NK 细胞增殖性疾病

同济医院血液内科

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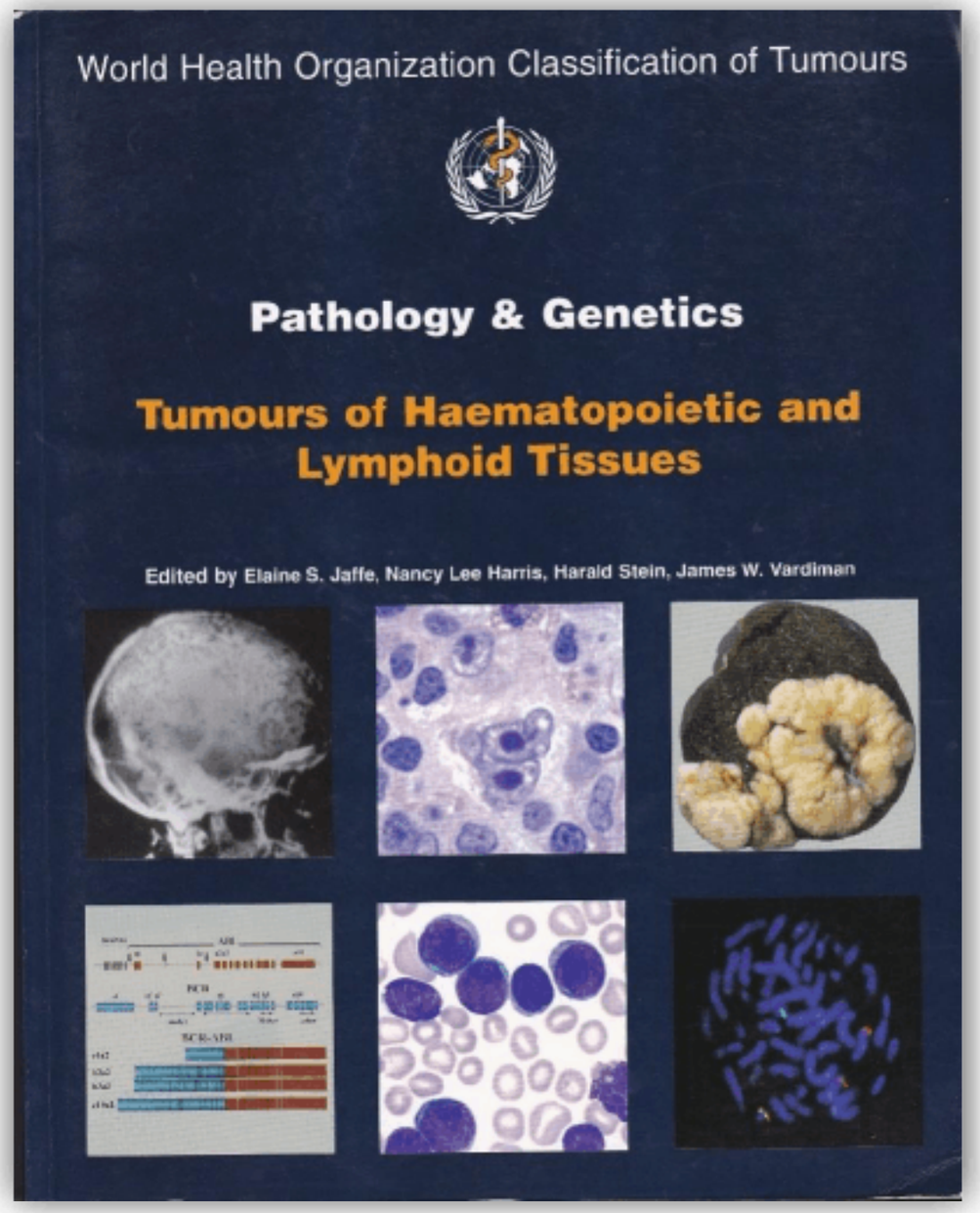
2015 年06月07日

T 和 NK 细胞肿瘤的分类：WHO 2008

WHO 2008: the mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells*
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with CAEBV)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorder
Lymphomatoid papulosis
Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma*
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium CD4+ T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK+
Anaplastic large cell lymphoma (ALCL), ALK?*



T 和 NK 细胞肿瘤分类的主要变化

2001 WHO	2008 WHO	Comments
Angioimmunoblastic Lymphoma	Angioimmunoblastic Lymphoma	Definition of origin cell
Anaplastic Large Cell Lymphoma	2 variants based on ALK (+/-) expression	Prognostic importance
Unspecified Peripheral T-cell Lymphoma	Peripheral T-cell Lymphomas not Otherwise Specified	3 variants: lymphoepitelioid lymphoma, T zone lymphoma (2001 WHO) and follicular lymphoma (2008 WHO)
T/NK-cell lymphoma, nasal type	T/NK-cell lymphoma, nasal type	No changes
Entheropathy-associated T-cell lymphoma	Entheropathy-associated T-cell lymphomas	Two variants: classical and monomorphic types with genetic changes common to both
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	No changes
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Only ab and associated with autoimmune disorder
Mycosis fungoides	Mycosis fungoides	New staging and new information about pathogenesis
Sézary syndrome	Sézary syndrome	New markers
Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma	Recognition of CD8+ cases
Lymphomatoid papulosis	Lymphomatoid papulosis	Three histological types
	Primary cutaneous gamma-delta T-cell lymphoma	Three histopathologic patterns: epidermotropic, dermic, and subcutaneous subtypes
	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Provisional entity
	Primary cutaneous CD4+ small/medium T-cell lymphoma	Provisional entity
Blastic NK-cell lymphoma	Plasmocytoid dendritic cell neoplasm	Now it is one of the myeloid neoplasms
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia	No changes
T-cell large granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia	New etiological features and new markers
	Chronic lymphoproliferative disorder of **NK-cells**	Provisional entity
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	No changes
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Definition of the regulatory T-cell normal counterpart

