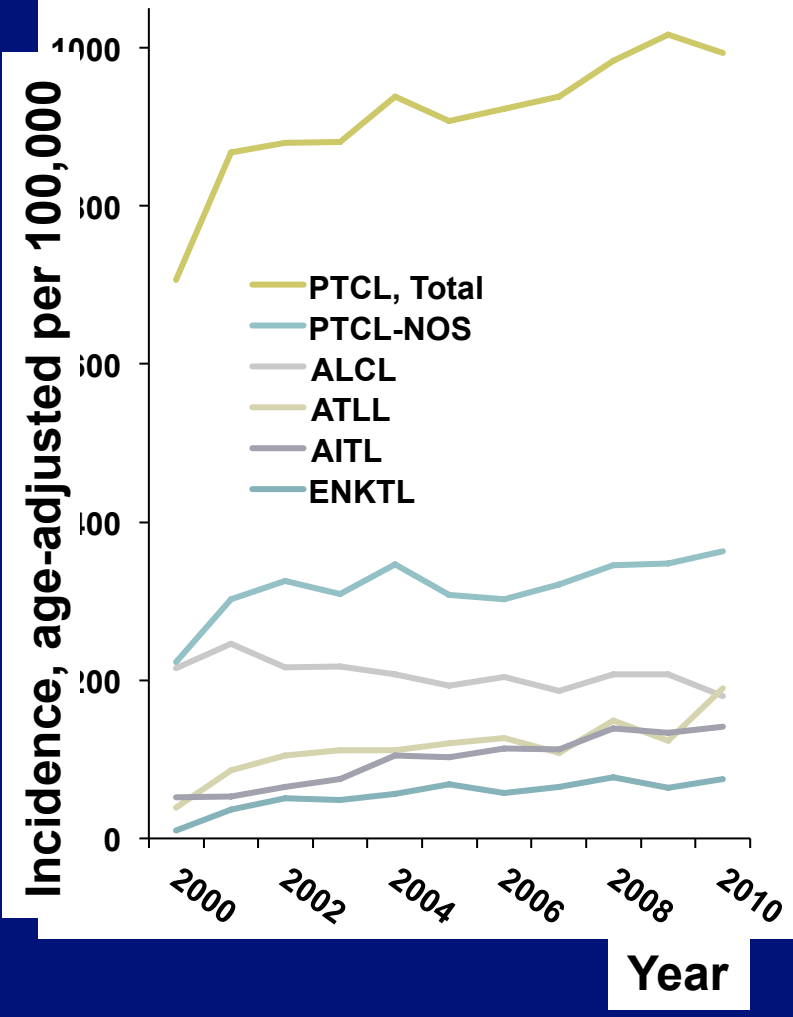
Variables Used in Prognostic Indices for PTCL

Variable	IPI	PIT	IPTCLP	mPIT
Age > 60	X	X	X	X
ECOG >1	X	X	X	X
LDH > N	X	X		X
Stage I/II vs. III/IV	X			
ENS > 1	X			
BM +		X		
Plt < 150			X	
Ki-67 > 75%				X

Overall survival of the patients with peripheral T-cell lymphoma (anaplastic large-cell lymphoma, ALK+ excluded) according to the different scores: (A) International Prognostic Index (IPI), P < 0.0001; (B) International peripheral T-cell lymphoma Project score (IPTCLP), P < 0.0001; (C) PIT, P < 0.0001 and (D) modified Prognostic Index for T-cell lymphoma (mPIT), P



G. Gutiérrez-García et al. Ann Oncol 2011;22:397-404



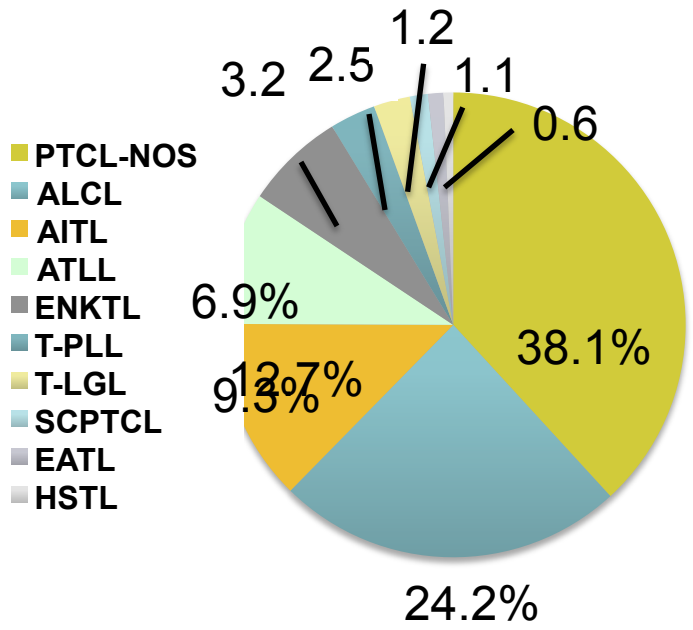


Figure 1: Incidence rates by year, age-adjusted to the 2000 US population, expressed per 100,000 population (A); and proportion of PTCL cases by histologic subtype (B). PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL not otherwise specified; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ENKTL, extrandoal NK/T-cell lymphoma, nasal type. (N= 8802 in SEER 2000-2010)

