The Challenge of T-Cell Lymphomas: So Many Different Unfriendly Faces

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Overview

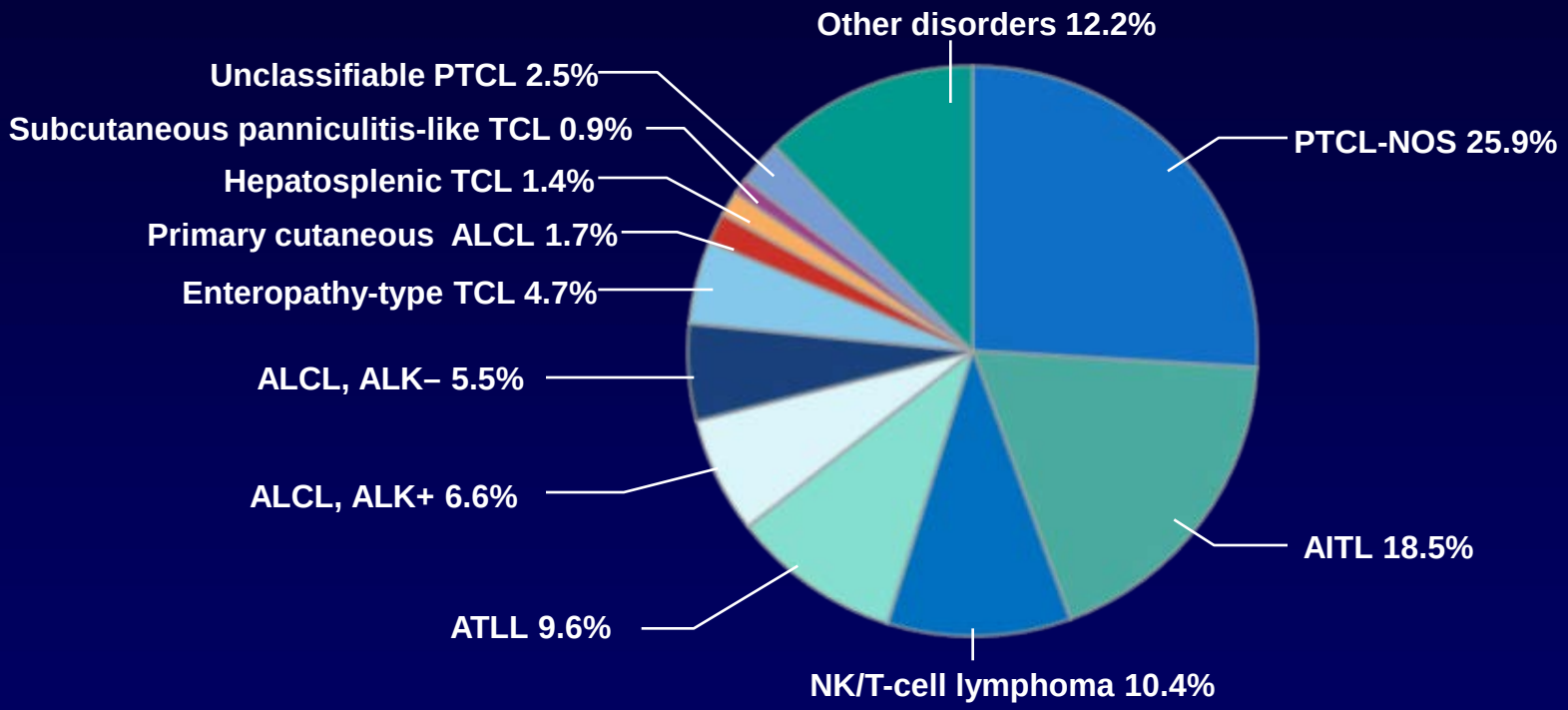
- Outline of clinical features of the most common peripheral T-cell lymphomas (PTCL)
- Recommendations for staging and prognostic markers
- Defining the challenges and the current guidelines for standard of care

Peripheral T-Cell Lymphoma

- Subset of NHL that arises from lymphocytes at the post-thymic stage of maturation; display T-cell or natural killer (NK) phenotypes
- Comprises 23 markedly different biologically and clinically heterogeneous distinct entities
  - Based on epidemiology, clinical features, morphology, immunophenotype, and underlying genetic lesions
- Worldwide PTCL represent 10%-15% of all non-Hodgkin lymphoma (NHL)
- Ethnic and geographic variations account for variations in prevalence, rates ranging from 24% in Asia to 4% in North America
  - Reasons between geographical variation not entirely clear; may be related to infection with human T-lymphotropic virus-1 (HTLV-1), adult T-cell leukemia/lymphoma (ATLL), Epstein-Barr virus (EBV)

Frequency of T-cell Lymphoma Subtypes: From the International PTCL Study

22 centres: 1314 cases over 12 years



PTCL, AITL, ALCL: 60% of T-cell NHL

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NOS, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma

O'Leary H, et al. *Curr Hematol Malig Rep.* 2009;4(4):227-235.

Outcomes in Common PTCL Subtypes

- Expected outcomes for patients with PTCL largely based on two large retrospective series:
  - The International T-Cell Project (ITCP): 1314 cases
  - British Columbia Cancer Agency (BCCA): 199 cases
- When interpreting the results of prospective studies for new treatment strategies, ITCP or BCCA series are used as point of references
- Series are problematic given the potential biases in retrospective analyses and phase II clinical trials

Moskowitz AJ, et al. *Blood*. 2014;123(17):2636-2644.