EBV 相关淋巴增殖性疾病

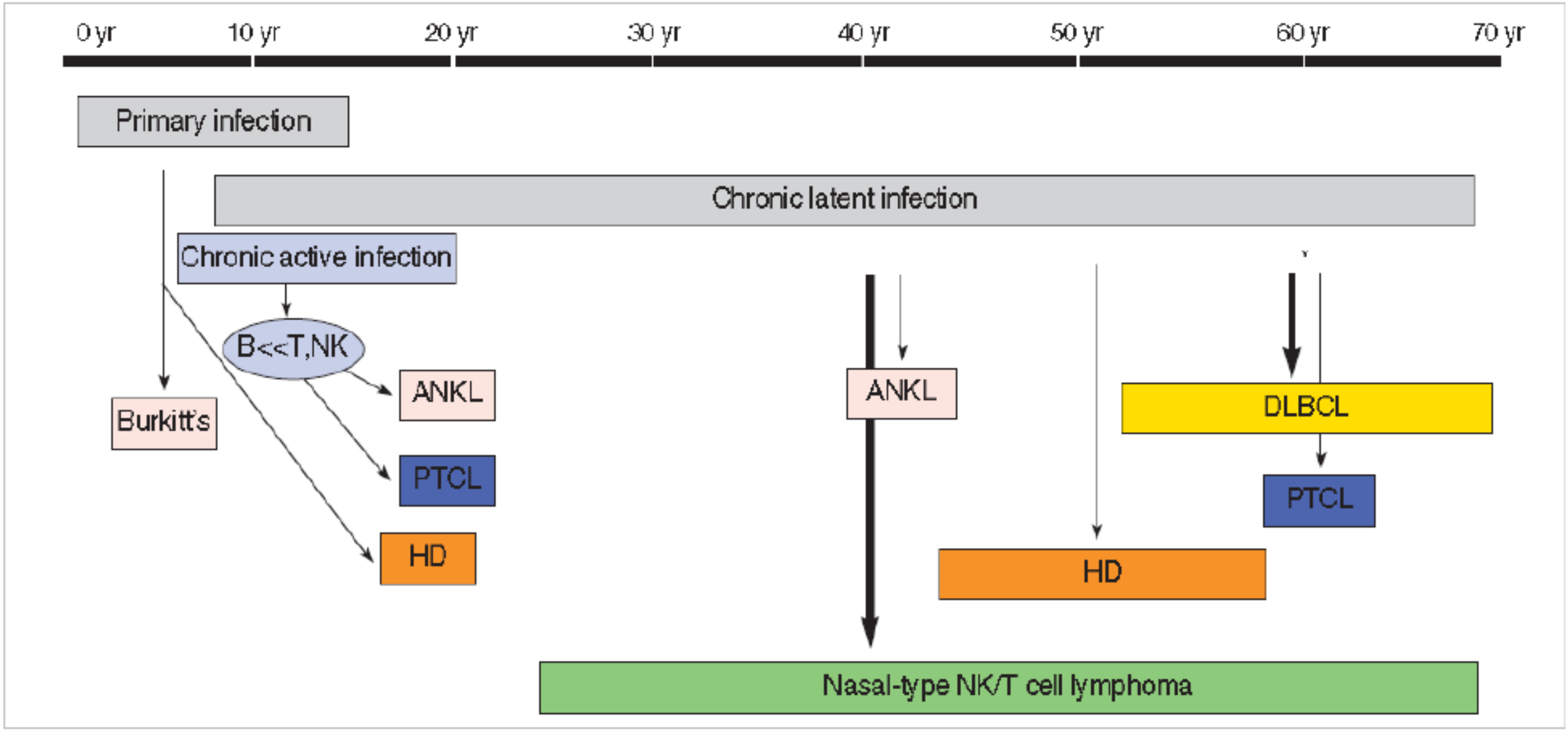


Fig. 4. The relation between EBV infection and development of EBV-associated lymphoproliferative disease by age group.
HD, Hodgkin's lymphoma; ANKL, aggressive NK cell leukemia; DLBCL, diffuse large B cell lymphoma; PTCL, peripheral T cell lymphoma.
*, environmental cofactor.

J Korean Med Sci. 2008 Apr;23(2)