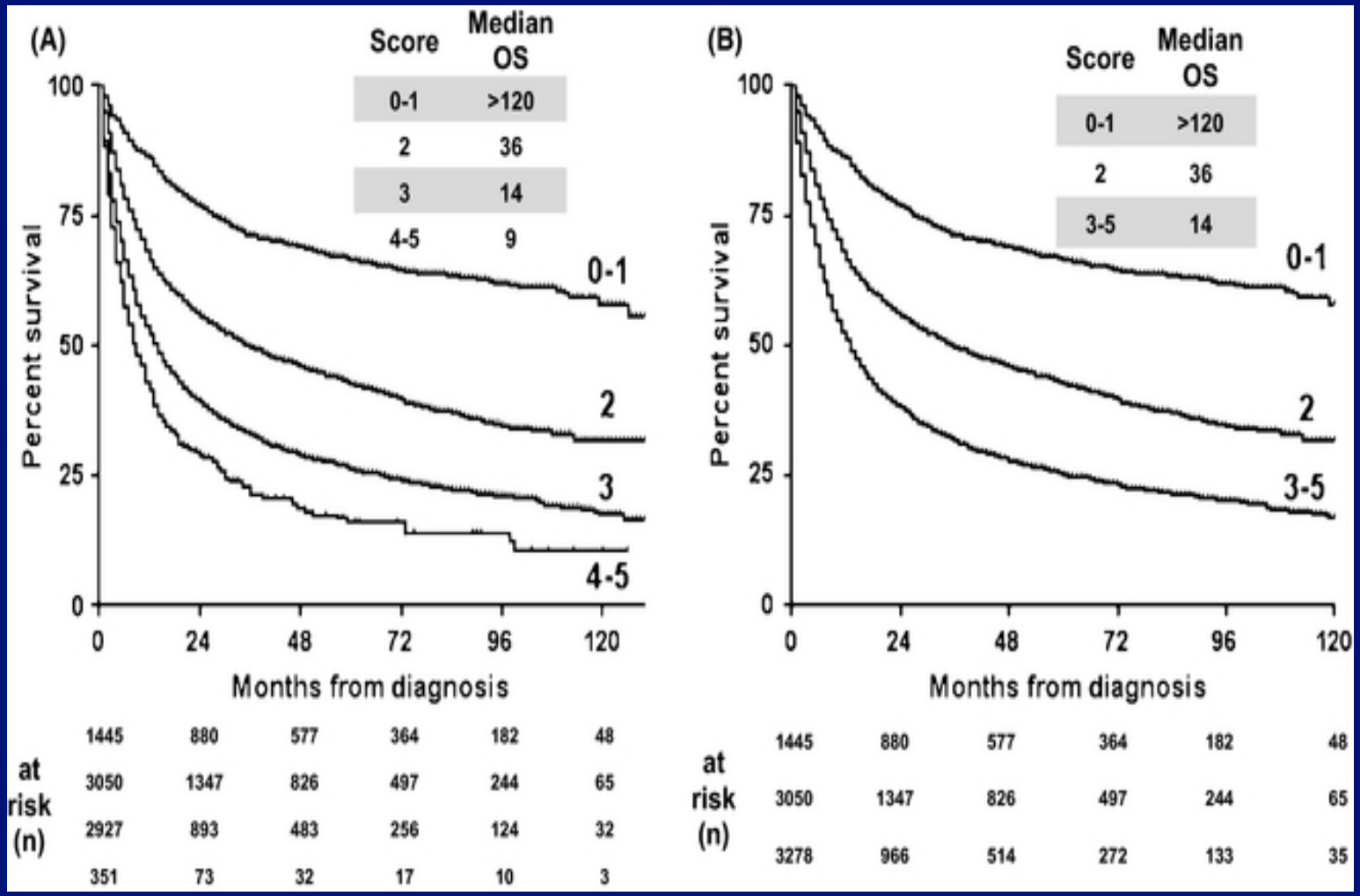
Petrich, et al: BJH 168: 708-718, 2015

Multivariate analysis of Survival

- Age ≥ 55 years – 1 point
- African American Race – 1 point
- Histology
  - HSTL, EATL, ENKTL, T-PLL – 2 points
  - PTCL-NOS, AITL, ATLL, ALCL – 1 point
  - SCPTL, T-LGL – 0 points
- Advanced stage – 1 point

