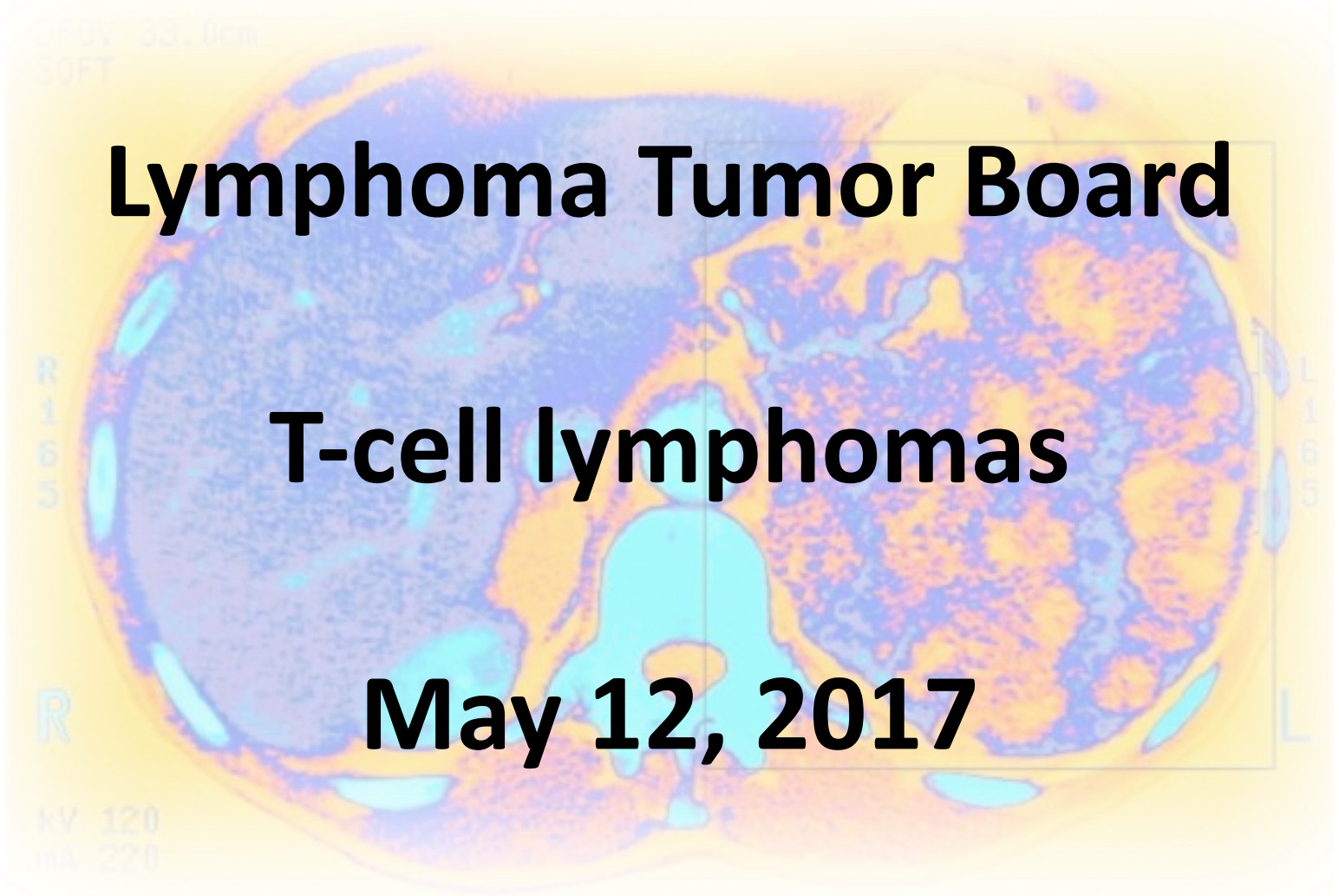


Lymphoma Tumor Board

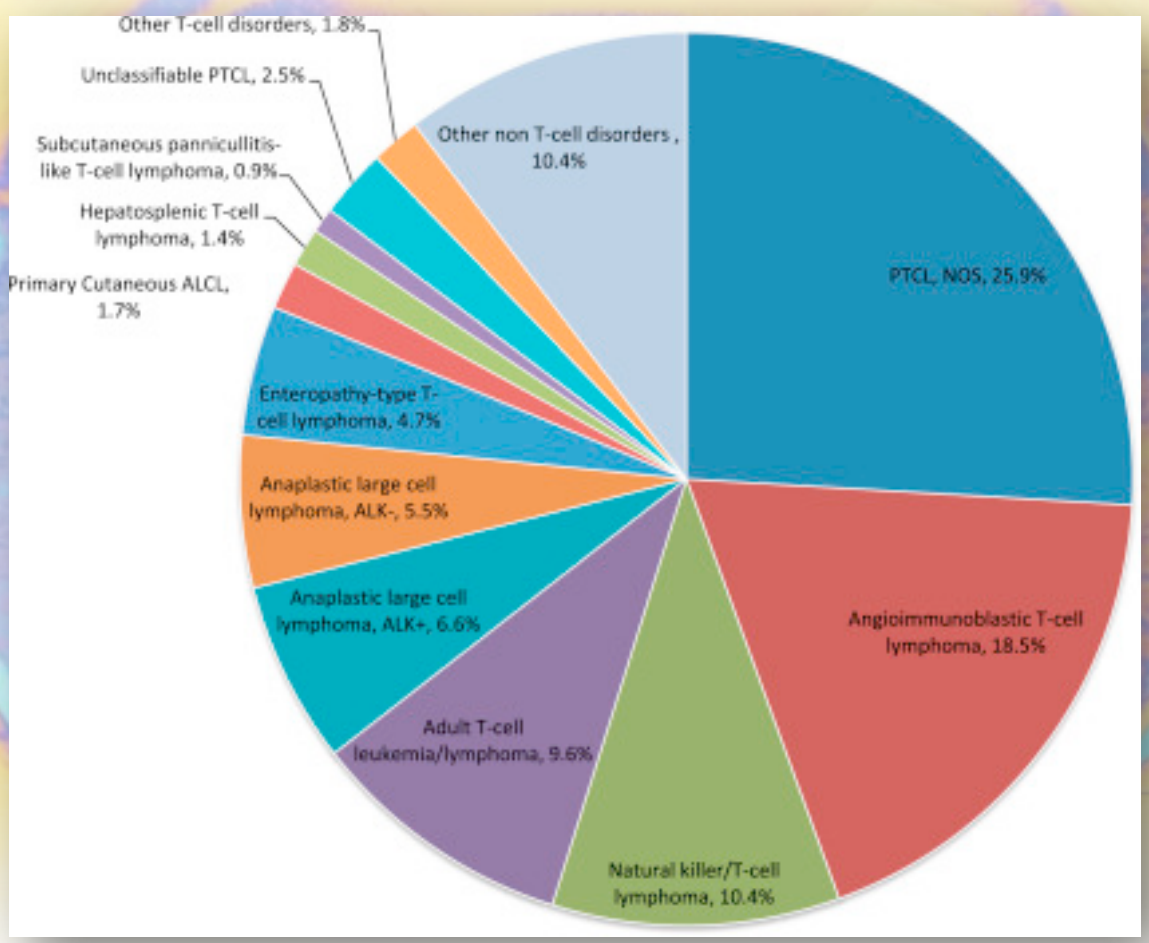
T-cell lymphomas

May 12, 2017

WHO / Revised European American Lymphoma (REAL) Classification

B-cell lymphomas(80% - 85%)	T-cell lymphomas (15% - 20%)
• Diffuse large B-cell lymphoma • **Follicular lymphoma** • **Chronic lymphocytic leukemia** /small lymphocytic lymphoma • Mantle cell lymphoma • Marginal zone B-cell lymphomas • Burkitt lymphoma • Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) • Hairy cell leukemia • Primary central nervous system (CNS) lymphoma	• Precursor T-lymphoblastic lymphoma/leukemia • Peripheral T-cell lymphomas • Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others) • Adult T-cell leukemia/lymphoma • Angioimmunoblastic T-cell lymphoma • Extranodal natural killer/T-cell lymphoma, nasal type • Enteropathy-associated intestinal T-cell lymphoma (EATL) • Anaplastic large cell lymphoma (ALCL) • Peripheral T-cell lymphoma, unspecified

Peripheral T-Cell Lymphomas – Incidence



Peripheral T-Cell Lymphomas

- T-cell lymphomas are rare and account for one in ten cases of non-Hodgkin lymphoma
- Can be associated with EBV and Human T-lymphotropic virus 1 (HTLV-1)
  - Only 1-5% of infected persons are thought to develop cancer as a result of infection with HTLV-1
- Peripheral T-cell non-Hodgkin lymphoma (PTCL), not otherwise specified (NOS), is the most common PTCL subtype, accounting for 25% of cases
- Four primary classes of T-cell lymphomas:
  - Extranodal T cell lymphoma
  - Cutaneous T cell lymphomas: Mycosis fungoides and Sézary syndrome