EBV 相关 T/NK 细胞增殖性疾病

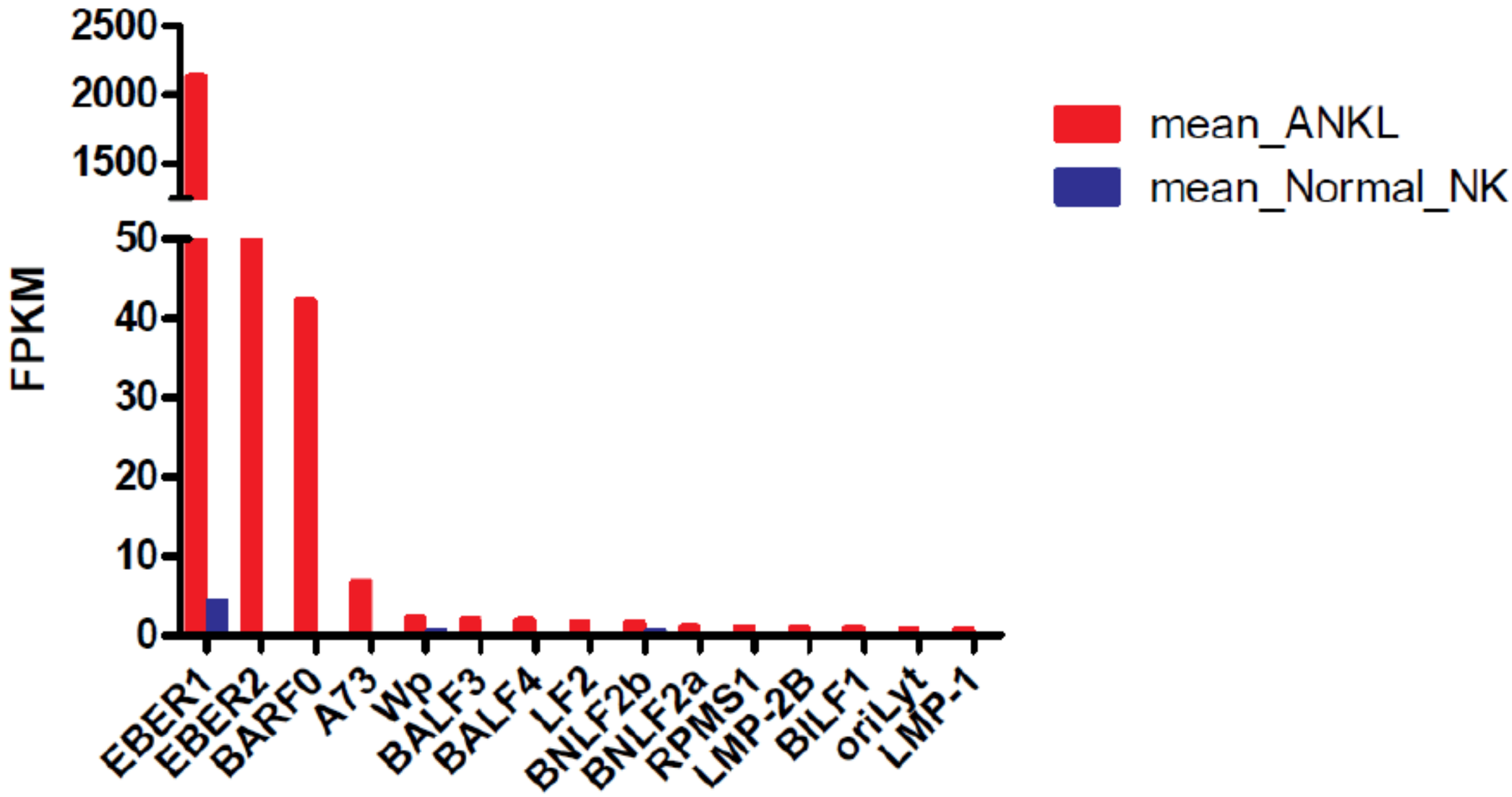
Table 1. Nomenclature for Epstein–Barr virus$^+$ T-cell and NK-cell lymphoproliferative diseases

Classification of EBV$^+$ T/NK LPD (2012 EAHP Workshop)	Classification of mature T-cell and NK-cell neoplasms (2008 WHO)	Classification for EBV$^+$ T/NK LPD of childhood type (2012 Asian Hematopathology Workshop)
Chronic active EBV infection Systemic (T, NK)		Chronic active EBV disease-type T/NK-cell LPD Polymorphic/polyclonal Polymorphic/monoclonal Monomorphic/monoclonal
	Systemic T-cell LPD of childhood*	
Chronic active EBV infection Hydroa vacciniforme (T)	Hydro vacciniforme-like lymphoma	Hydroa vacciniforme -like T-cell LPD Hydroa vacciniforme Classic type Severe type Hydroa vacciniforme-like T-cell lymphoma
Chronic active EBV infection, Mosquito-bite hypersensitivity (NK)	Mosquito-bite hypersensitivity	Mosquito-bite hypersensitivity
Systemic, malignant EBV$^+$ LPD Aggressive NK-cell leukemia/ lymphoma (NK)	Aggressive NK-cell leukemia	Aggressive NK-cell leukemia
Systemic, malignant EBV$^+$ LPD Systemic EBV$^+$ T-cell LPD	Systemic T-cell LPD of childhood	Systemic EBV$^+$ T/NK-cell LPD of childhood type
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma
Nodal T/NK-cell lymphoma		

*Monoclonal LPD among chronic active EBV infection. EBV, Epstein–Barr virus; LPD, lymphoproliferative diseases; NK, natural killer.

J Dermatol. 2014;41(1):