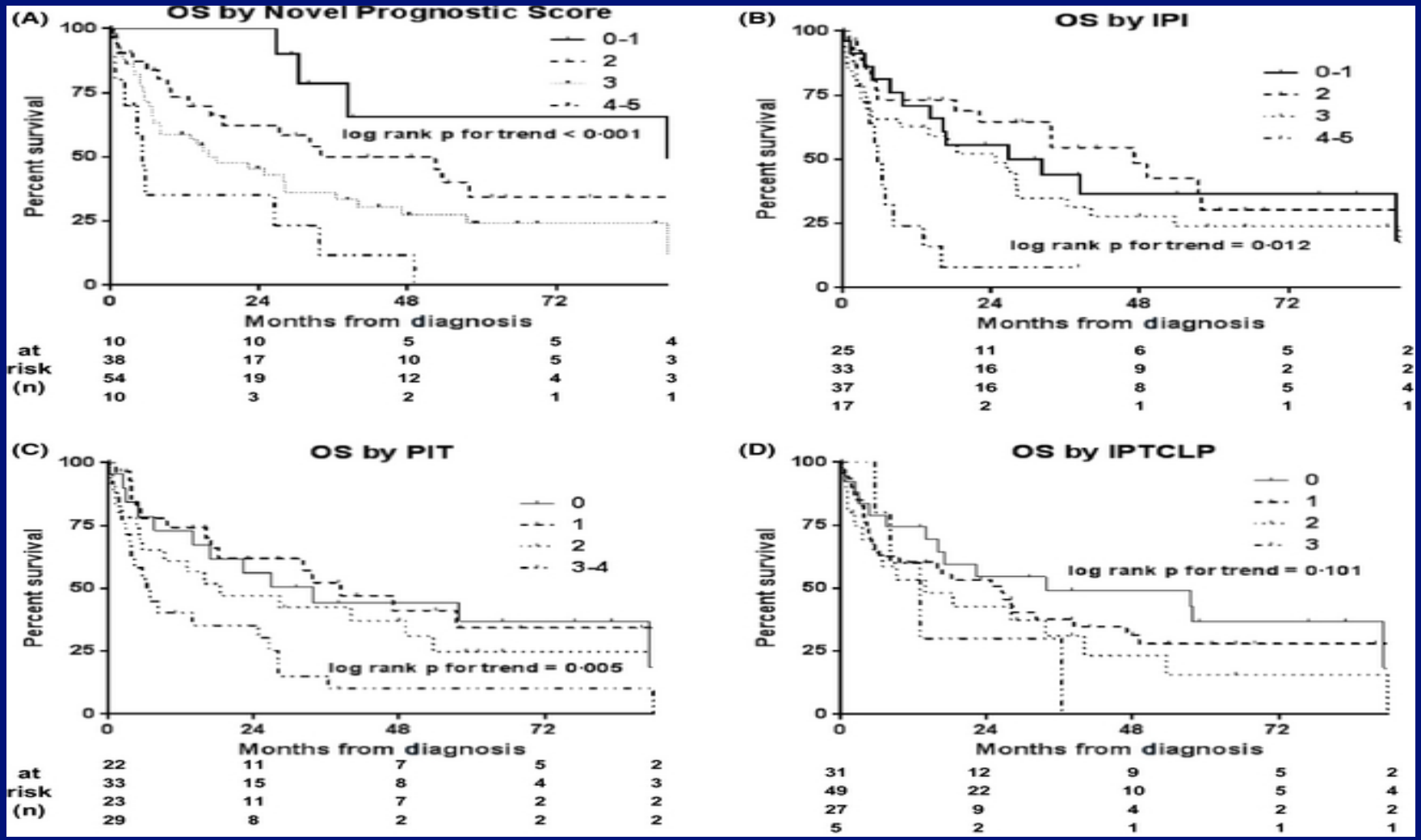
Petrich, et al: BJH 168: 708-718, 2015

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era



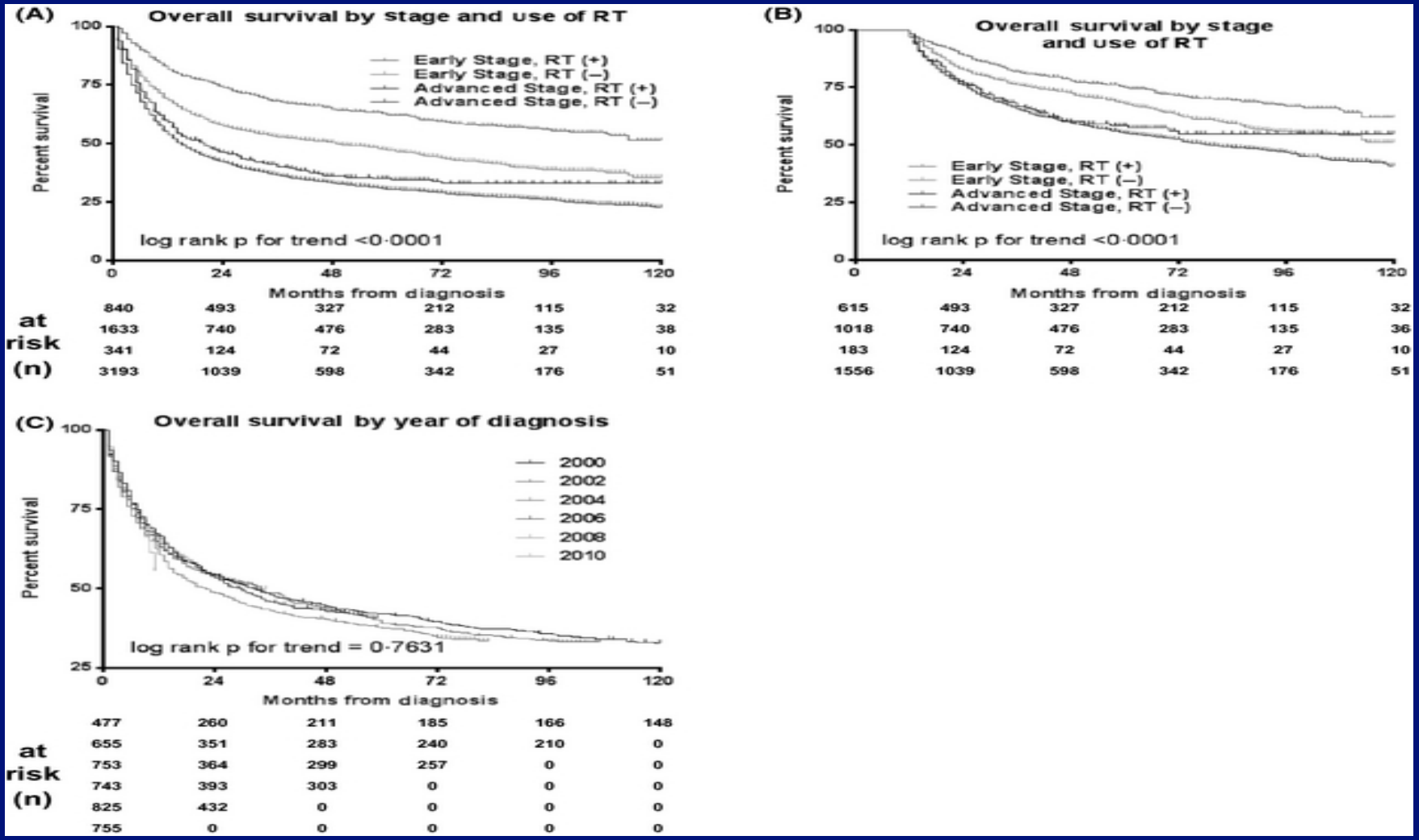
Petrich, et al: BJH 168: 708-718, 2015

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era



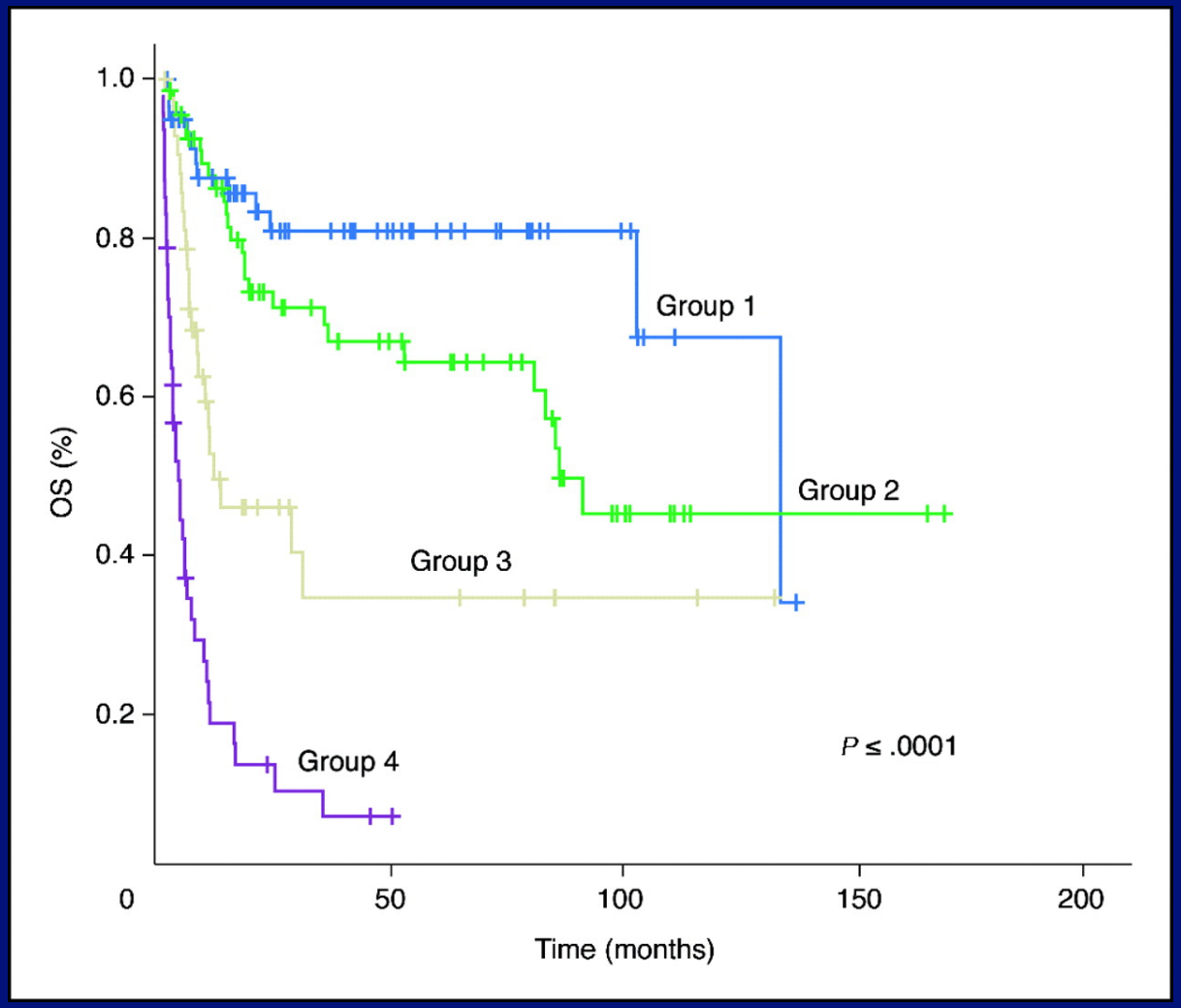
Petrich, et al: BJH 168: 708-718, 2015

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era



Petrich, et al: BJH 168: 708-718, 2015

Survival according to the new prognostic index. For NKT-cell – nasal type



1. B symptoms
2. Stage ≥ III
3. LDH > normal
4. LN N1-N3, not M1

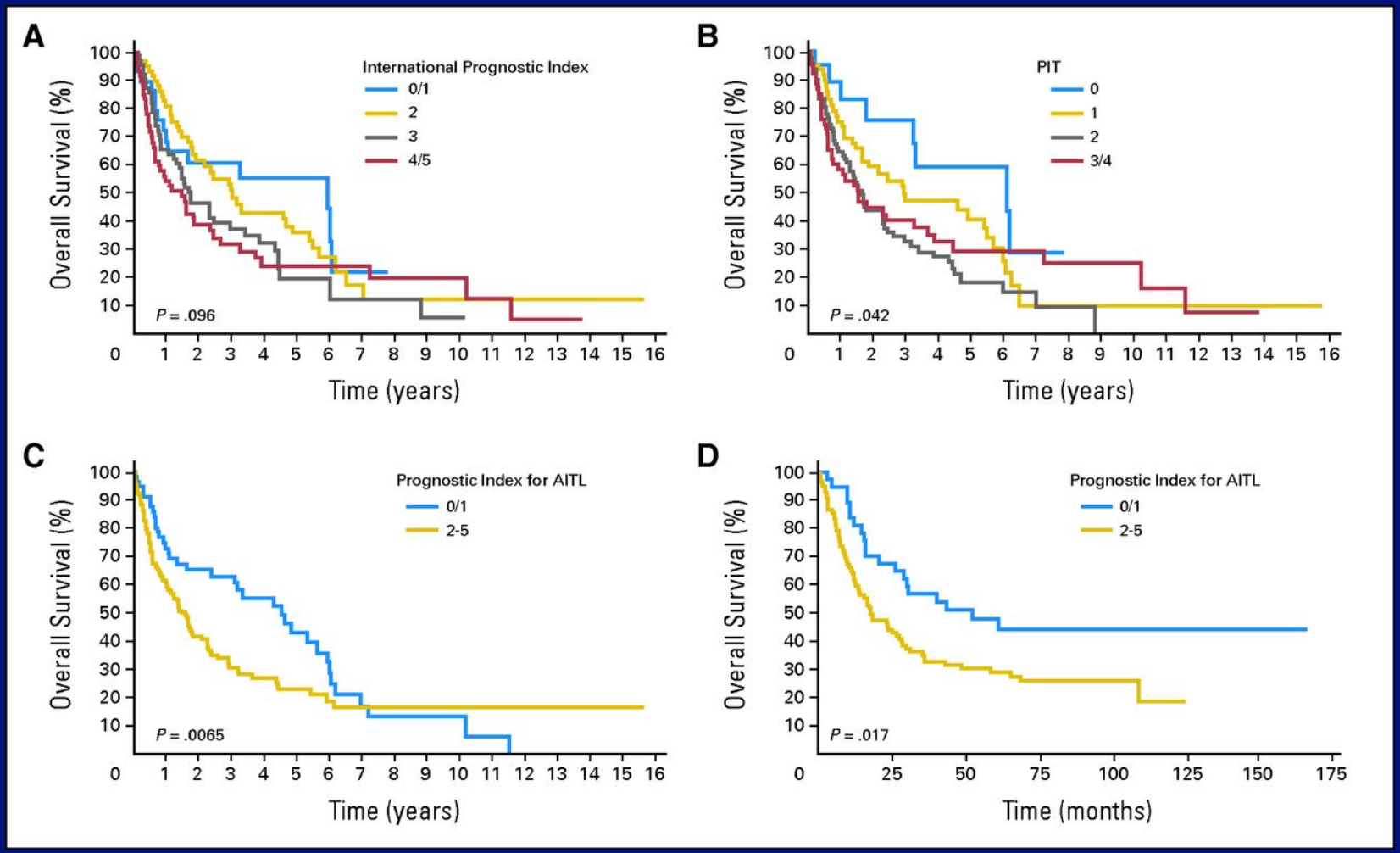