  - Anaplastic large cell lymphoma
  - Angioimmunoblastic T cell lymphoma

Karyotypic abnormalities in a patient with PTCL

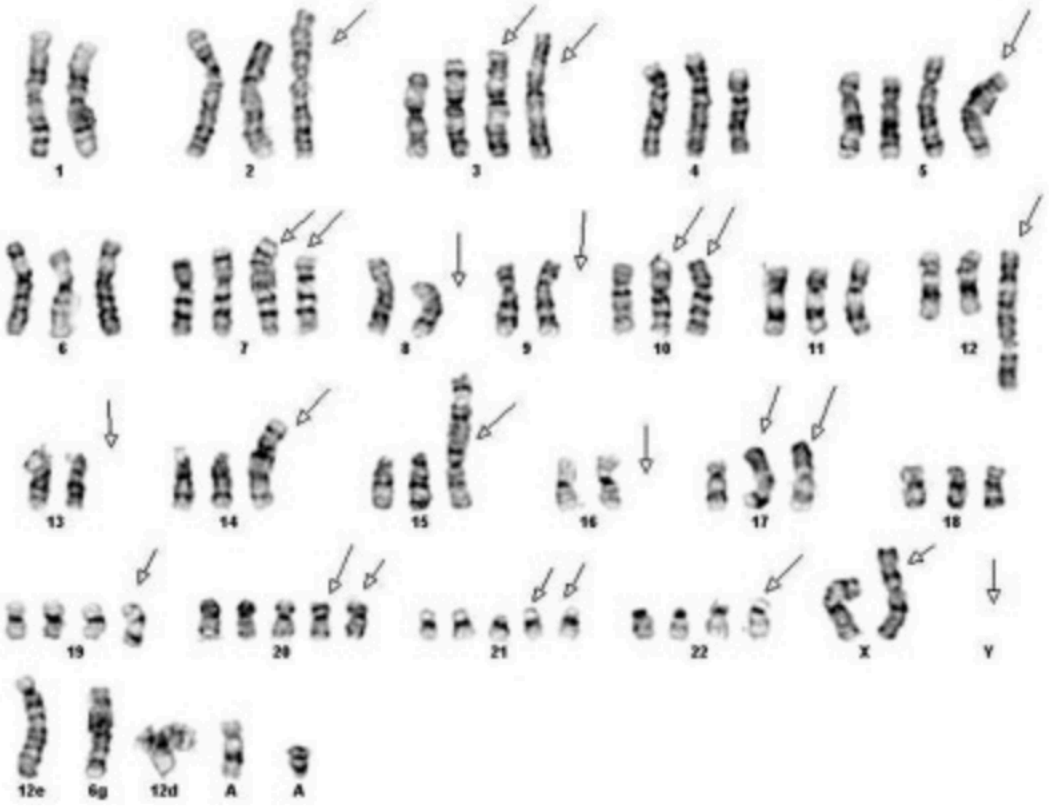


Figure 42.7

Complex karyotype abnormalities observed in a patient with peripheral T-cell lymphoma.

Subsets of T_h cells and corresponding T-cell lymphomas

T_H1		IFN-γ	Subset of PTCL, NOS
T_H2		IL4 IL5 IL13	Subset of PTCL, NOS poor overall survival
T_{FH}		IL21 CXCL13	Angioimmunoblastic T-cell lymphoma
T_{reg}		TGF-β IL10	Adult T-cell lymphoma/leukemia (HTLV1)

Laurence de Leval, and Philippe Gaulard Blood
2014;123:2909-2910

blood

Cutaneous T cell lymphoma (CTCL)

- As malignant T cell migrate, they can form skin lesions that appear as rashes
- These lesions progress to plaques and can be itchy
- Subtypes of CTCL:
  - Mycosis fungoides
  - Pagetoid reticulosis
  - Sézary syndrome
  - Granulomatous slack skin
  - Lymphomatoid papulosis
  - Pityriasis lichenoides chronica
  - Pityriasis lichenoides et varioliformis acuta
  - CD30+ cutaneous T-cell lymphoma
  - Secondary cutaneous CD30+ large cell lymphoma
  - Non-mycosis fungoides CD30-cutaneous large T-cell lymphoma
  - Pleomorphic T-cell lymphoma
  - Lennert lymphoma
  - Subcutaneous T-cell lymphoma
  - Angiocentric lymphoma
  - Blastic NK-cell lymphoma

Cutaneous T cell lymphoma (CTCL) – (2)

- US FDA approved treatments:
  - (1999) Denileukin diftitox (Ontak)
  - (2000) Bexarotene (Targretin) a retinoid
  - (2006) Vorinostat (Zolinza), a hydroxymate histone deacetylase (HDAC) inhibitor
  - (2009) Romidepsin (Istodax), a cyclic peptide histone deacetylase (HDAC) inhibitor