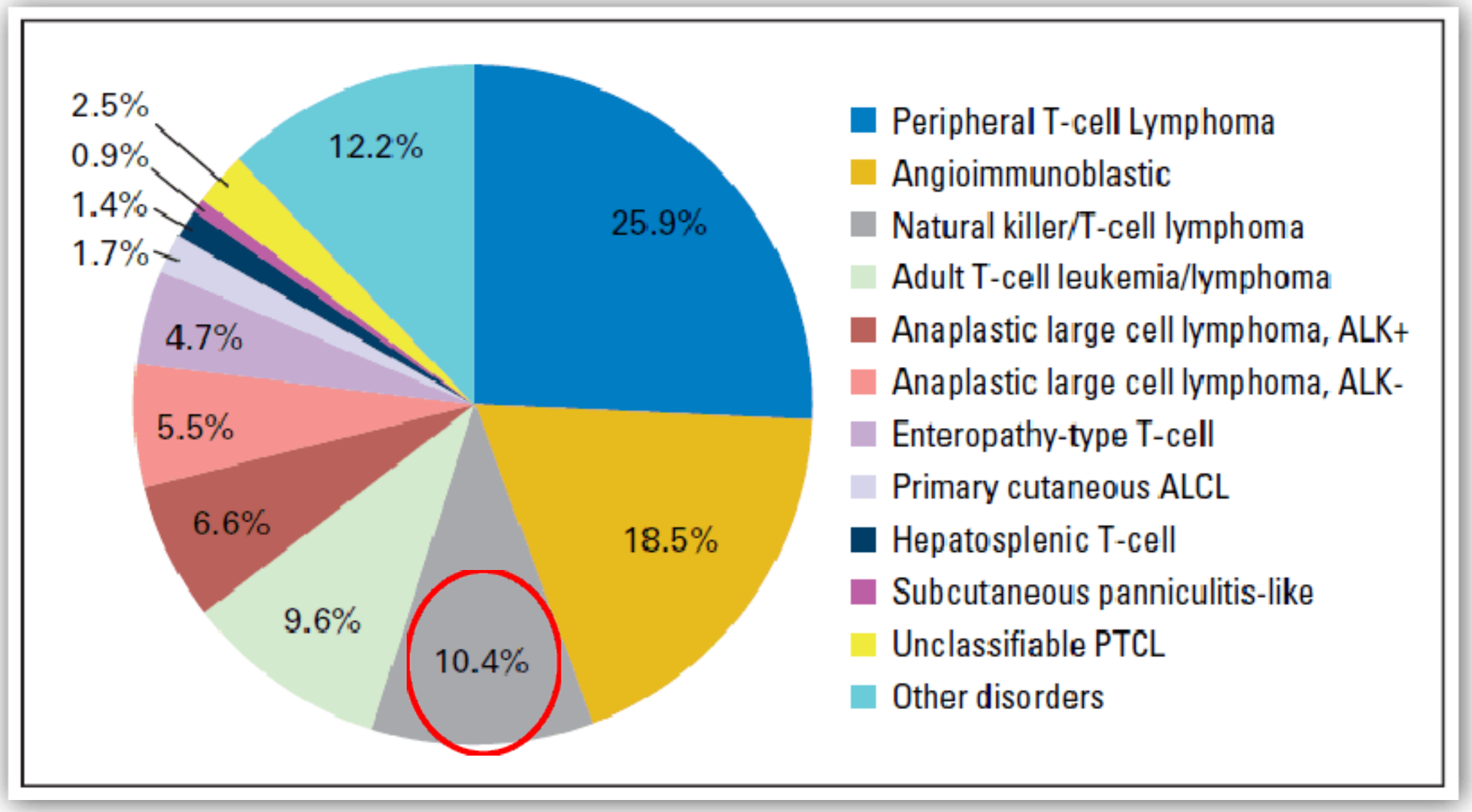
Top15 Expressed EBV genes in ANKL



潜伏性感染，不是裂解式感染，抗病毒治疗无效

NK/T 细胞淋巴瘤

NK/T 细胞淋巴瘤亚型分布

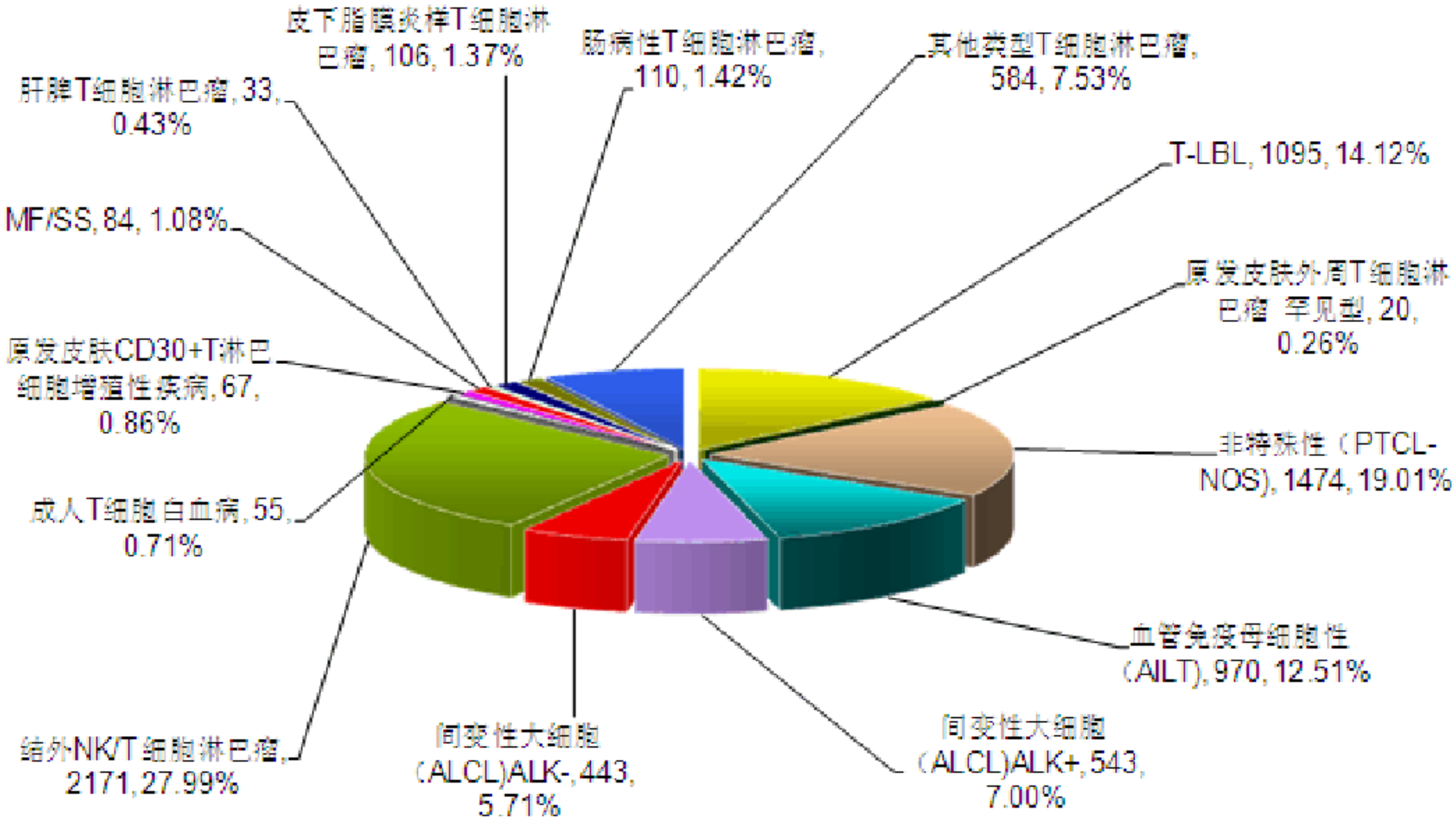


NK/T 细胞淋巴瘤占到所有 PTCL 的10.4%

J Clin Oncol, 2008, 26(25):