Jeeyun Lee et al. JCO 2006;24:612-618

Analysis of Angioimmunoblastic T-cell lymphoma of the IPTCLP

- 243 AITL patients, Validation GELA cohort
- Standard IPI evaluated
- Alternative Prognostic Index for AITL (PIAI)
  - Age > 60
  - PS $\geq$ 2
  - ENS > 1
  - B-symptoms present
  - Platelet count < 150K

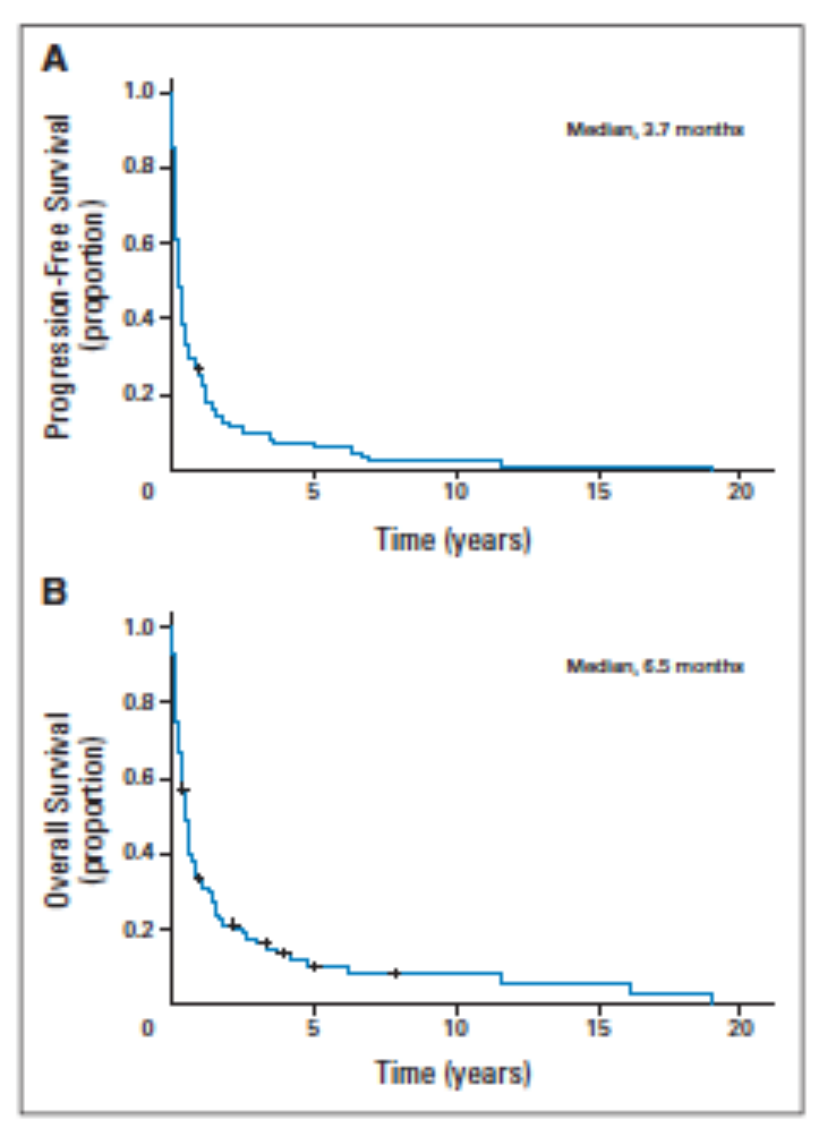
Federico, et al: JCO 31: 240-246, 2013

Overall survival (OS) for patients with angioimmunoblastic T-cell lymphoma (AITL) using the (A) International Prognostic Index, (B) Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified (PIT), and (C) Prognostic Index for AITL (PIAI); (D) OS for GELA...