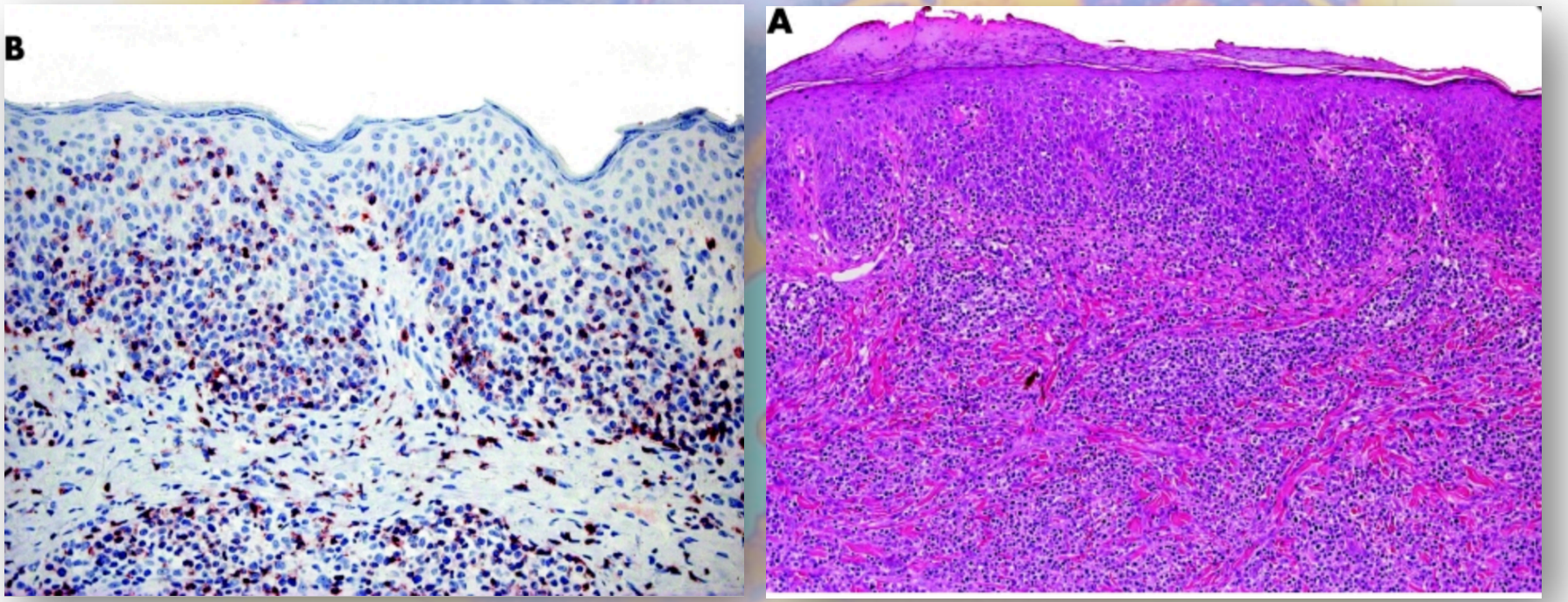
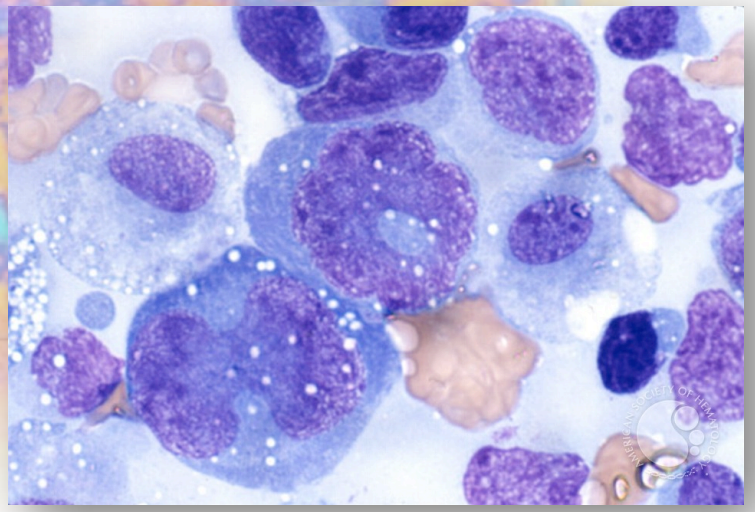


Figure 10. Cutaneous CD8 epidermotropic T cell lymphoma. (A) Lymphoid infiltrate with marked epidermotropism; and (B) positivity for CD8.

Anaplastic large-cell lymphoma (ALCL)

- Encompasses at least 4 clinical entities that histologically have in common the presence of large pleomorphic cells that express CD30 and T-cell markers
- Out of the 4 types of ALCL, one subtype of systemic ALCL expresses the protein anaplastic lymphoma kinase (ALK); the other types of ALCL do not express ALK
- Greater than 90% of the cases contain a clonal rearrangement of a T cell receptor
- Morphologic variants include the following types:
  - Common (featuring a predominance of hallmark cells)
  - Small-cell (featuring smaller cells with the same immunophenotype as the hallmark cells)
  - Lymphohistiocytic
  - Sarcomatoid
  - Signet ring
- CHOP is currently the first line of treatment
- Radiation therapy as per institutional preference, but usually added for bulky disease



Anaplastic large cell lymphoma - cytology of tumor cells showing binucleated cells and ring-shaped nuclei

Angioimmunoblastic T-cell lymphoma

- Represents only 1-2% of all cases of NHL, and 1 in 5 cases of PTCL per yr.
- Early stage AITL is very uncommon and median age of diagnosis is 65
- Strong association with EBV
- Nearly 70% of patients will have bone marrow involvement
- 20-50% of patients will experience skin manifestations in the form of rashes and urticarial lesions to nodular tumors
- Cell of origin is the T follicular helper (T_{FH}) cell, which is an effector T-cell subset
- Karyotypic abnormalities are seen in 9 out 10 cases