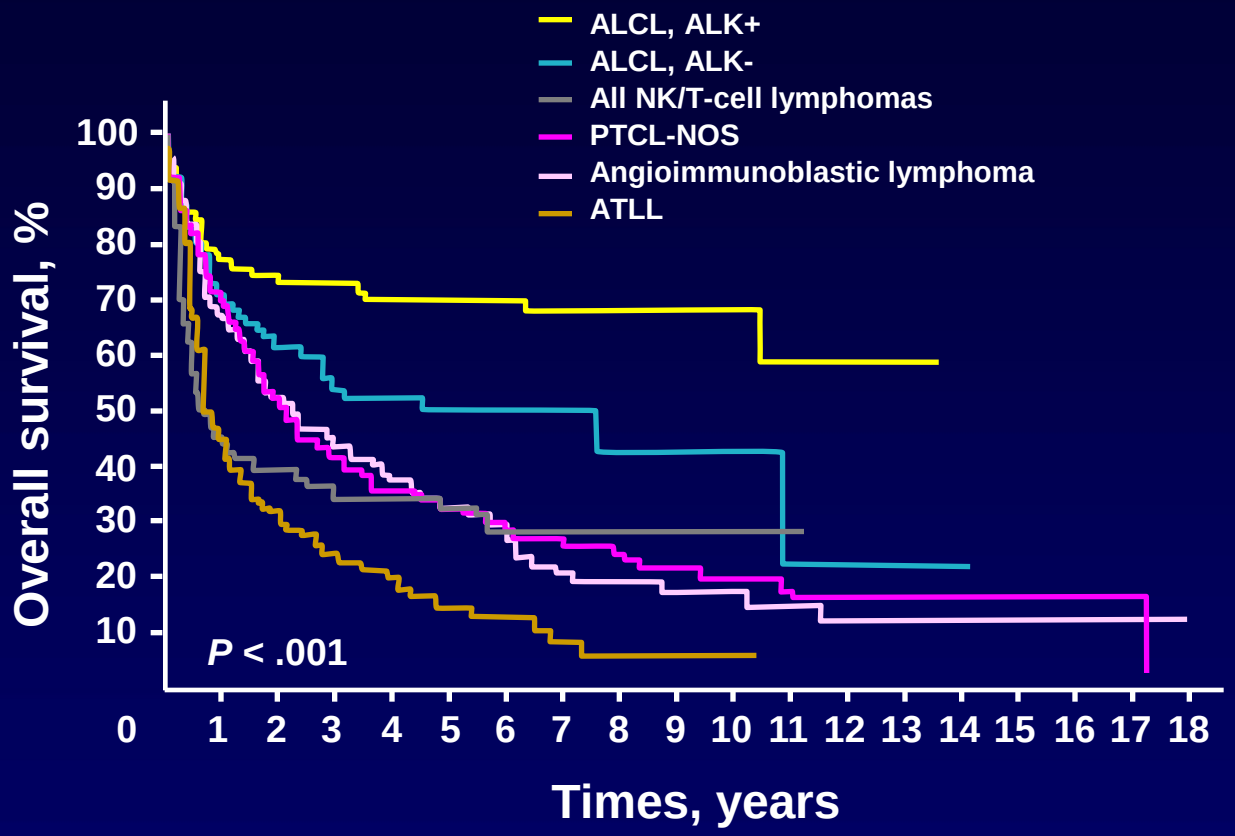
Outcomes in Common PTCL Subtypes

- The ITCP and BCCA series are useful in informing us on the expected survival outcomes with CHOP in PTCL
- In the ITCP, 85% of patients received CHOP-based therapy, 5-year failure-free survival (FFS)
  - ALK positive ALCL: 60%
  - ALK negative ALCL: 36%
  - PTCL-NOS: 20%
  - AITL: 18 %
- Similar poor outcomes were observed in the BCCA series with 5-year progression-free survival (PFS) of ALCL (28%) , PTCL-NOS (29%), and AITL (13%)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone

Moskowitz AJ, et al. *Blood*. 2014;123(17):2636-2644.

Outcomes in Common PTCL Subtypes



- In the ITCP 5-year FFS
  - ALK positive ALCL: 60%; ALK negative ALCL: 36%
  - PTCL-NOS: 20%
  - AITL: 18 %

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

PTCL-NOS: Clinical Features

- **PTCL-NOS: Heterogeneous group of nodal and extranodal mature T-cell lymphomas**
  - **25% of all PTCL, typically occurs in adults (median age 55-60 years), higher prevalence in males**

- **Presentation: Often disseminated disease, generalized lymphadenopathy, bone marrow infiltration, extranodal involvement**
  - **B symptoms frequent**
  - **High or high-intermediate IPI score in 50%-70% of cases**
  - **Occasionally eosinophilia, pruritus**
  - **Hemophagocytic syndrome**

AITL: Clinical Presentation

- AITL second most common form of PTCL: ITCP 18.5%
- More common in Europe (29% of cases) than in North America (16%) or Asia (18%)
- AITL affects elderly adults 6th or 7th decades, median age 59-65 years, male predominance
- Peculiar clinical features: A subacute or acute systemic illness, after drugs (especially antibiotics) or viral, bacterial, or fungal infections
- Generalized lymphadenopathy noted in 76% of patients, and 89% had stages III to IV disease. Lymph node enlargement often mild to moderate (<1 cm–3 cm), peripheral drainage areas