中国抗癌协会淋巴瘤专业委员会

09年8月-11年2月份NHL-T亚型分类数量比例图



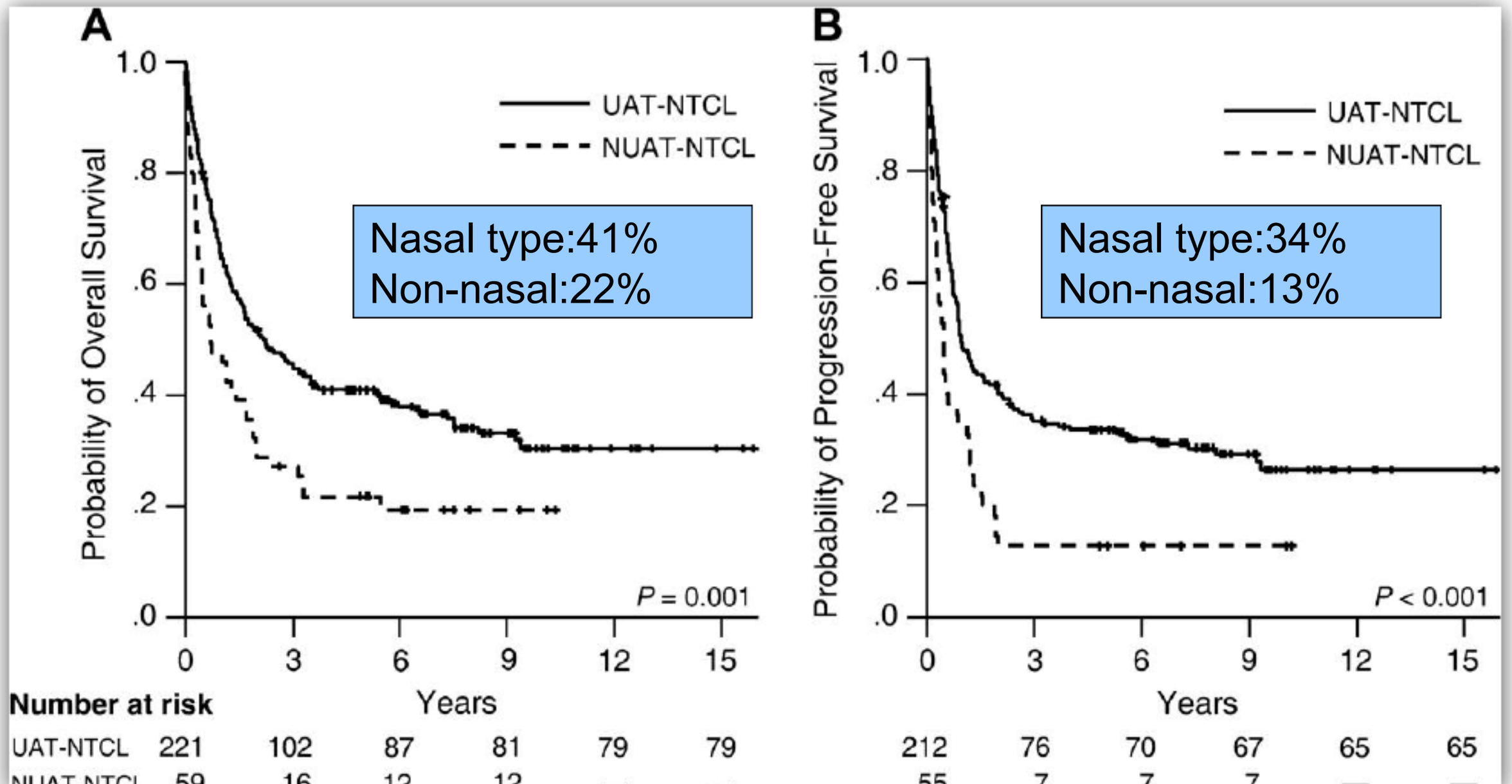
NK/T 细胞淋巴瘤特征

- 分为鼻型 (68%) 和非鼻型 (**26%**),其他为侵袭型（6%）
- 病理表现：形态多样，表现为血管中心性、大量坏死和血管浸润
- 表型：大部分为NK 细胞（EBV+，CD56+）

鼻型与非鼻型 NK/T 细胞淋巴瘤

	鼻型	非鼻型
侵犯部位	上呼吸	皮肤、睾丸、胃肠道
疾病晚期	27%	68%
肿块>5cm	12%	68%
超过2个鼻外病灶	16%	55%
LDH升高	45%	60%
B症状	39%	54%
5年OS率	42%	9%
中位OS	19月	4月