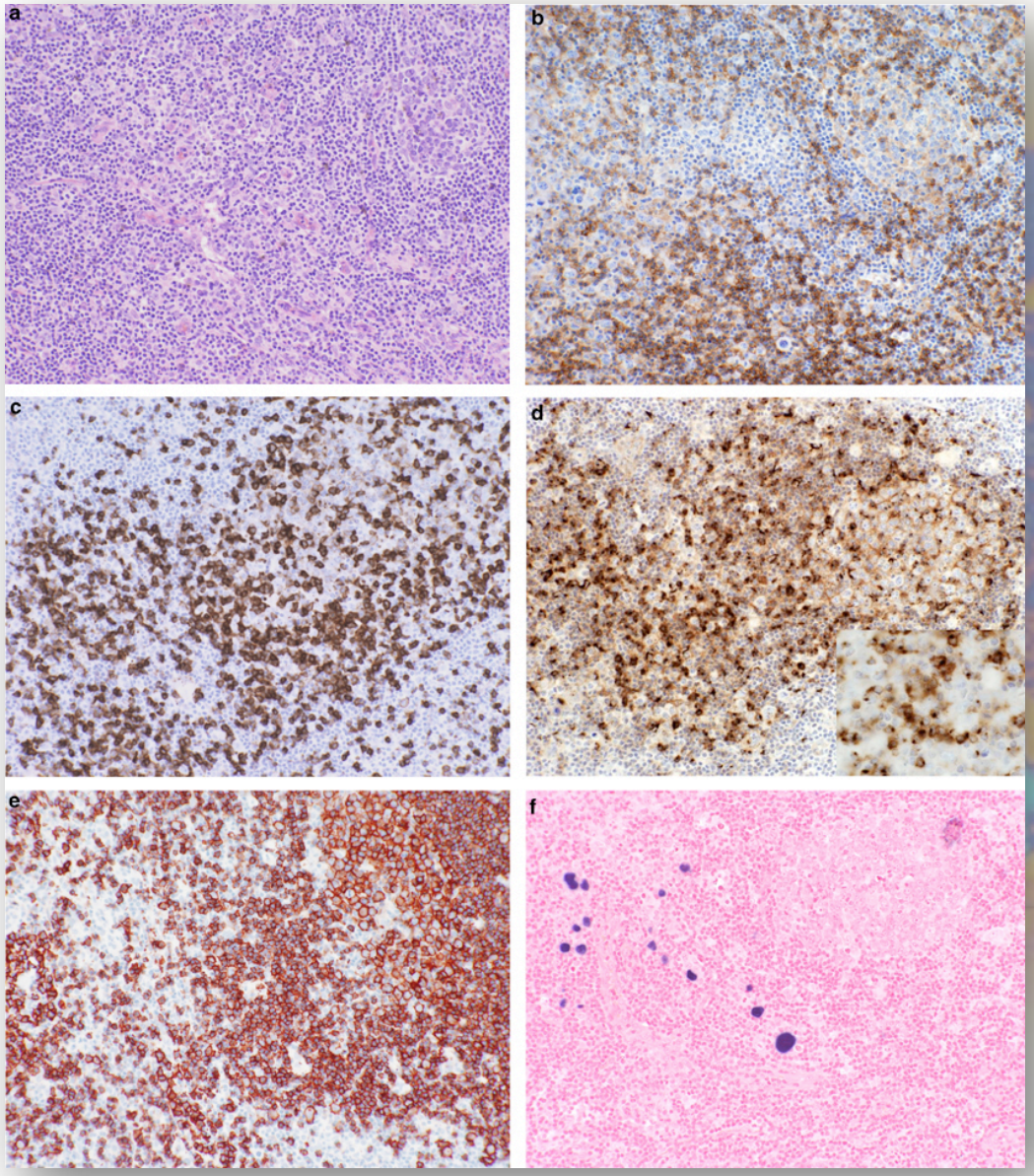
Table 1. Clinical and laboratory features of AITL

Publications reviewed	1975 to 1999*	2007 to 2016*
ATIL cases reviewed	77	556
Males, %	42-48	56-74
Median age range	62-68	62-65
General clinical features, %		
B-symptoms	29-85	55-77
Performance status >1	57	37-50
LDH elevation	25-74	60-86
Advanced stage (III/IV)	94	81-92
Low-risk IPI (0-1)	No reported	11-21
Areas of involvement, %		
Multiple nodal stations	97-100	76-99
Bone marrow	61	28-70
Skin rash	38-48	31-45
Laboratory tests, %		
Anemia	40-83	33-65
Positive DAT (Coomb's)	43-57	13-75
Thrombocytopenia	9	20-31
Hypergammaglobulinemia	50-77	50-84
Hypereosinophilia	29-39	32-34

DAT, direct anti-globulin test; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

*Article referenced in reference section; not all parameters were recorded for all patients.

Angioimmunoblastic T-cell lymphoma



Angioimmunoblastic T-cell lymphoma expresses CXCL13. (a) A polymorphous paracortical infiltrate is seen in this case of angioimmunoblastic T-cell lymphoma (hematoxylin and eosin). (b) CD4-positive neoplastic T cells are clustered in the perifollicular area and extend into the paracortex (immunoperoxidase). (c) The neoplastic T cells show intense CD10 positivity (immunoperoxidase). (d) Strong cytoplasmic staining for CXCL13 is seen in the same cell population (inset, immunoperoxidase). (e) Increased numbers of CD20-positive B cells and immunoblasts are present in the paracortex (immunoperoxidase). (f) Immunoblasts are positive for EBV (in situ hybridization).

Extranodal NK/T-Cell Lymphoma

- Also known as nasal-type NK lymphoma and polymorphic/malignant midline reticulosis
- The nasal cavity, nasopharynx and upper aerodigestive tract are often involved, although extranasal presentations do occur (skin, gastrointestinal, eye, testis, lung, soft tissue)
- Strong association with EBV
- "The NCCN guidelines recommend either high-dose radiotherapy alone for stage I without high risk features, or concurrent chemoradiotherapy for stage I and II with either of two regimens"