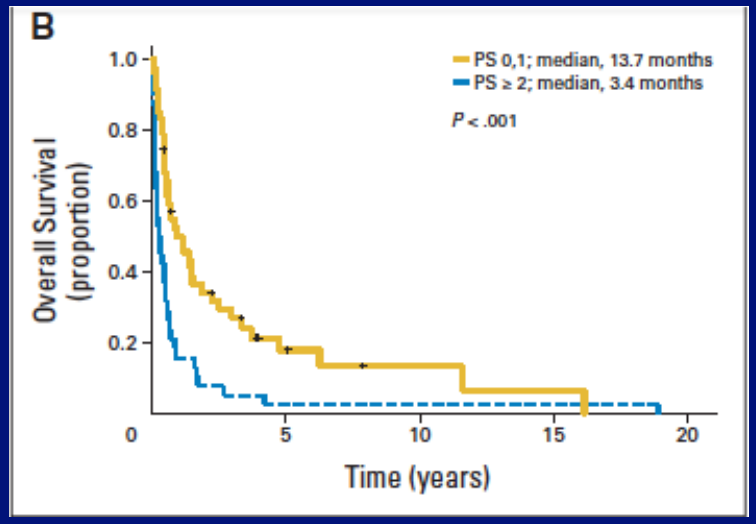


Massimo Federico et al. JCO 2013;31:240-246

Survival of Relapsing PTCL



153 Relapsed patients
89 treated with chemotherapy ; no HSCT
52% PTCL NOS
Median time to PD: 6.7 months
Better outcome with good PS



NOS, not otherwise specified; PD, progressive disease; PS, performance status; PTCL, peripheral T-cell lymphoma

Mak V, et al. *J Clin Oncol.* 2013;31(16):1970-1976.

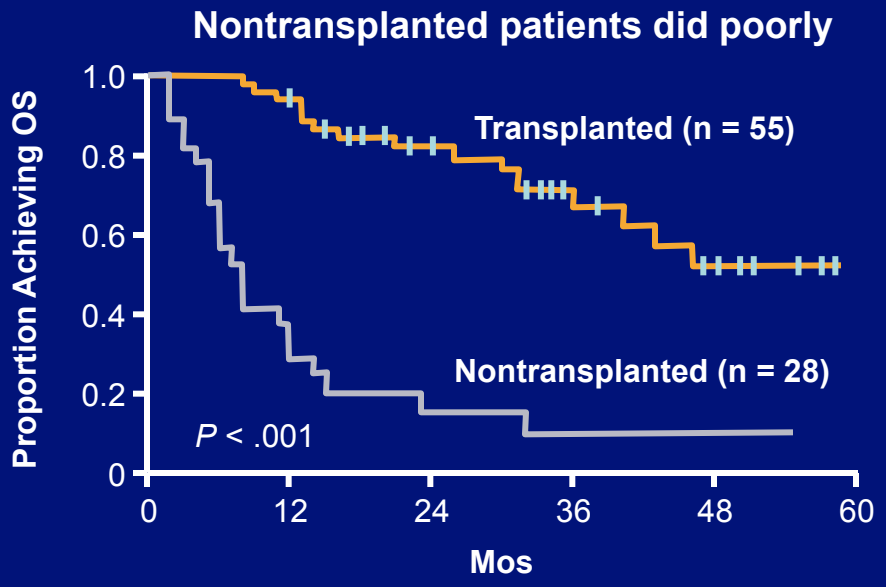
Table 3.

Multivariate Analysis of Prognostic Factors for Second PFS and OS After Relapse or Progression in Chemotherapy-Treated Group (n = 89)

Prognostic Factor	Second PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Elevated LDH	—	—	.094	—	—	.099
PS ≥ 2	1.66	1.05 to 2.63	**.030**	2.09	1.31 to 3.35	**.002**
Bone marrow involvement			.987	2.02	1.05 to 3.86	**.034**
Type of chemotherapy			.638			.815
Combination chemotherapy	0.63	0.40 to 0.99	**.043**	0.55	0.35 to 0.87	**.011**
Time to relapse, months						.230
< 6				—	—	
6-12	0.37	0.21 to 0.67	**.001**			
12-24	0.42	0.22 to 0.81	**.010**			
> 24	0.23	0.41 to 0.99	**< .001**			
Response to prior therapy	—	—	0.170	—	—	.426

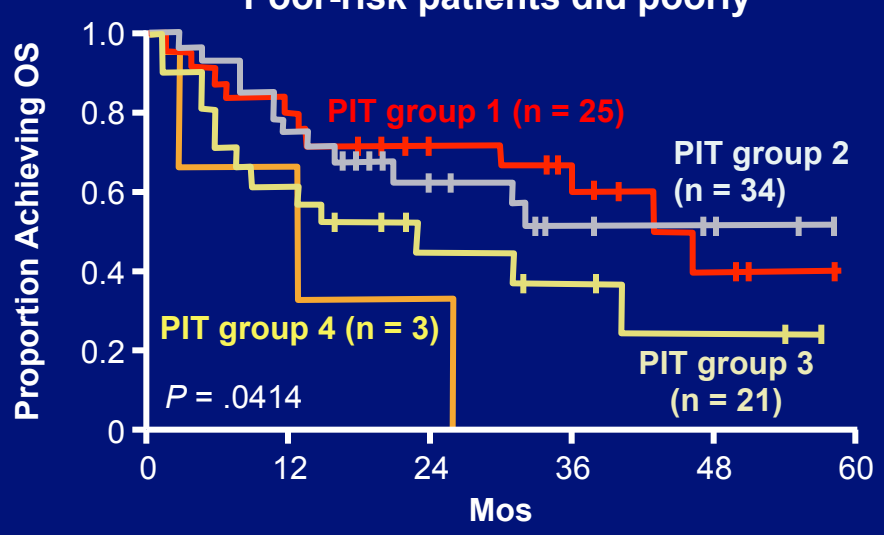
Mak V, et al. *J Clin Oncol.* 2013;31(16):1970-1976

German Prospective Trial of ASCT in First Remission



- PIT group 1: 0 risk factors
- PIT group 2: 1 risk factor
- PIT group 3: 2 risk factors
- PIT group 4: 3-4 risk factors

- N = 83 untreated patients
- CHOP x 4-6
- If ≥ PR, dexaBEAM or ESHAP
- dexaBEAM or ESHAP ± TBI, ASCT
- Median follow-up: 33 mos