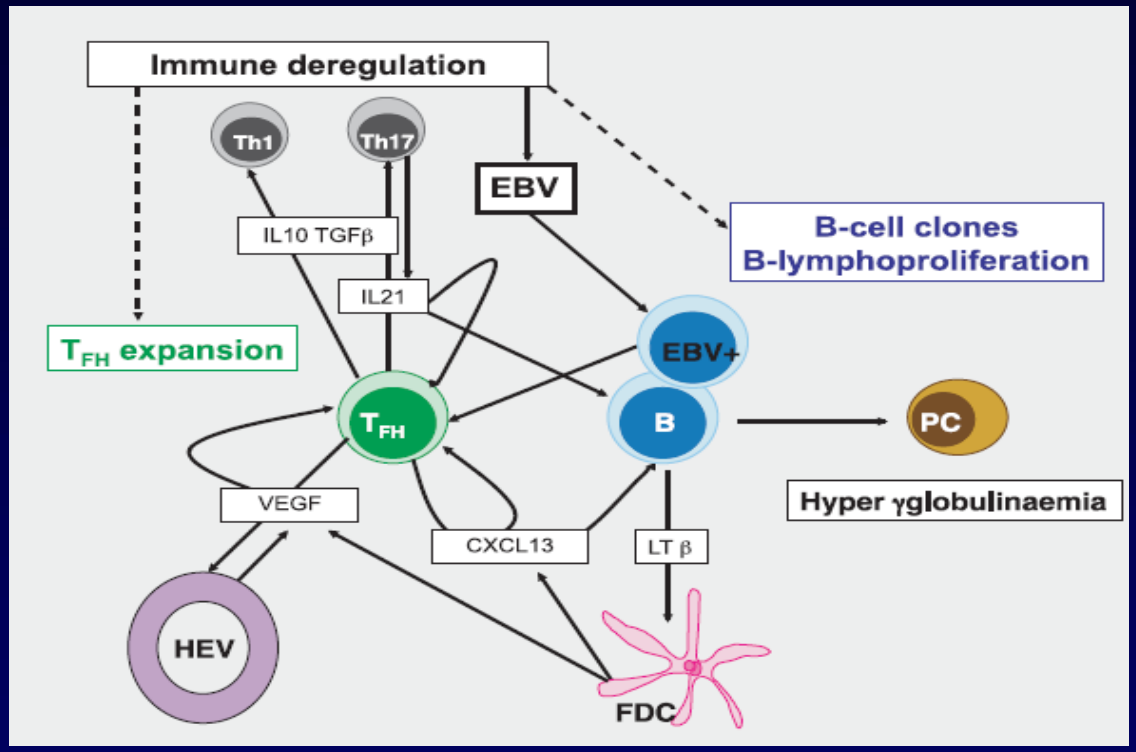
Clinicopathologic Characteristics of AITL: Analysis of the International Peripheral T-Cell Lymphoma Project

- Bone marrow (BM) involvement 70%; high proportion of hepatosplenomegaly
- Skin rash was observed in 21% of patients
  - Either generalized or a predominantly pruritic truncular maculopapular eruption mimicking an inflammatory dermatosis
  - Nodular lesions, plaques, purpura, and urticarial lesions can also be seen
- Hemolytic anemia (13%) and hypergammaglobulinemia (30%)
- Arthralgias or arthritis, pleural effusions, ascitis and/or oedema, lung involvement, neurological manifestations, gastrointestinal involvement less common

Federico M, et al. *J Clin Oncol*. 2013;31(2):240-246.

Pathogenetic Model of AITL

Network of interactions between tumor cells and reactive microenvironment



- **Complex lymphoproliferative disorder: Epstein-Barr virus and B cell dysregulation implicated in disease pathogenesis, mechanistic roles remain largely unknown.**
- **Recent identification of follicular helper T cells: Cell of origin of neoplasm is major step in understanding the pathobiological characteristics in diagnostic criteria for AITL from PTCL-NOS (distinct gene signature)**

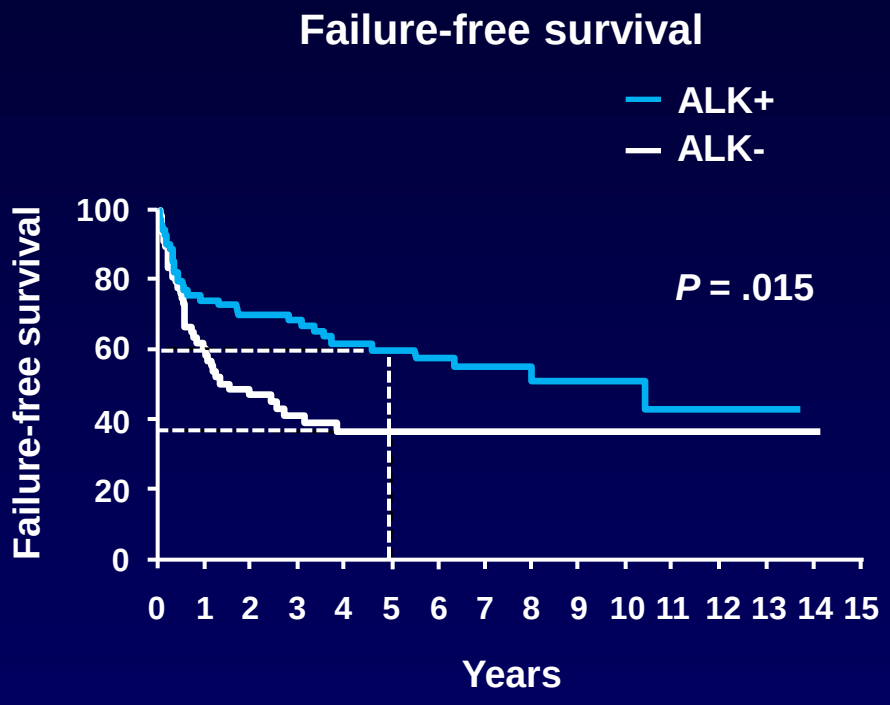
de Leval L, et al. *Br J Haematol*. 2010;148(5):673-689.