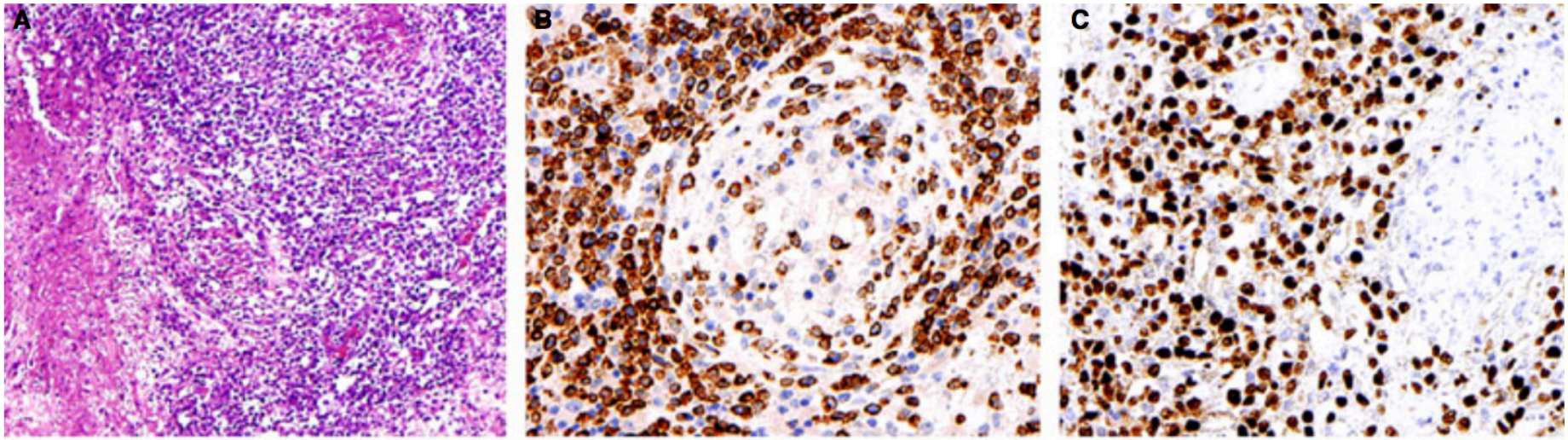
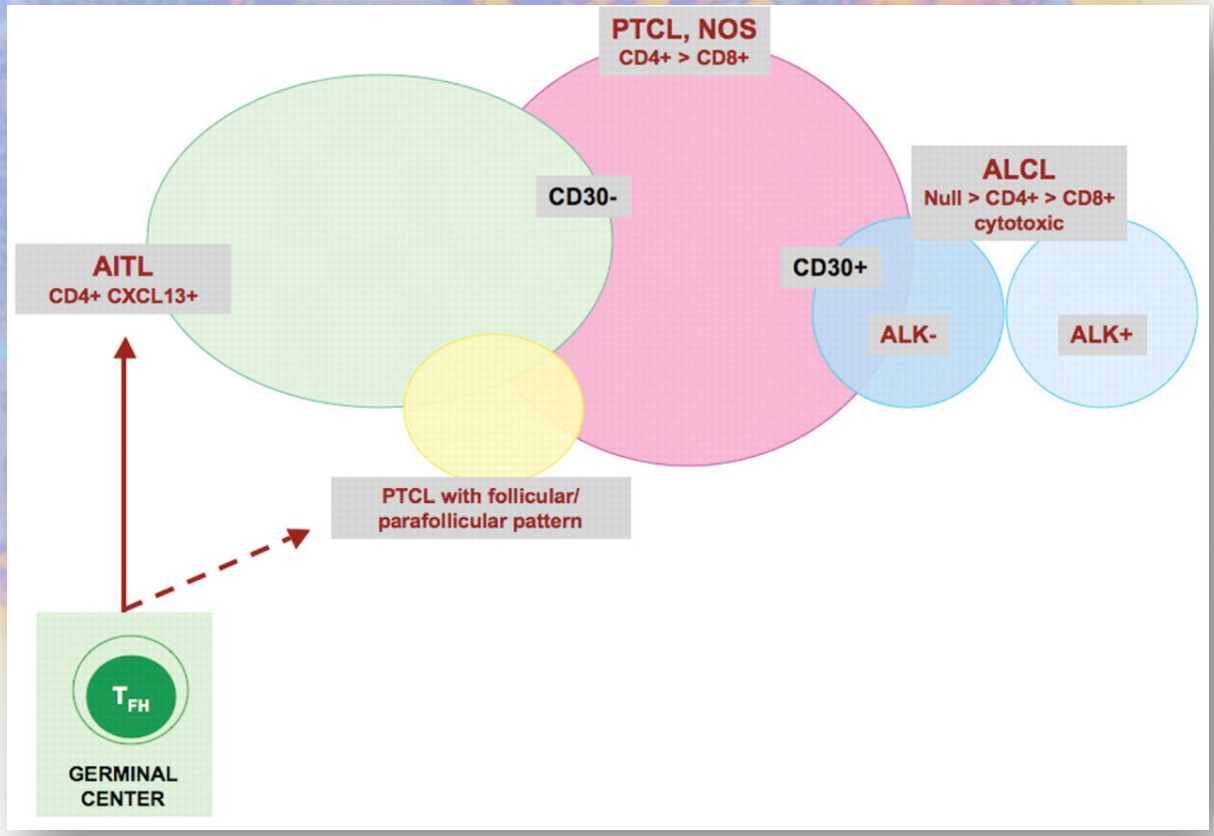


Figure 6. A–C, Extranodal NK-cell/T-cell lymphoma, nasal type. A, H&E-stained section shows infiltration by atypical lymphocytes with necrosis and haemorrhage (case 32, Dr Goodlad, Western General Hospital & University of Edinburgh, UK). The patient, a 70-year-old Cau- casian man, presented with facial swelling and induration. The tumour involved paranasal sinuses, skin, and testis. B, Perforin-positive neo- plastic cells show prominent angioinvasive growth. C, Almost all tumour cells are EBER-positive.

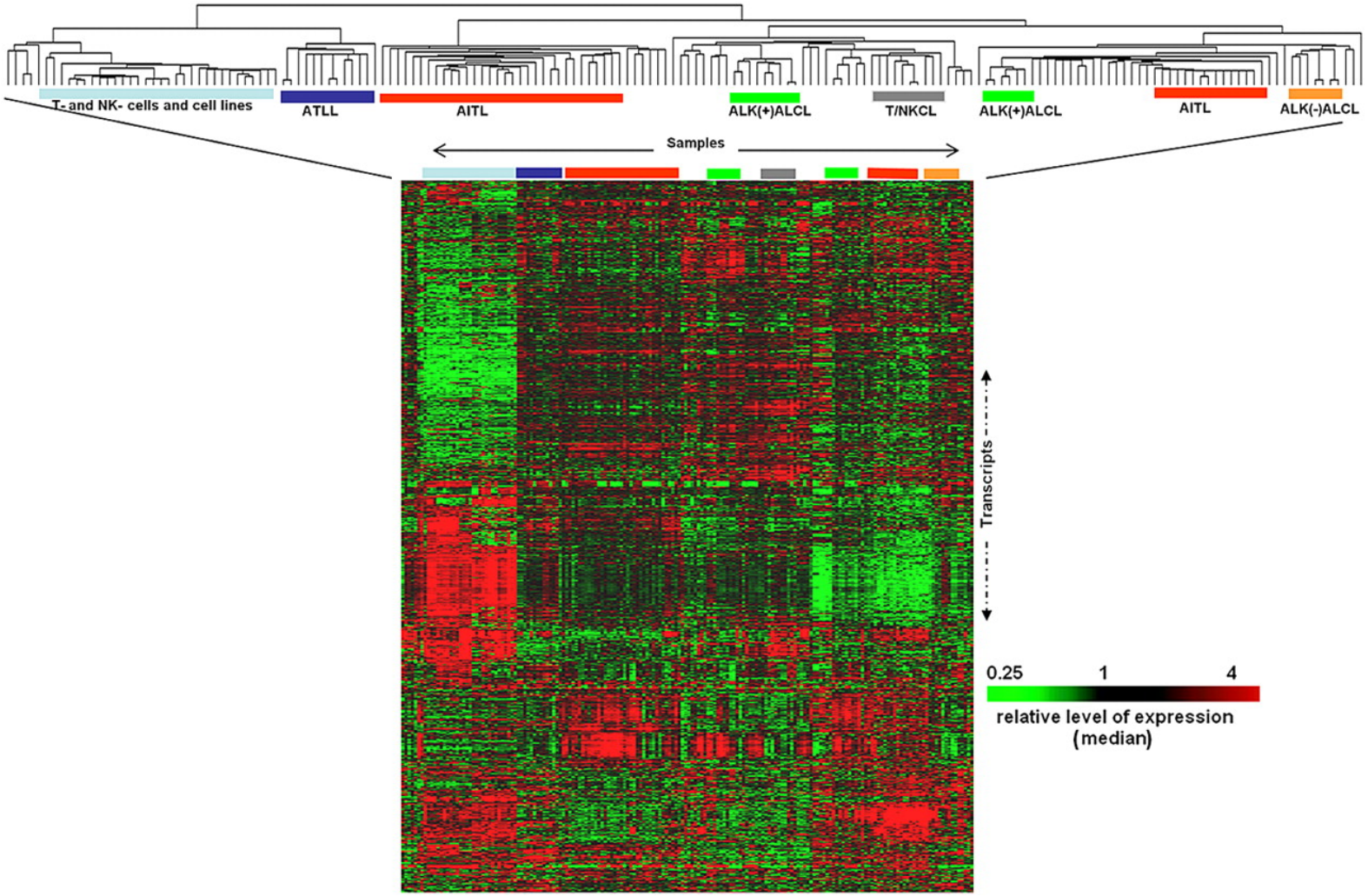
Peripheral T-cell Lymphoma, not otherwise specified