鼻型与非鼻型 NK/T 细胞淋巴瘤



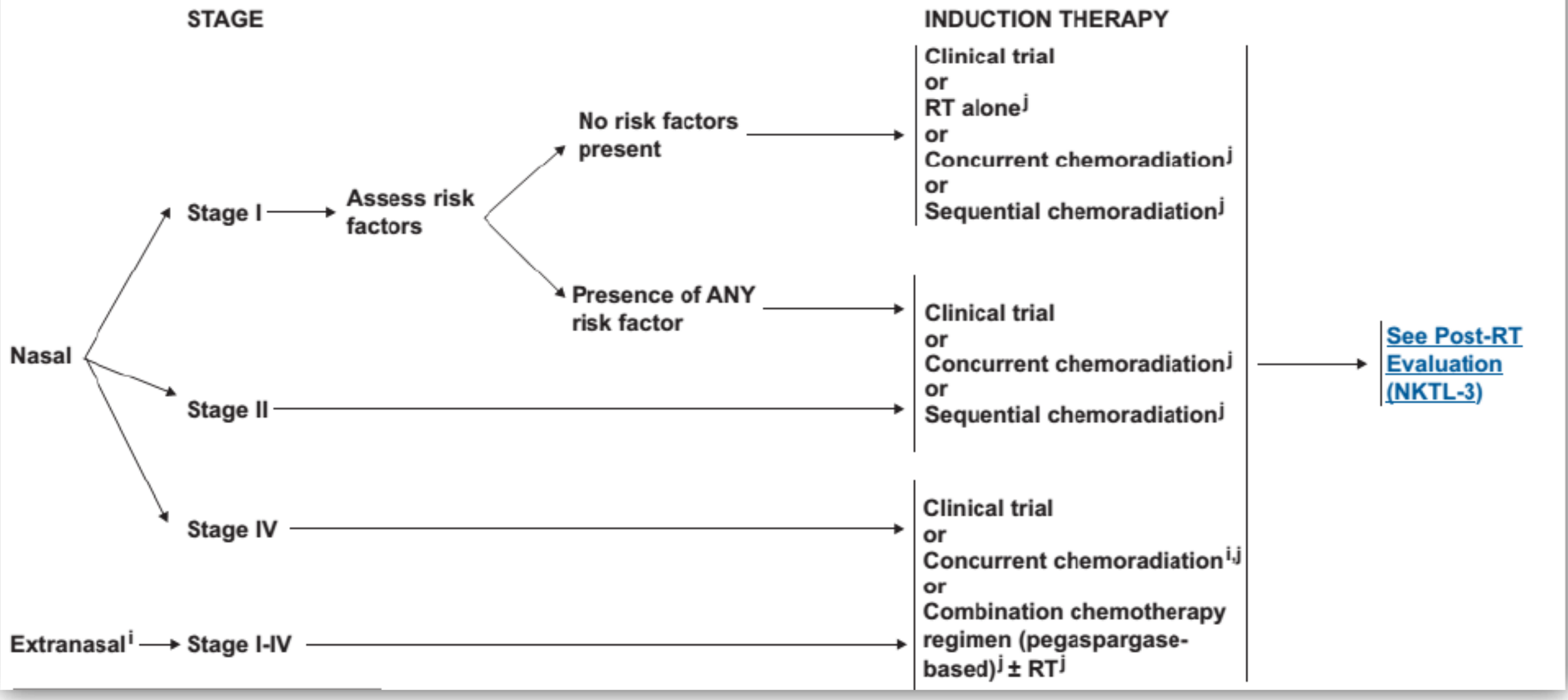
Ann Oncol 2008;19:1477-1

放疗在 NK/T 细胞淋巴瘤中的地位

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Extranodal NK/T-Cell Lymphoma, nasal type

NCCN Guidelines Index
NHL Table of Contents
Discussion



仅早期患者可作为根治手段，其余多数与化疗联用

什么样的 NK/T 细胞淋巴瘤可以单纯放疗？

Nasal versus extra-nasal

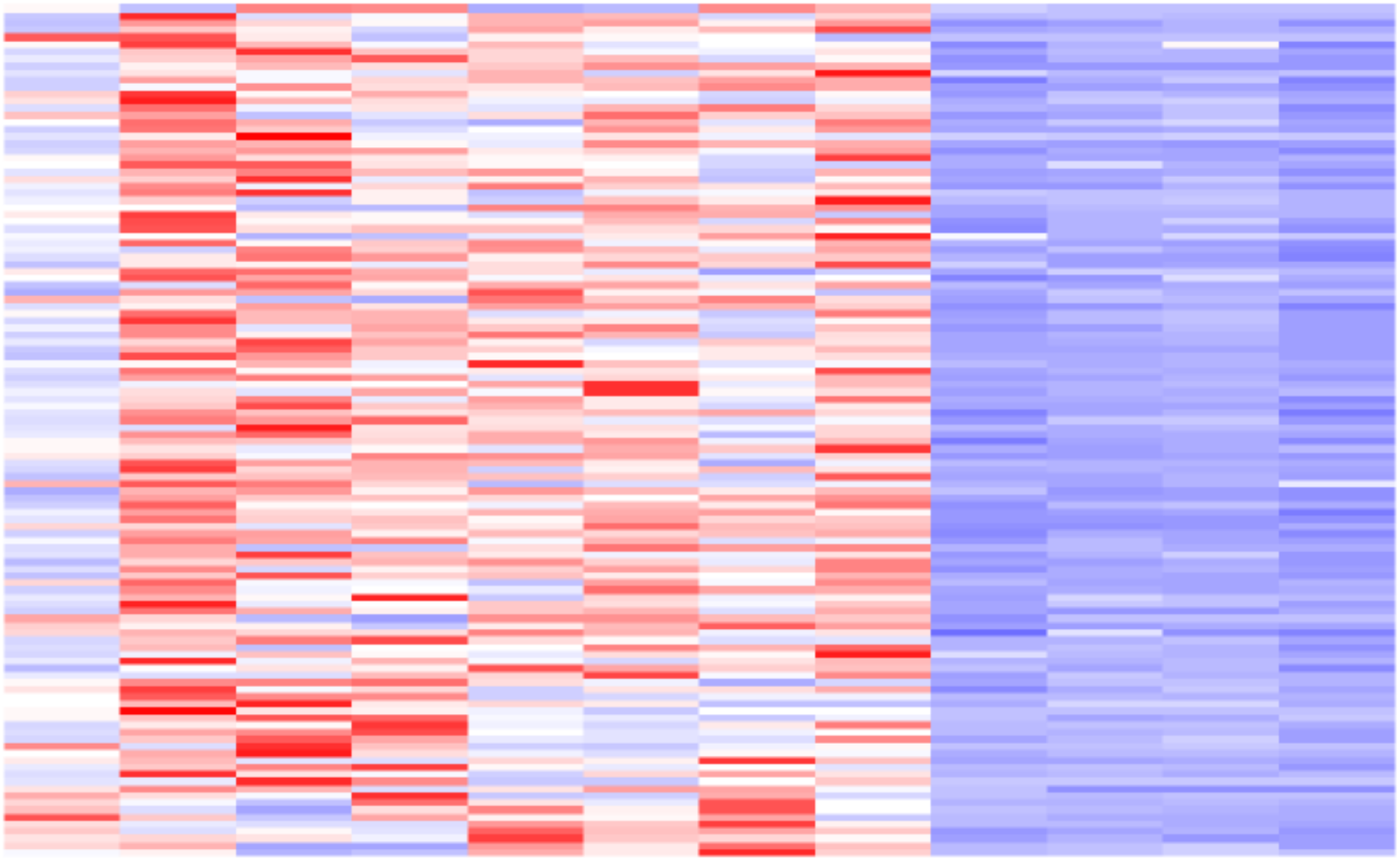
the stage of the disease

Stage I disease are further stratified based on risk factors

Age ≥60 years,
B symptoms,
ECOG performance status ≥ 2
Regional lymph node involvement Local tumor invasion
Elevated LDH
High Ki-67 staining
EBV DNA ≥6.1 x 10^7 copies/mL