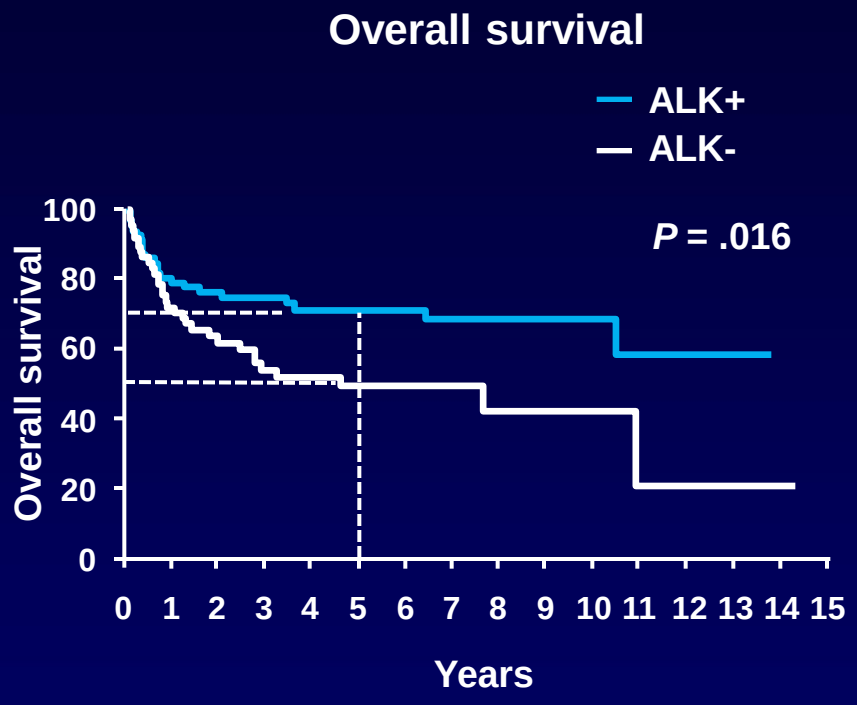
ALCL: Clinical Picture

- Three clinical/molecular entities[1]: Ki-1/CD30 expression – defining feature of ALCL
  - Primary systemic ALK(+)
    - Younger/male patients: 20%-30% of large cell lymphomas in children
  - Primary systemic ALK(-)
    - Older/both genders
  - Primary cutaneous
    - Generally affects older patients; 9% of cutaneous lymphomas
    - Better prognosis than systemic disease
- ALK(+) and ALK(-) clinically and immunophenotypically distinct[2]
- Prognostic implications of ALK status[2]
    - ALK(+) associated with significantly better prognosis than ALK(-)

1. Stein H, et al. *Blood.* 2000;96(12):3681-3695. 2. Savage KJ, et al. *Blood.* 2008;111:5496-5504.

International PTCL Project Prognostic Implications of ALK Status





- ALK(+) associated with significantly better prognosis than ALK(-)
  - 5-year event-free survival ALK(+) 60% vs ALK(-) 36%
  - 5-year overall survival ALK(+) 70% vs ALK(-) 49%

Savage KJ, et al. *Blood.* 2008;111:5496-5504.

Age and ALK Status in ALCL

- Retrospective analysis from GELA (138 patients) with ALCL treated on various prospective clinical trials
- Age (over 40 years) one of strongest prognostic factors in ALCL (even stronger that ALK status)
- Patients with ALK-negative ALCL >40 years old have similar outcomes to the ALK-positive patients
- Younger patients with ALK-negative ALCL may represent a more favorable subset

Sibon D, et al. *J Clin Oncol*. 2012;30(32):3939-3946.