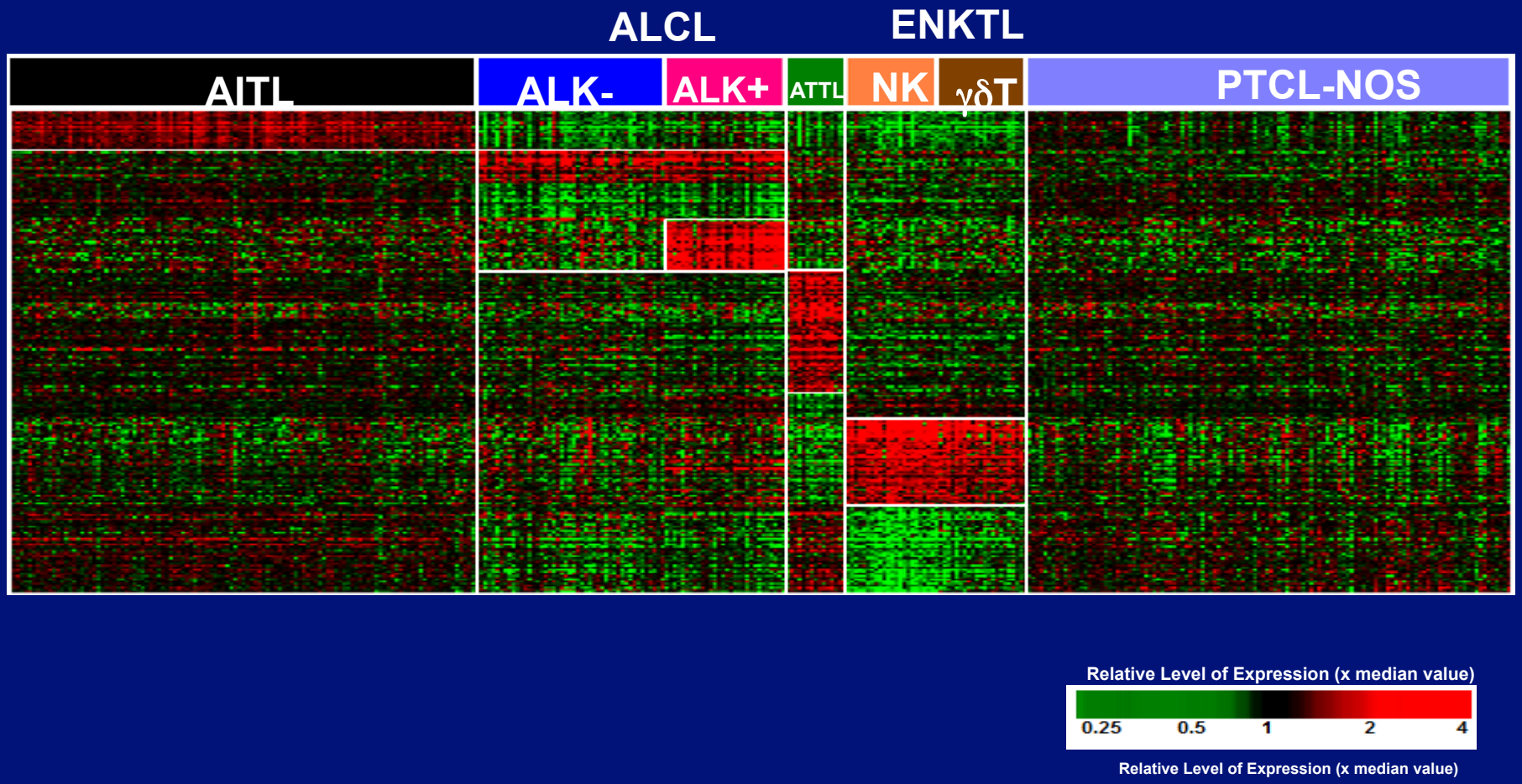


Reimer P, et al. J Clin Oncol. 2009;27:106-113.

Molecular Prognostic Indices

- PTCL- NOS: many different entities
- AITL – model using
  - P53 upregulation signal
  - Cytotoxic phenotype
  - Monocytic/dendritic signature
  - B-cell signature

Refinement of molecular diagnostic signatures for PTCL subgroups

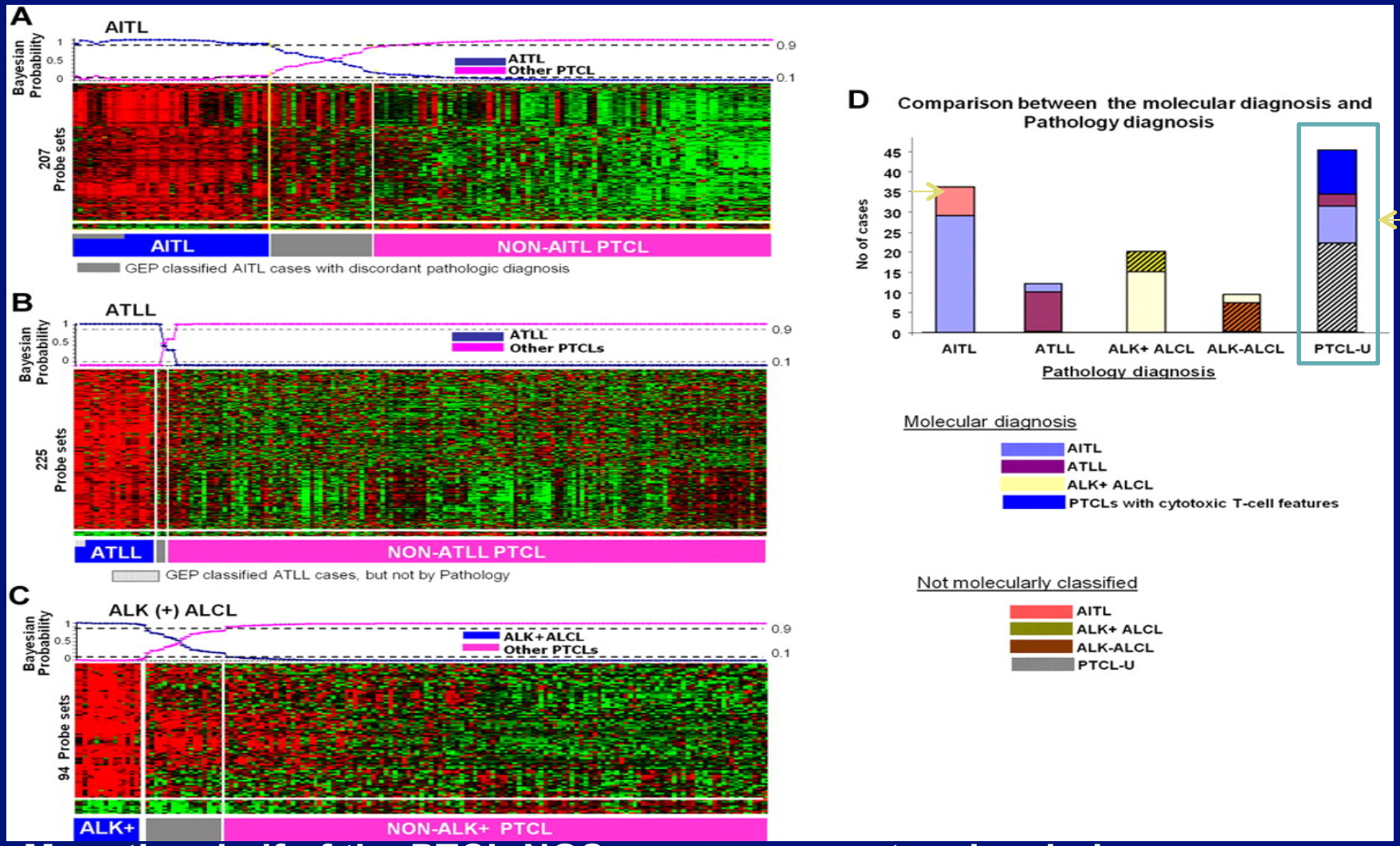


- **Unique molecular signatures were identified for major PTCL entities**

Lymphoma and Leukemia Molecular Profiling Project (LLMPP) initiative

Blood. 2014 May 8;123(19):2915-23.