更新了治疗方案后，化疗是必不可少的治疗手段

- 局限期鼻型NK/T细胞淋巴瘤单纯放疗RR和CR分别达78-94%和 66-94%，但 5y-OS 和中位 OS仅分别为35%-83% 和 50%
- 患者出现皮肤、骨髓、睾丸、内脏和淋巴结侵犯较常见
- 化疗仍然是必不可少的治疗手段



NK/T 细胞肿瘤具有不同寻常的表型特征

含门冬酰胺酶的方案

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Extranodal NK/T-Cell Lymphoma, nasal type

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NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (pegaspargase-based)
- **AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen.)**
- **SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide)**

Concurrent chemoradiation therapy (CCRT)
- **CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])**
- **CCRT (radiation 40–52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)**

Sequential chemoradiation
- **SMILE followed by RT 45–50.4 Gy**
- **VIPD followed by RT 45–50.4 Gy**

Radiation therapy alone
- **Recommended tumor dose is ≥50 Gy**
  - **Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.**
  - **Up-front RT may yield more benefits on survival in patients with stage I disease.**

SMILE 方案

? Smile方案

– Steroid (DXM) 40 mg, iv, d2-4

– MTX 2 g/m2, iv, d1

– IFO 1.5g/m2, iv, d2-4

– L-ASP 6000U/m2, iv, d8,10,12,14, 16,18,20

– Etopside 100mg/m2, iv ,d2-4

? G-CSF 从第 6 天开始解救， wbc > 5000/ml

Yamaguchi M, et al. JCO, 2011; 29(33):4410-6

SMILE 方案疗效及毒性

- CR率45%, CR+PR 79%
- 1y-OS 55%
- 毒性反应：92%患者出现IV度骨髓抑制，61%出现感染
- 8%出现早期死亡

Yamaguchi M, et al. JCO, 2011; 29(33):4410-6

AspaMetDex 方案

- ? Steroid （DXM）, 40mg, d1-4, po
- ? MTX 3.0g/m^2, d1, iv drip
- ? ~~IFO 1.5g/m2, iv~~, d2-4
- ? L-Asp 6000U/m^2, d2,4,6,8, im
- ? ~~Etopside 100mg/m2~~, iv ,d2-4

- ? Smile方案
  - Steroid (DXM) 40 mg, iv, d2-4
  - MTX 2 g/m2, iv, d1
  - IFO 1.5g/m2, iv, d2-4
  - L-ASP 6000U/m2, iv, d8,10,12,14, 16,18,20
  - Etopside 100mg/m2, iv ,d2-4

Jaccard A, et al. Blood, 2011,117:1834-1839.