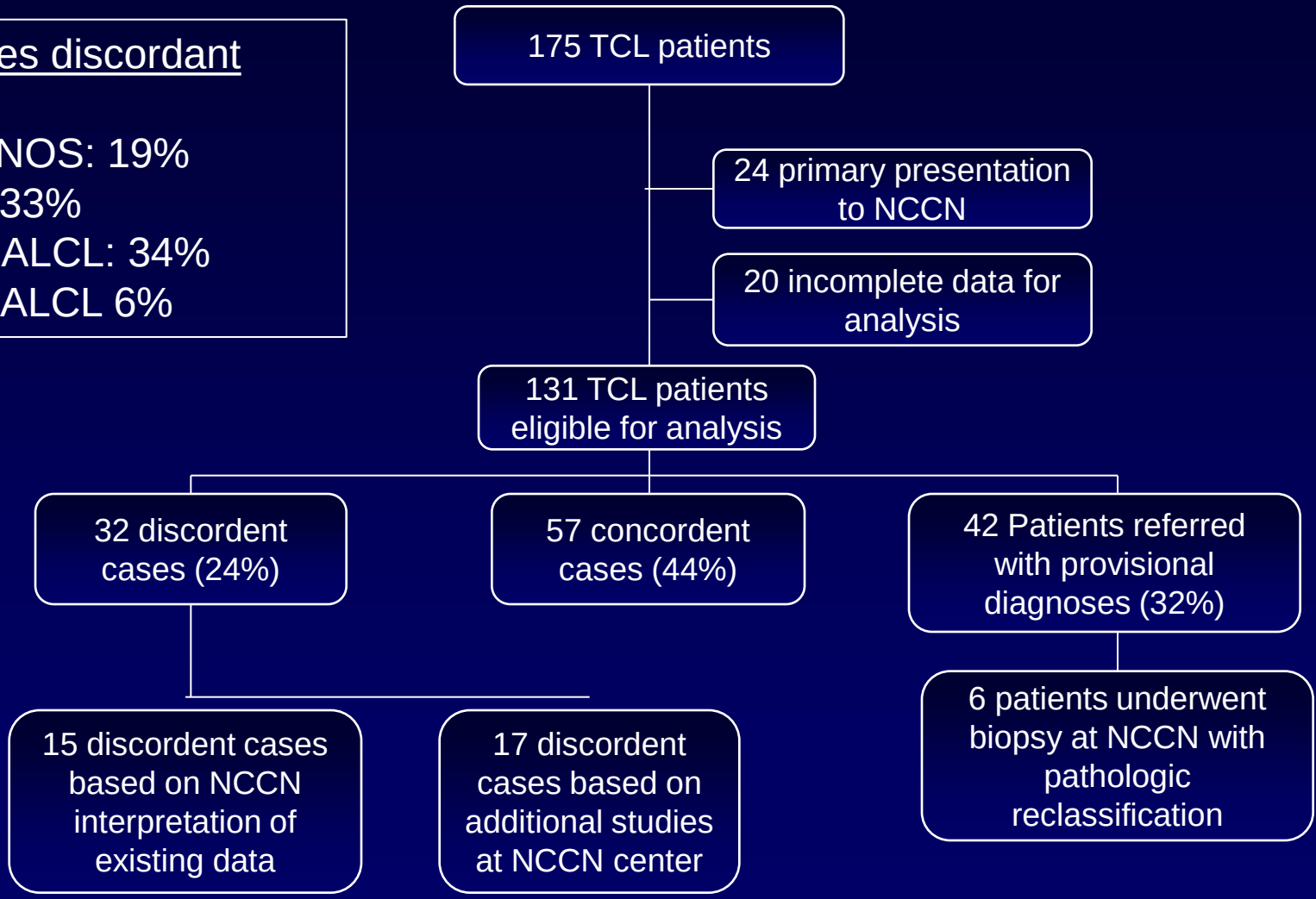
Diagnosis of PTCL

- Fine needle aspiration is not sufficient for initial diagnosis of PTCL
- Review by an expert hematopathologist with expertise in PTCL working in collaboration / dialogue with hemato-oncologists
- In ITCP consensus diagnosis (3 of 4 expert pathologists arriving at same diagnosis) only reached 74%-81% of the time for ALK-negative ALCL, PTCL-NOS, and AITL
- Distinguishing subtype of PTCLs is going to become critical, with better understanding of the underlying biology, treatment strategies are more specific to particular PTCL subtypes

Expert Pathology is Important: Discordant Cases in NCCN

<u>36% cases discordant</u>

- PTCLNOS: 19%
- AITL: 33%
- ALK - ALCL: 34%
- ALK+ ALCL 6%



Herrera AF, et al. *Cancer*. 2014;XX(X):1993-1999.

Initial Assessment: Staging Investigations and Tests at Diagnosis

- B symptoms, physical exam, performance status (PS), full blood count, biochemistry, serum LDH, calculate IPI
- Staging: CT chest, abdomen, and pelvis and/ or positron emission tomography (PET)-CT, head CT / MRI
- Bone marrow aspirate / biopsy, skin biopsy
- HIV testing, fertility issues / sperm banking
- HTLV-1 serology, adult T-cell lymphoma / leukemia represents up to 10% of PTCL population - not all present from endemic areas
- HTLV-1 status was the most common reason for reclassification in the ITCP, and knowledge of HTLV-1 status greatly affects treatment strategy

PTCL: Clinical Prognostic Biomarkers

- Prognostic biomarkers -IPI or prognostic index for T-cell lymphoma (PIT) score
- PIT modified IPI with BM involvement, most effective prognostic factor
- IPI works less well for AITL and PTCL-NOS
- Modified prognostic index for T-cell lymphoma and alternative prognostic index for AITL (PIAI)
- None provide a significant improvement over IPI in terms of impacting treatment strategies.

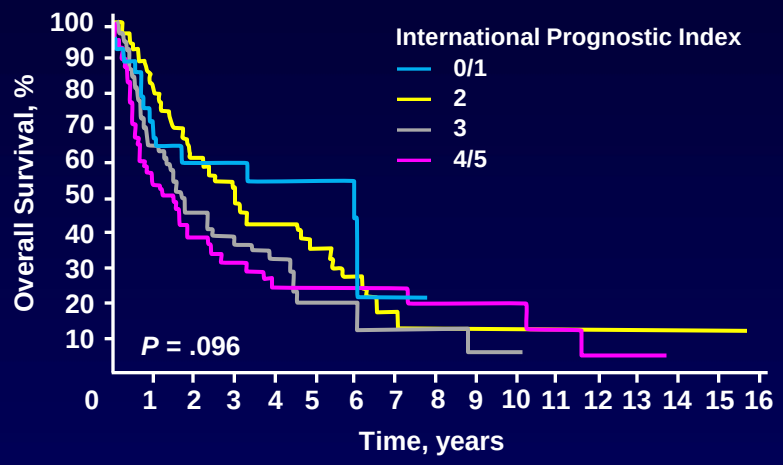
Prognostic Index for PTCL-U (PIT)

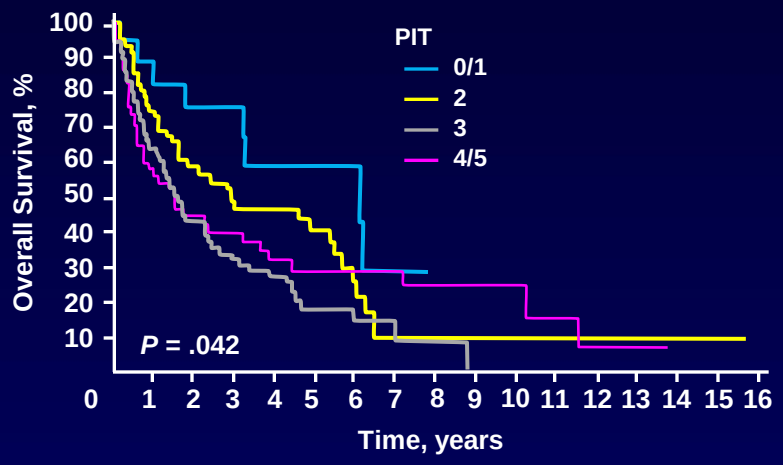
Risk factors	Prognostic risk	
Age >60 years	Group 1	0
Serum LDH >normal	Group 2	1
PS 2-4	Group 3	2
Bone marrow involvement	Group 4	3 or 4