Gene expression-based molecular predictors of the major subgroups of PTCL

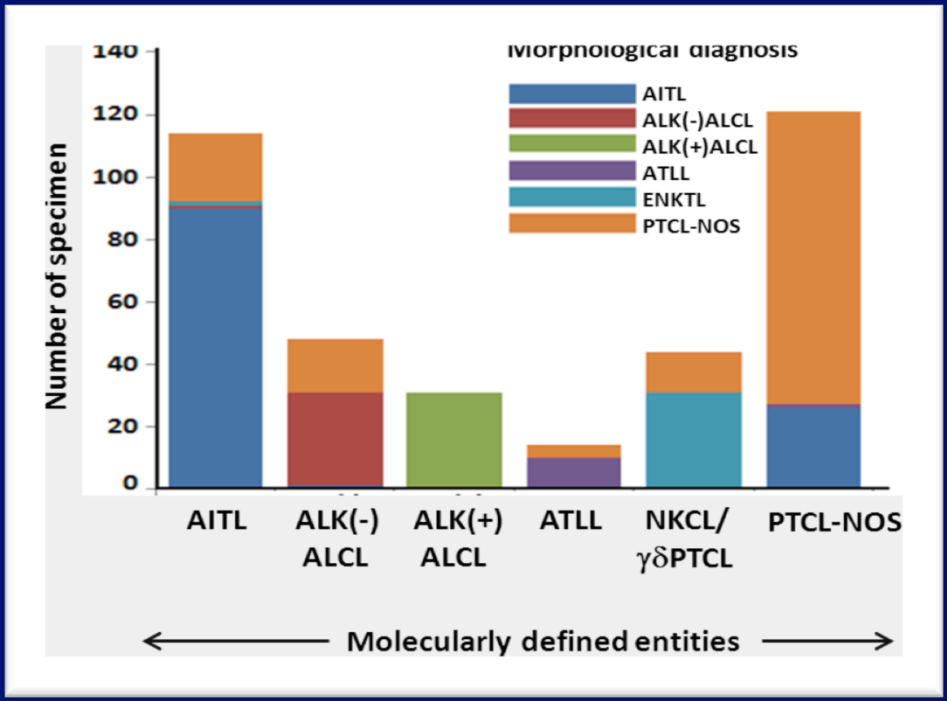


- More than half of the PTCL-NOS cases were <u>not</u> molecularly classified

International peripheral T-cell lymphoma Project

Blood 2010;115:1026-1036

Evaluation of pathological *vs* molecular diagnosis



-of 152 PTCL-NOS cases, a subset of cases were classified into

i. AITL [14%]
ii. ALK(-)ALCL [11%]
iii.ATLL [03%]
iv.γδ- PTCL [09%]

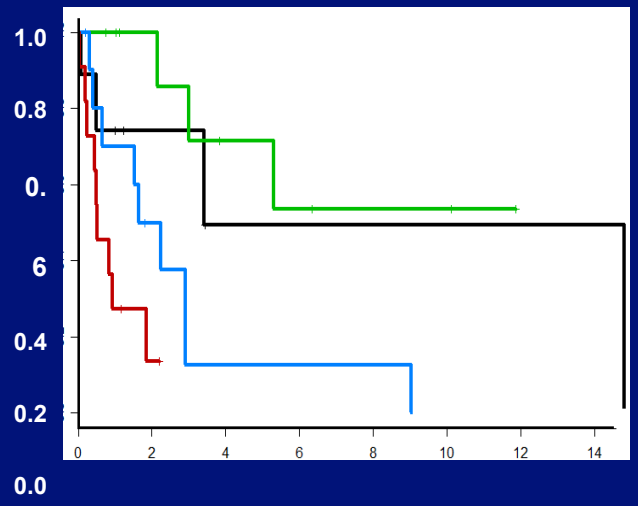
- Of 117 AITL cases 26 cases (22%) changed to PTCL-NOS.

Blood. 2014 May 8;123(19):2915-23.

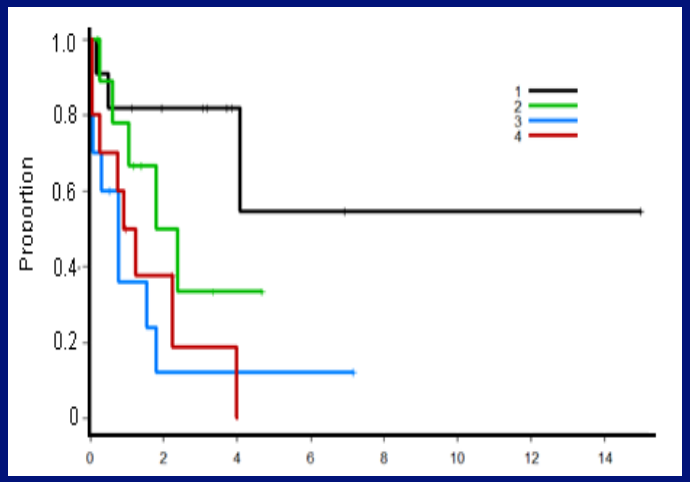
Survival prediction on AITL: role of tumor microenvironment

Signature Cluster	Effect of high expression	Training p-value	Validation p-value
p53 upregulated signature	Poor prognosis	0.001	0.014
Cytotoxic signature	Poor prognosis	0.005	0.046
Monocytic/dendritic signature	Poor prognosis	0.011	0.010
B- cell signature	Good prognosis	0.002	0.017

Training set



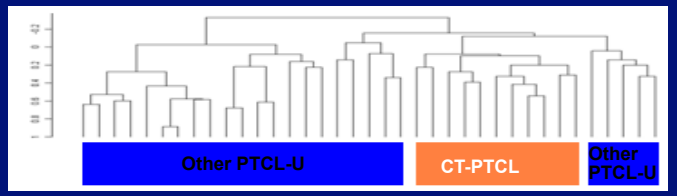
Validation set



- Tumor microenvironment significantly influences the prognosis in AITL
- Role of macrophages (M1) vs (M2) and dendritic cells are being investigated

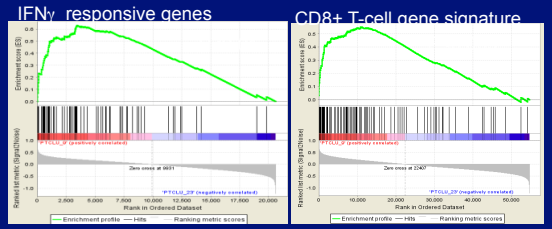
Identification of cytotoxic (αβ) PTCL group from PTCL-NOS

(A) Hierarchal clustering

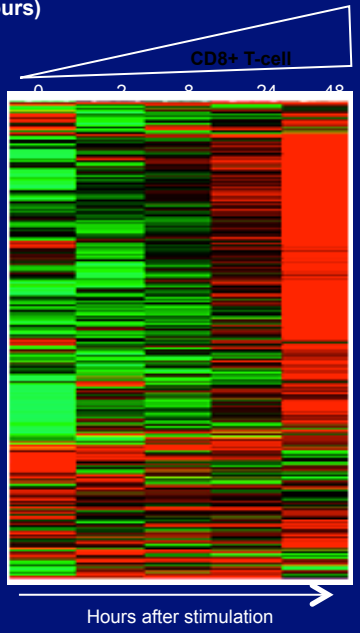


Dendrogram for clustering PTCL-NOS cases using centered correlation and complete linkage