- "With current immunophenotypic and molecular markers, about 30% to 50% of PTCL cases are not further classifiable and are categorized as PTCL-NOS"

- Genetic studies point to recurrent genetic abnormalities of the following genes:
  - *TET2*
  - *IDH2*
  - *DNMT3A*
  - *RHOA*
  - *CD28*

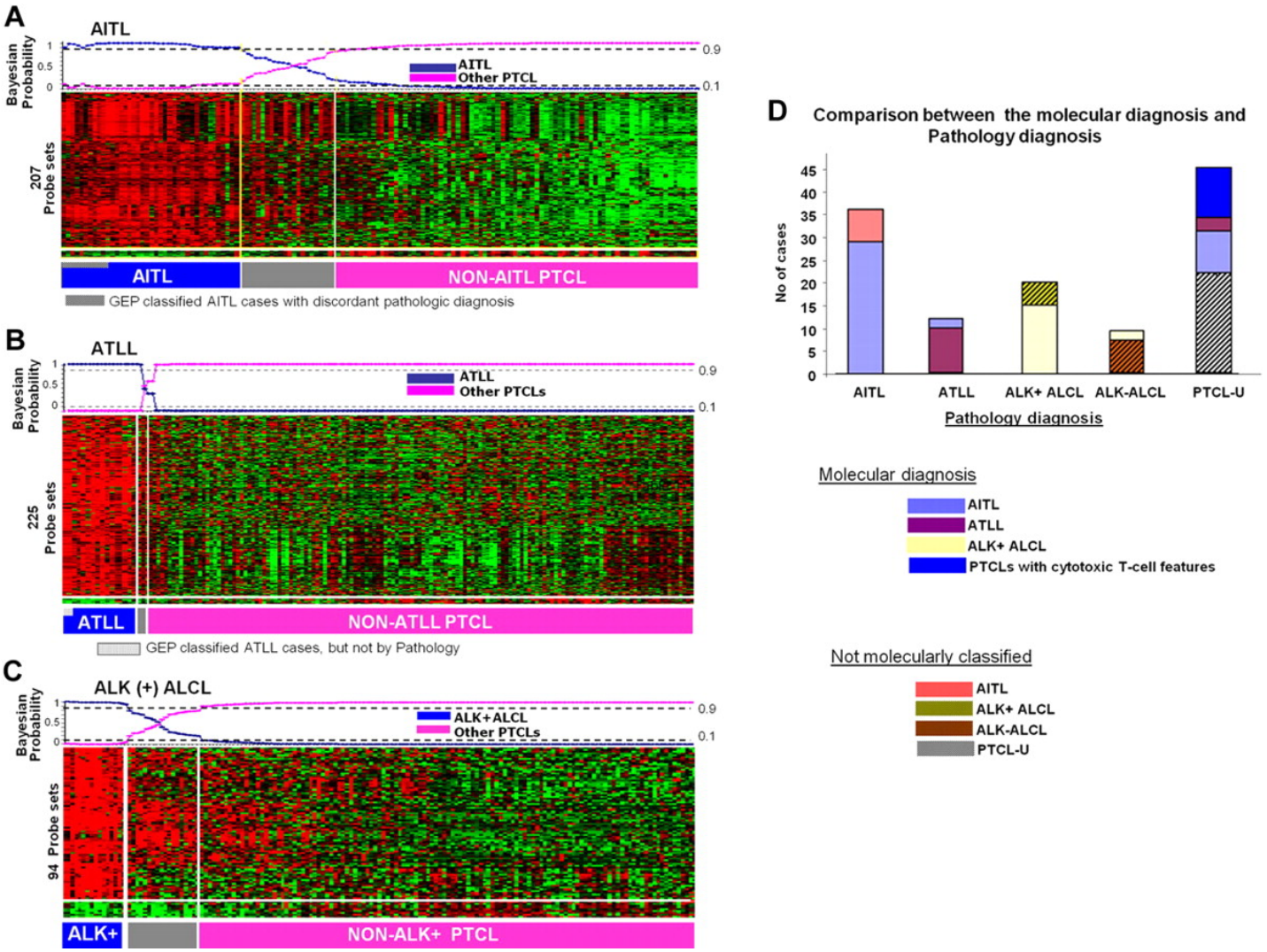


Normal T and NK cells, cell lines, and PTCL cases classified by unsupervised hierarchical clustering: Major entities of PTCL form tight clusters with cases of PTCL-NOS and other rare entities interspersed



Javeed Iqbal et al. Blood 2010;115:1026-1036

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



Javeed Iqbal et al. Blood 2010;115:1026-1036

Estimating prognosis in patients with PTCL

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2014
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:	
• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0
• Serum LDH > normal	• Group 2	1
• Performance status 2-4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

[a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b]Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment overview – peripheral T cell lymphomas

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2014
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

STAGE | **INDUCTION THERAPY**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

ALCL, ALK +

- **Stage I, II** → **Multiagent chemotherapy[h] x 6 cycles ± RT (30-40 Gy to involved region) or Multiagent chemotherapy[h] x 3-4 cycles + RT (30-40 Gy to involved region)**
- **Stage III, IV** → **Multiagent chemotherapy[h] x 6 cycles**

→ **Relapse, See Additional Therapy (TCEL-4)**

• PTCL, NOS
• ALCL, ALK -
• AITL[g]
• EATL

→ **Stage I-IV** → **Clinical trial (preferred) or Multiagent chemotherapy[h] 6 cycles ± RT (30-40 Gy for locoregional disease)** → **At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.**

- **Complete response[j]** → **Clinical trial or Consider high-dose therapy with stem cell rescue[k] or Observe**
- **Partial response or no response or progressive disease[j]**

→ **Relapse, See Additional Therapy (TCEL-4)**

Breast implant-associated ALCL →

- **Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.**
- **However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.**
- **Optimal treatment of these cases is not well defined and management should be individualized.**

[g] For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

[h] See Suggested Treatment Regimens (TCEL-B).