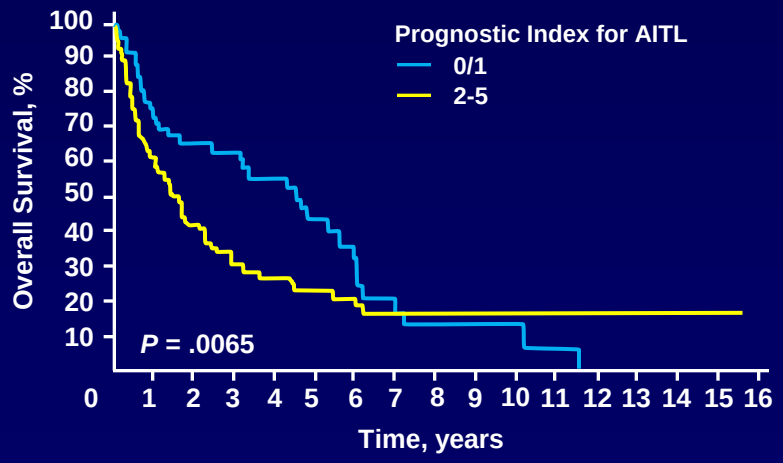
Prognostic Index for AITL

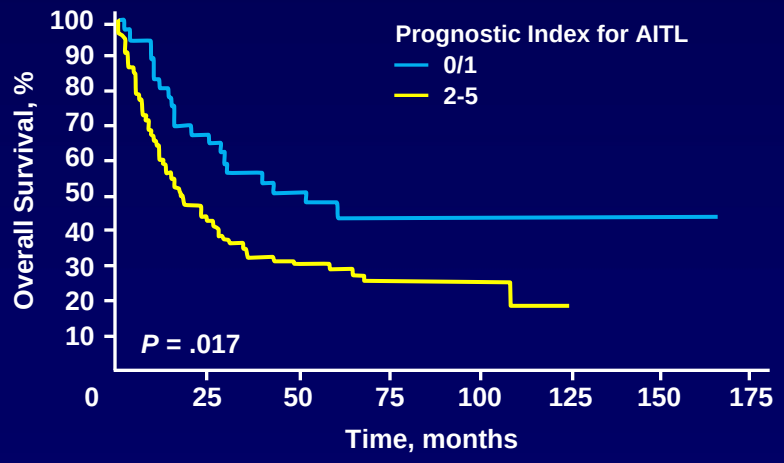
Risk factors	Prognostic risk	
Age >60 years	Group 1	0
Serum LDH >normal	Group 2	1
Extra nodal disease	Group 3	2
B symptoms	Group 4	4
Platelet count 150 x 10^9/L	Group 5	5

OS With AITL Using IPI, Prognostic Index for PTCL and AITL









5-year OS and FFS 33% and 18%, respectively

Federico M, et al. *J Clin Oncol*. 2013;31(2):240-246.

Is There a Favorable Risk PTCL Who Should Be Treated Differently?

- ITCP: 5-year FFS IPI 0,1 risk factors was only 33% and 34% for PTCL-NOS (33%), and AITL (34%), respectively, reduced therapy not validated
- IPI may factor into our treatment recommendations in ALK-positive ALCL; FFS by IPI risk factor:
  - 0/1 = 80%
  - 2 = 60%
  - 3 = 40%
  - 4/5 = 25%
- Suggests that CHOP-based therapy alone may not be adequate for patients with higher-risk disease
  - ALK-positive ALCL over the age of 40: Treat these higher-risk patients similar to patients who present with the less favorable PTCL entities

18-Fluoro-2-Deoxyglucose (FDG)-PET in T-Cell Lymphomas

- Identifying and following extranodal disease; common in PTCL
- Most patients have advanced stage disease on conventional staging; stage or treatment plans rarely change following PET imaging
- Interim PET response in patients where curative strategies intended (ASCT) appears highly predictive of outcome; a baseline study is needed
- Most powerful predictor of outcome: Interim PET; 53% of patients normalized their PET after 4 cycles of chemotherapy and in those who achieved interim PET negative status, 59% were progression free at 5 years, including 53% of those with IPI of 3 (Moskowitz , et al)

ASCT, autologous stem-cell transplantation

Mehta N, et al. Clin Lymphoma Myeloma Leuk. 2013 Dec;13(6):664-70. Moskowitz AJ, et al. *Blood*. 2014;123(17):2636-2644.

18-Fluoro-2-Deoxyglucose (FDG)-PET in T-Cell Lymphomas

- FDG avidity for PTCL-NOS 91%; extranodal NK-cell lymphoma 100%, ALCL 60%, AILT 100%; and mycosis fungoides and Sezary syndrome (MF/SS) 33%
- Overall positive rate for cutaneous lesions 50%
  - 0% for MF/SS and 40% for ALCL
  - FDG-PET also poor for identifying bone marrow disease[1,2]
- Summary: PET is neither sufficiently sensitive nor specific for the assessment of cutaneous T-cell lymphoma: Traditional criteria remain standard, such as Severity Weighted Assessment Tool
- Clinical trials should provide prospective validation of PET in T-NHL before it can be considered a standard part of patient management

1. Berk V, et al. *Clin Nucl Med*. 2008;33(5):365-366. 2. Kako S, et al. *Ann Oncol*. 2007;18(10):1685-1690.

The Problem: Many Different Diseases but the Same Approach

- **Most common entities PTCL-NOS, AITL, and ALK-negative ALCL (60% of cases)**
  - **Despite their significant differences in pathologic appearance and clinical presentation they are treated similarly**
- **The management of other less common PTCLs, such as adult T-cell lymphoma/leukemia or extranodal NK T-cell lymphoma, nasal type, and EATL have unique treatment plans**
- **In the absence of randomized clinical trials to drive treatment decisions in PTCL, rely on best data currently available and experience**

Outcomes in T-Cell Lymphomas: Prospective Clinical Trials: Is Anything Better Than CHOP?