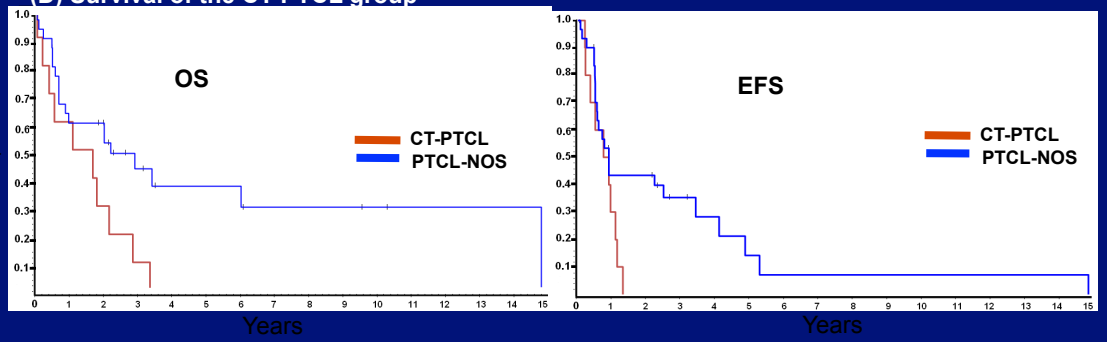
(C) GSEA analysis



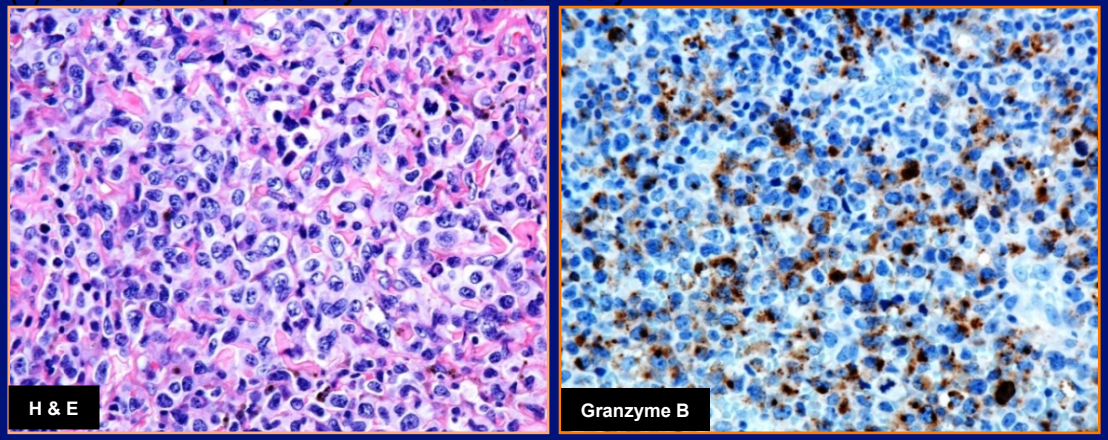
(B) Expression of the CT-PTCL signature in normal CD8+ T-cells stimulated with anti-CD3, anti-CD28 and IL12 for various time intervals (hours)



(D) Survival of the CT-PTCL group



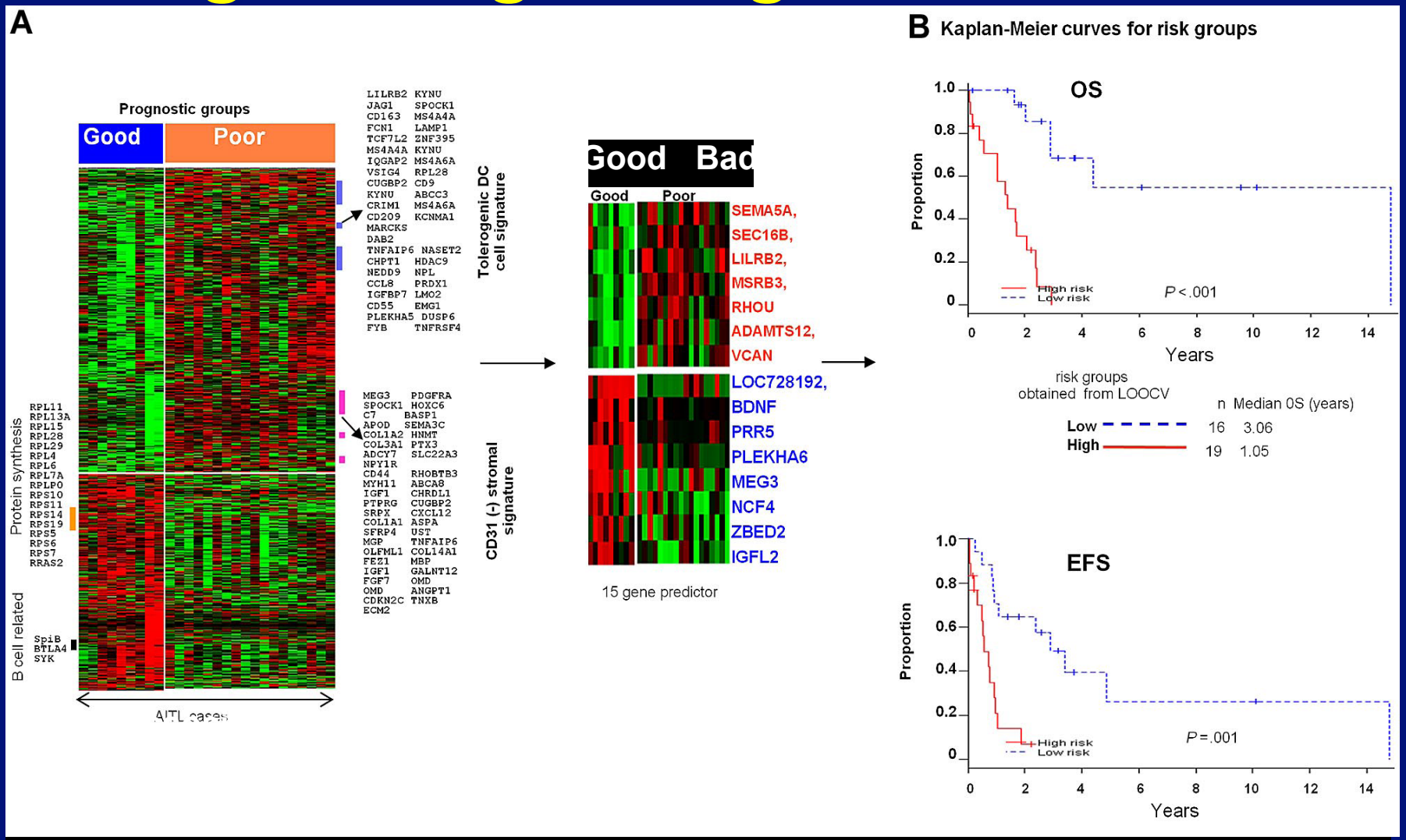
(E) Granzyme B expression by immunohistochemistry in CT-PTCL



International peripheral T-cell lymphoma Project

Blood 2010;115:1026-1036

Prognostic gene signatures in AITL



Long term survivors with AILT do occur – further study needed to identify these patients - ?alternate therapy

Prognostic Factors for PTCL

- Clinical factors – still important. IPI, PIT, individual histologic models work for low risk groups best
- Biologic factors – pathways, molecular profiling may be more helpful in the future for treatment choices