[j] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[k] Localized areas can be irradiated before or after high-dose therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment of peripheral T-cell lymphomas - regimens

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2014
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy:
- Clinical trial[b]
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- Other histologies (ALCL, ALK-; PTCL, NOS; AITL; EATL), regimens that can be used include:
  - CHOEP
  - CHOP-14
  - CHOP-21
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

First-line Consolidation:
- Consider consolidation with high-dose therapy and stem cell rescue.
  (ALCL, ALK + is a subtype with good prognosis and does not need consolidative transplant if in remission.)

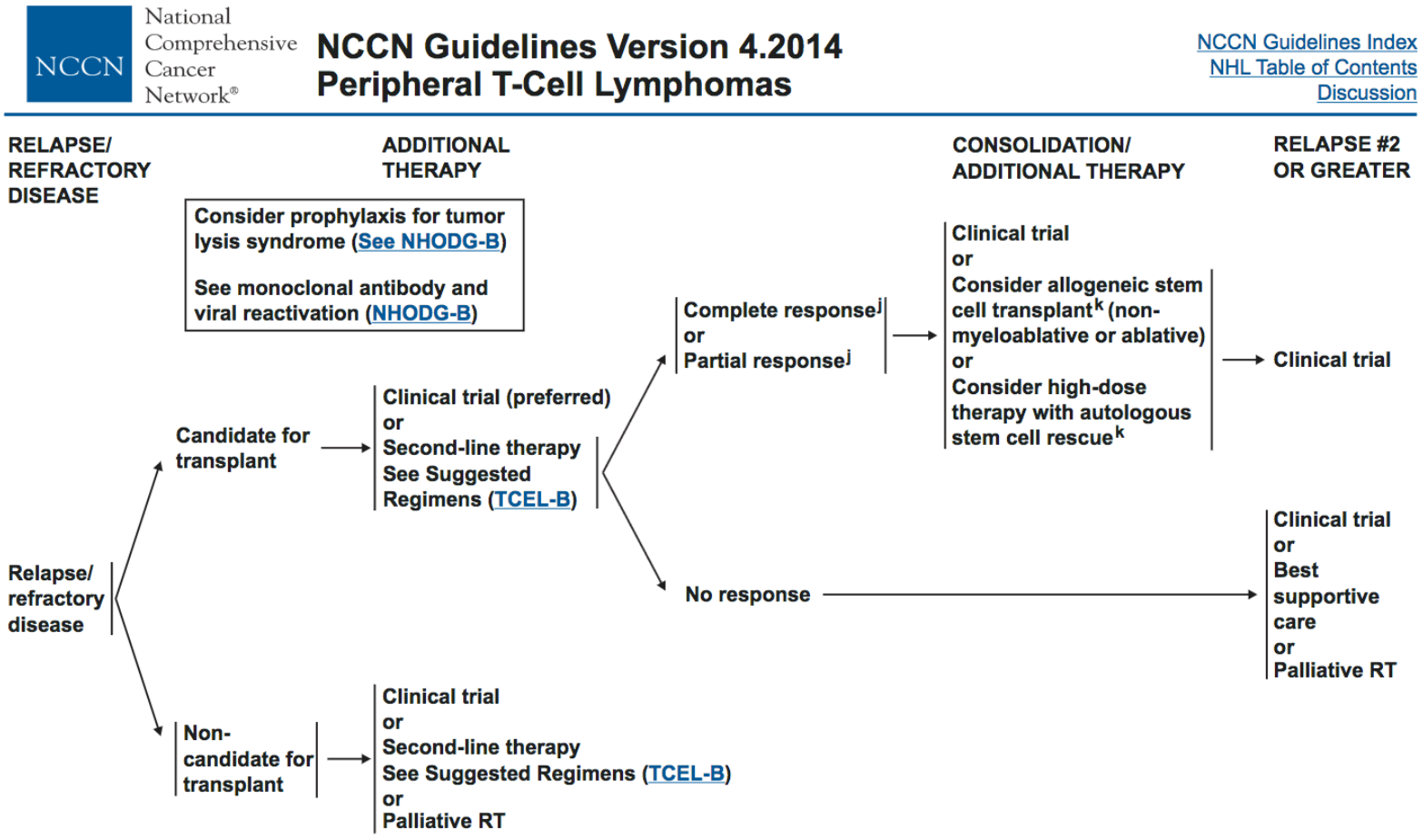
Second-line Therapy (candidate for transplant):
- Clinical trial preferred
- Belinostat (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL (category 2B)
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- Dose-adjusted EPOCH
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)
- Pralatrexate[c]
- Romidepsin

Second-line Therapy (non-candidate for transplant):
- Clinical trial preferred
- Alemtuzumab[d]
- Belinostat (category 2B)
- Bortezomib[d]
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL (category 2B)
- Cyclosporine for AITL only[e]
- Dose-adjusted EPOCH
- Gemcitabine
- Pralatrexate[c]
- Radiation therapy
- Romidepsin

[a] See references for regimens TCEL-B 2 of 2.
[b] While CHOP-21 and CHOEP-21 regimens confer a favorable prognosis in ALCL, ALK +, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.
[c] In AITL, pralatrexate has limited activity.
[d] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[e] With close follow-up of renal function.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