- CHOP provides initial responses for many
  - Fewer achieve CRs
  - Even fewer achieve durable remissions
  - Those with ALCL consistently fared better than those with AITL and PTCL-NOS
- Attempts at using non anthracycline based therapy disappointing
  - SWOG group Cisplatin, etoposide, gemcitabine, Solu-medrol
    - Overall response rate (ORR) of only 39% and 2-year PFS of 12%
  - Phase III study GOELAMS group CHOP vs etoposide, ifosfamide, cisplatin alternating with adriamycin, bleomycin, vinblastine, and dacarbazine
    - No difference in outcome for the 2 arms ORR of 70% and CR rate of 35% with CHOP

NCCN Guidelines PTCL: Induction Therapy

- PTCL, NOS
- ALCL, ALK-
- AITL
- EATL

→ Stage I-IV →

Clinical trial (preferred)

Multiagent chemotherapy 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

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – Non-Hodgkin's Lymphomas. Version 5.2014. Available at: www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed December 2, 2014.

NCCN Suggested Treatment Regimens

First-line therapy:

- Clinical trial
- ALCL, ALK+ histology
  - CHOP-21
  - CHOEP-21
- Other histologies (ALCL, ALK-; PTCL, NOS, AITL, EATL), regimens that can be used include:
- CHOEP
- CHOP-14
- CHOP-21
- CHOP followed by ICE
- CHOP followed by IVE alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
- Dose-adjusted EPOCH
- HyperCVAD 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)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – Non-Hodgkin's Lymphomas. Version 5.2014. Available at: www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed December 2, 2014.

Intensified Induction + Upfront ASCT in EATL Retrospective Analysis of Prospectively Collected Data

Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation

Michal Sieniawski,[1] Nithia Angamuthu,[1] Kathryn Boyd,[2] Richard Chasty,[3] John Davies,[4] Peter Forsyth,[5] Fergus Jack,[6] Simon Lyons,[7] Philip Mounter,[8] Paul Revell,[9] Stephen J. Proctor,[1] and Anne L. Lennard[1]

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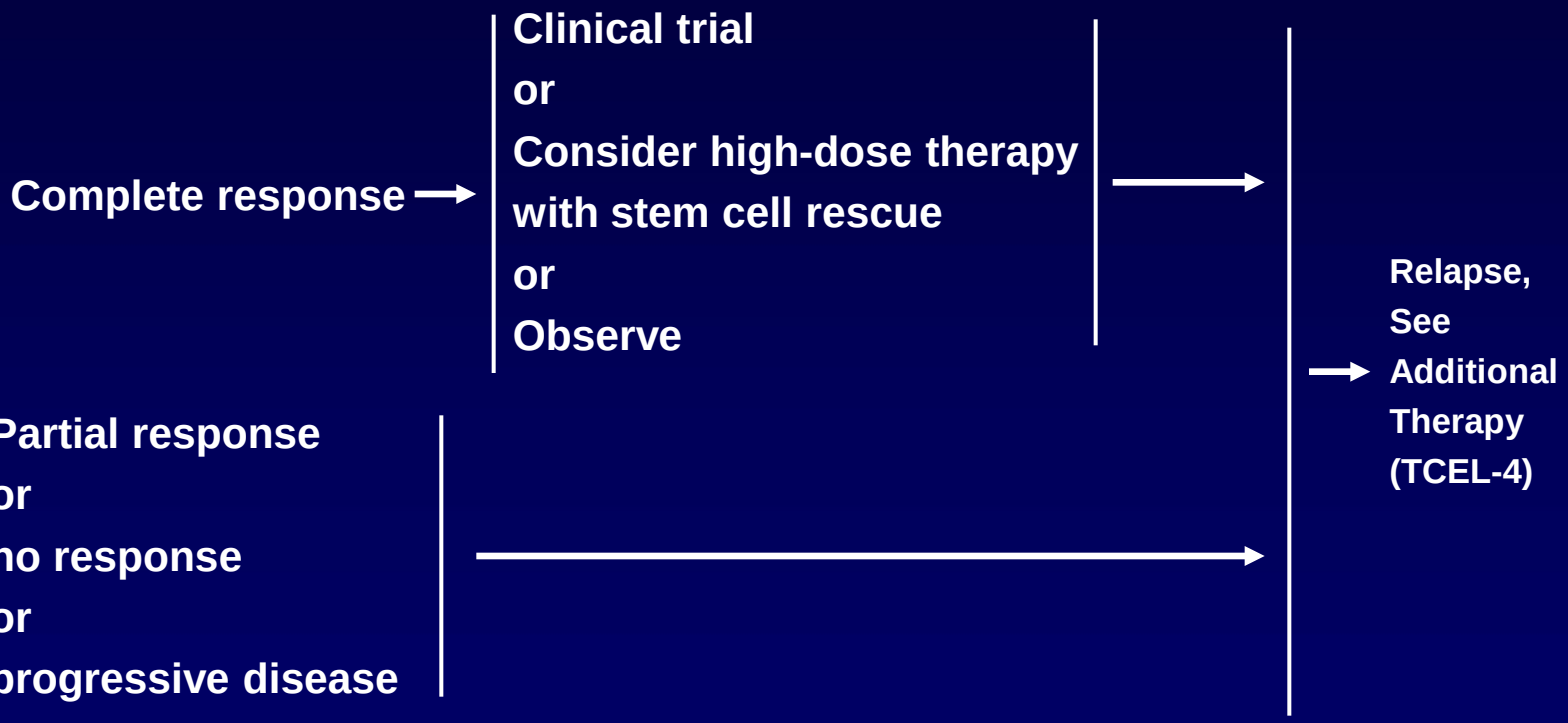
Parameter	Comment	Values
N patients	CHOP-like	N_{tot}= 54
	IVE + MTX+ASCT	N_{tot}= 26
Data period	CHOP-like	1994-1998
	IVE + MTX+ASCT	1998-2009
Endpoints (historical comparison)	5-year OS	22% vs 52%
	5-year PFS	22% vs 60%

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

NCCN Guidelines PTCL

Stage III, IV, aaIPI high/high intermediate



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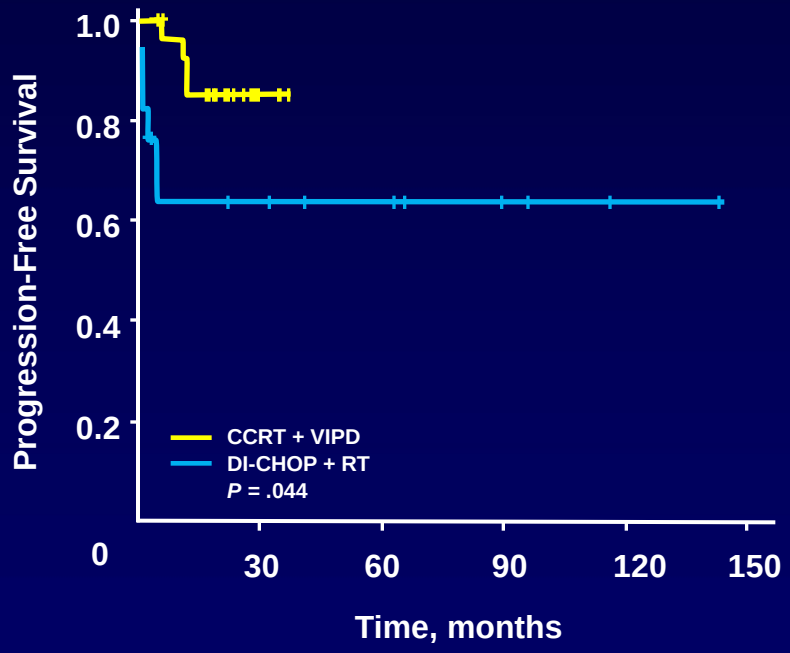
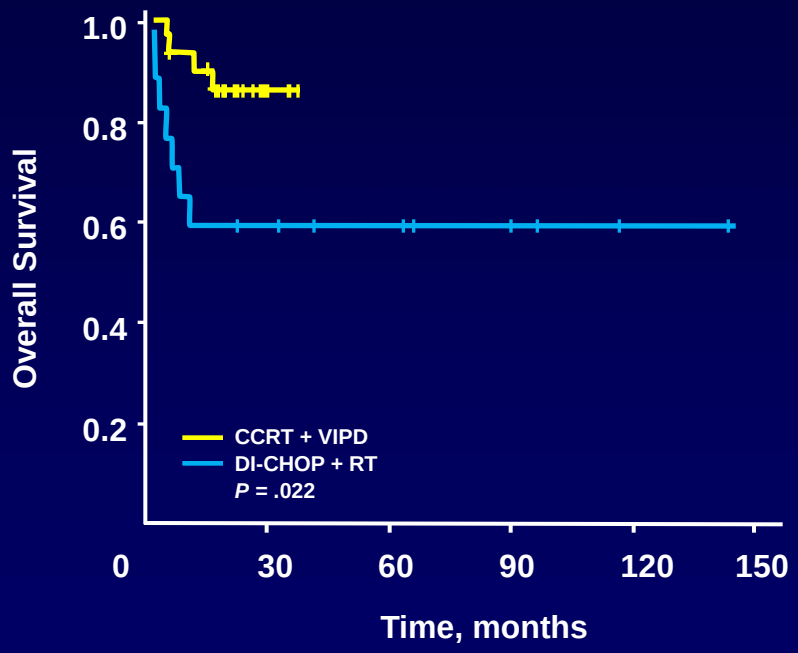
Localized NK/T-Cell Lymphomas Nasal Type: The Importance of Radiotherapy

- **Multiple studies confirming critical role of RT for long term control of localized (IE and IIE) extranodal NK/T cell lymphoma, nasal type (NKTCL)**
- **Prospective studies (Kim, et al; Yamaguchi, et al [JCOG0211-DeVIC]) using concurrent platinum based chemoradiotherapy: improved therapeutic outcomes: high locoregional control rate of 96%, excellent survival**
- **Relatively radioresistant and angioinvasive histolopathological characteristics of NKTCL are suggested to lead to hypoxia and doses of 40-50 Gy recommended**

Kim BS, et al. *Ann Oncol*. 2009;20(1):121-128. Yamaguchi M, et al. *J Clin Oncol*. 2009;27(33):5594-5600. Kim SJ, et al. *Ann Hematol.* 2014;93:1895-1901.

Concurrent Chemoradiotherapy (CCRT) Followed by Etoposide, Ifosfamide, Cisplatin, and Dexamethasone (VIPD) Produced a Significantly Longer (A) Progression-Free Survival and (B) Overall Survival Than Previous Cohort Treated Dose-intensified CHOP Chemotherapy Followed by RT





Kim SJ, et al, *J Clin Oncol.* 2009;27(35):6027-6032.

Summary of Current Management of PTCL

Limitations

- Most PTCL responds poorly to CHOP / CHOP-like chemotherapy, (exception ALCL ALK + and concurrent chemo-RT for NKTCL)
- Relapsed and chemotherapy-refractory disease difficult to manage
- Relapse following high-dose chemotherapy and ASCT, novel treatment options

Chemotherapy

Intensification and relapsed high-dose chemotherapy plus ASCT

Novel disease specific therapies needed Allogeneic SCT (last resort and limited patient groups)

The Failing T-cell Lymphoma Patient: Three Main Clinical Scenarios

Type of failure	Clinical course	Possible strategy
Primary refractory	No signs of chemosensitivity. Progression during induction treatment	➢ Exploit new biological insights with targeted therapeutics
Early relapse	Responds to induction. If eligible → ASCT. Relapses shortly after completion of first line therapy	➢ Improvement of induction ➢ Early consolidation
Late relapse	Chemosensitive. Reaches CR. Long cCR. Relapses > 1 year after completion of first-line therapy	➢ Reinduction of remission with personalized targeted therapy and consolidation