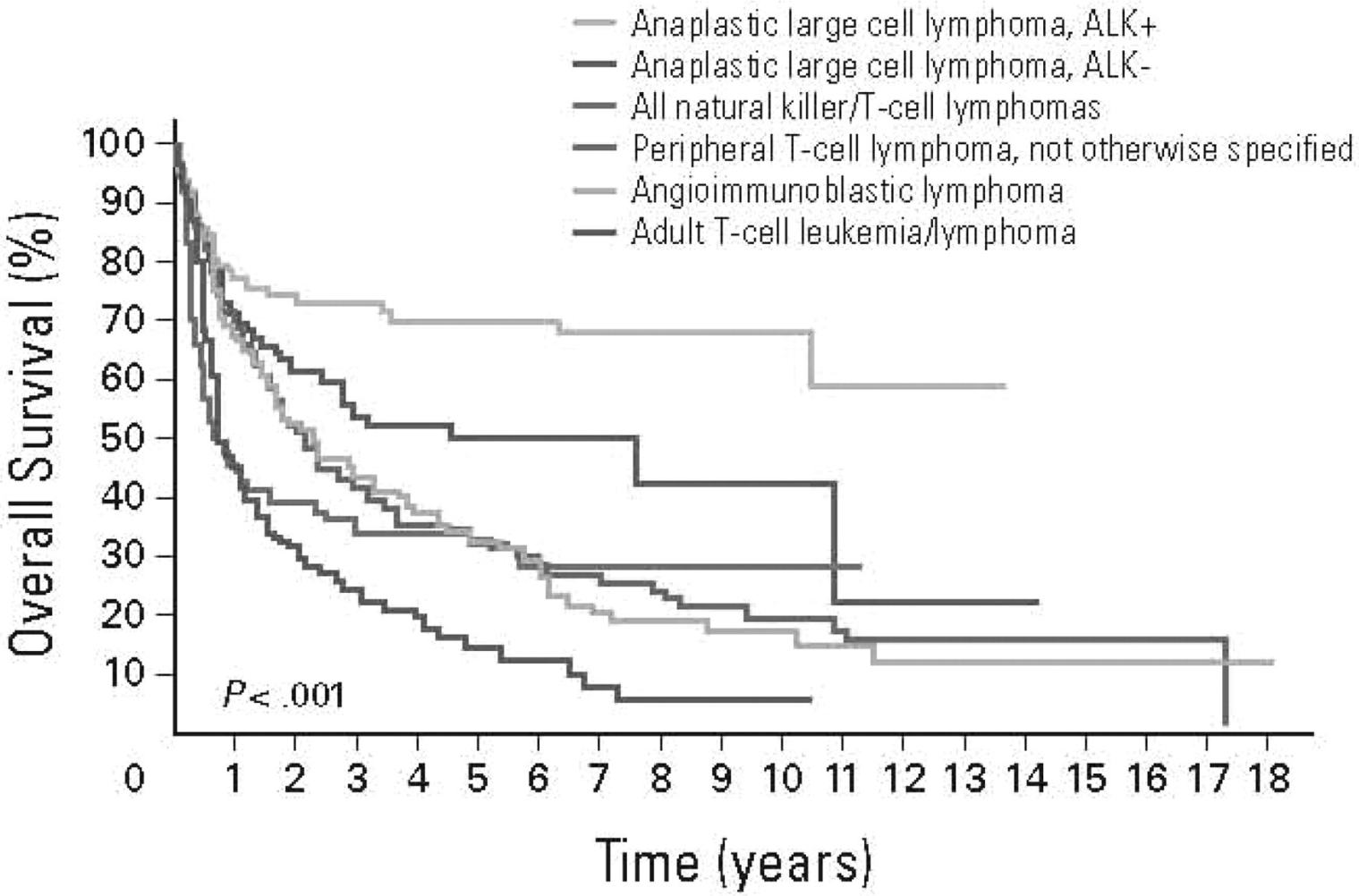
Treatment of relapsed/refractory PTCL



[j] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Localized areas can be irradiated before or after high-dose therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

OS of patients with the common subtypes of PTCL



Francine M. Foss et al. Blood 2011;117:6756-6767

Survival Outcomes for PTCL

Table 2. Comparison of IPI and PIT-calculated survival outcomes in four PTCL-NOS case series. Survival figures are given as percentages. IPI, International Prognostic Index; PIT, Prognostic Index for PTCL-NOS; OS, overall survival; FFS, failure-free survival; PFS, progression-free survival.

Index	Score		Gallamini, 2004[21]	Weisenburger, 2011[24]		Ellin, 2014[25]	Xu, 2015[26]	
			5-year OS	5-year OS	5-year FFS	5-year OS	5-year OS	5-year PFS
IPI[20]	low	0/1	59	50	36	58	48	43
	low-intermediate	2	46	33	18	27 (*)	38	19
	intermediate-high	3	40	16	15		13	0
	high	4/5	18	11	9	15	0	0
PIT[21]	group 1	0	62	50	34	71	56	33
	group 2	1	53	40	22	38	40	21
	group 3	2	33	22	13	25	25	14
	group 4	3/4	18	11	8	18	NR	0

(*) Low-intermediate and high-intermediate risk patients according to IPI are grouped together as intermediate risk patients.

References

- https://www.verywell.com/angioimmunoblastic-t-cell-lymphoma-aitl-2252380
- https://www.slideshare.net/nohasalah/nhl-updates-2016-59716919
- https://imagebank.hematology.org/
- Cerroni, L. (2006). Lymphoproliferative lesions of the skin. *Journal of Clinical Pathology*, *59*(8), 813–826. http://doi.org/10.1136/jcp.2005.033019
- Marchi, E., Raufi, A. G., & O'Connor, O. A. (2017). Novel Agents in the Treatment of Relapsed or Refractory Peripheral T-Cell Lymphoma. *Hematol Oncol Clin North Am, 31*(2), 359-375. doi:10.1016/j.hoc.2016.11.002
- Lunning, M. A., & Vose, J. M. (2017). Angioimmunoblastic T-cell lymphoma: the many faced lymphoma. Blood, (), blood-2016-09-692541. Accessed April 18, 2017. https://doi.org/10.1182/blood-2016-09-692541.
- Grogg, K. L., Attygalle, A. D., Macon, W. R., Remstein, E. D., Kurtin, P. J., & Dogan, A. (2006). Expression of CXCL13, a chemokine highly upregulated in germinal center T-helper cells, distinguishes angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified. *Mod Pathol, 19*(8), 1101-1107. doi:10.1038/modpathol.3800625
- de Leval, L., & Gaulard, P. (2014). Cellular origin of T-cell lymphomas. Blood, 123(19), 2909-2910. Accessed April 18, 2017. https://doi.org/10.1182/blood-2014-02-555763.
- https://www.nccn.org/about/nhl.pdf
- Foss, F. M., Zinzani, P. L., Vose, J. M., Gascoyne, R. D., Rosen, S. T., & Tobinai, K. (2011). Peripheral T-cell lymphoma. Blood, 117(25), 6756-6767. Accessed April 18, 2017. https://doi.org/10.1182/blood-2010-05-231548.
- Broccoli, A., & Zinzani, P. L. (2017). Peripheral T-cell lymphoma, not otherwise specified. Blood, (), blood-2016-08-692566. Accessed April 18, 2017. https://doi.org/10.1182/blood-2016-08-692566.
- Iqbal, J., Weisenburger, D. D., Greiner, T. C., Vose, J. M., McKeithan, T., Kucuk, C., Geng, H., Deffenbacher, K., Smith, L., Dybkaer, K., Nakamura, S., Seto, M., Delabie, J., Berger, F., Loong, F., Au, W. Y., Ko, Y., Sng, I., Armitage, J. O., Chan, W. C., & , . (2010). Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood, 115(5), 1026-1036. Accessed April 17, 2017. https://doi.org/10.1182/blood-2009-06-227579.
- http://asheducationbook.hematologylibrary.org/content/2008/1/491/F25.expansion
- Faramarz Naeim P. Nagesh Rao Sophie X. Song Wayne W. Grody, in Atlas of Hematopathology, 2013.
    - http://topics.sciencedirect.com/topics/page/T_cell?