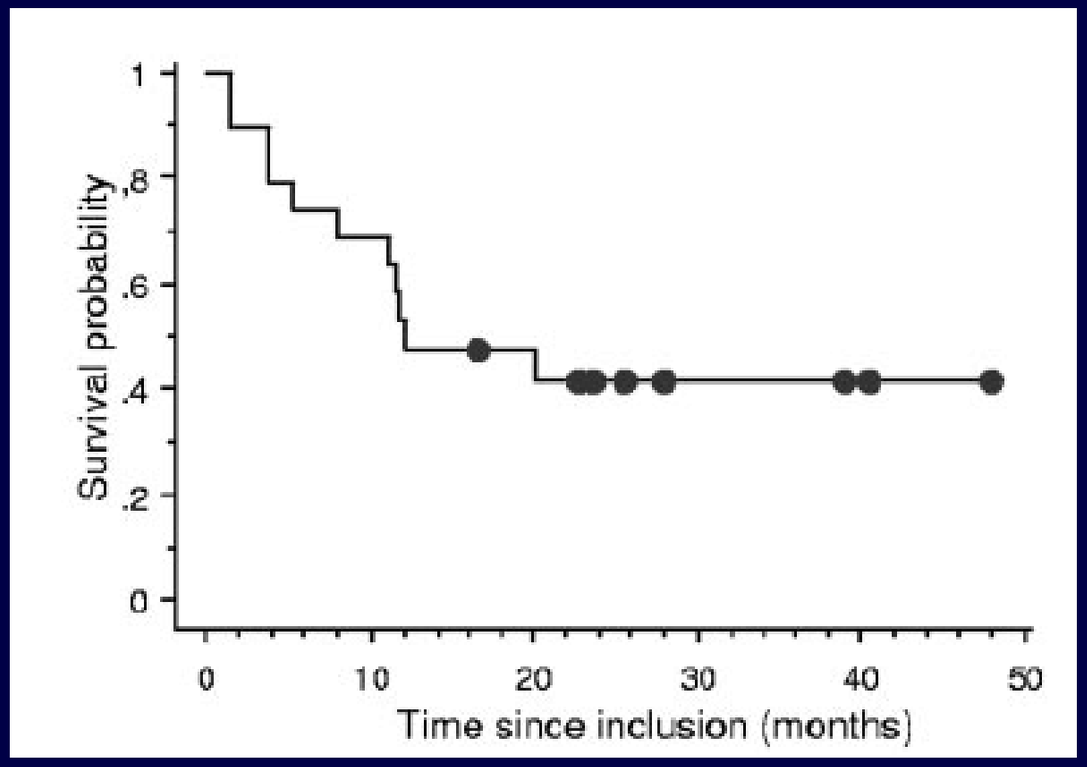
近期疗效和毒性

? 近期疗效
  – 18 例可评价，14 例获得缓解（78%），11 例完全缓解（61%）
  – 3 例治疗中死亡

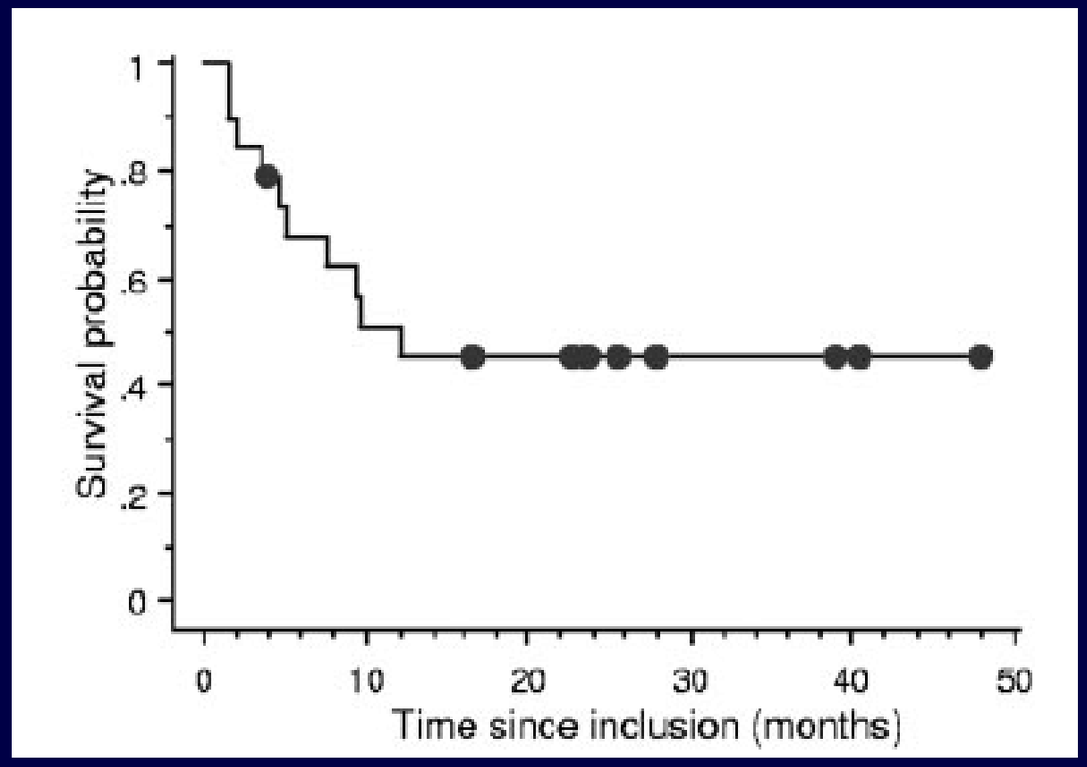
? 14 例有效患者，6 例在治疗结束后 9 个月内复发

AspaMetDex 方案

远期生存



中位OS12.2个月
无效患者4.2个月
有效后进展患者3.6个月



PFS 12.2个月

晚期结外NK/T细胞淋巴瘤治疗GOLD方案

Efficacy of gemcitabine combined with oxaliplatin, L-asparaginase and dexamethasone in patients with **newly-diagnosed extranodal NK/T-cell lymphoma**

G：gemcitabine 1g/m2，d1， D8

O：Oxaliplatin 100mg/m2，d1

L：L-Asparaginase 10,000 U/m2，d1-5

D：dexamethasone 40mg，d1-4

14-day cycle，Ann Arbor I/II期化疗后给予IFRT

2008-2012 新诊断的ENKTL

Guo HQ, Liu L, Wang XF, Lin TY, et al. Mol Clin Oncol. 2014 Nov;2(6):1172-1176

GOLD 方案

Table Patient characteristics (n=55).

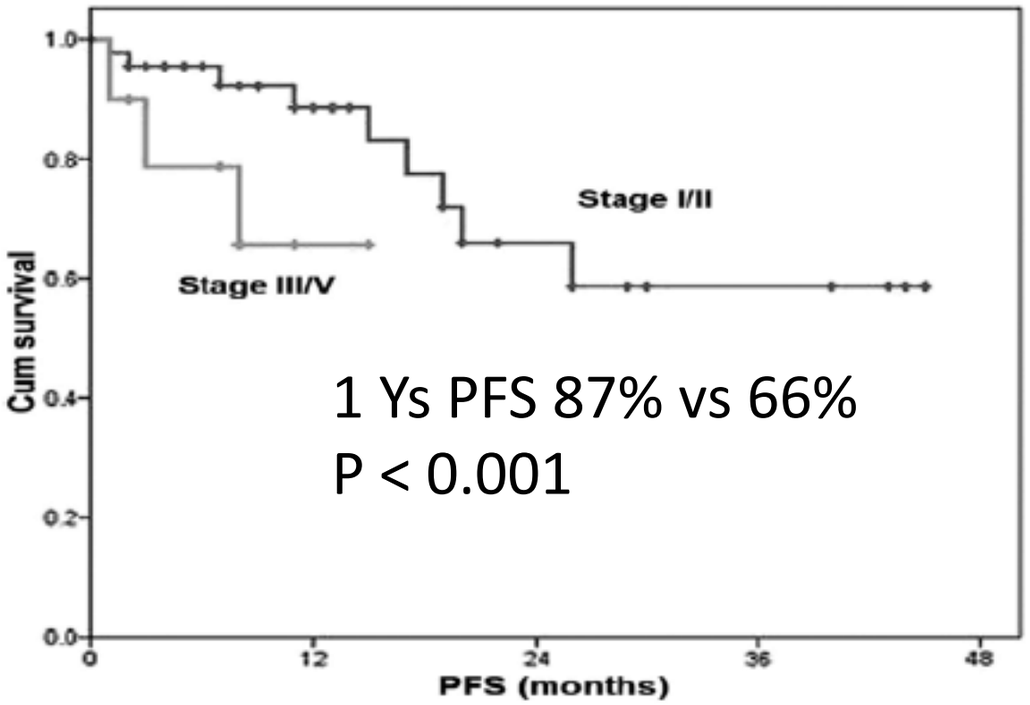
Characteristics	Patient no.	Percentage
B symptoms		
Yes	32	58
No	23	42
Ann Arbor stage		
I/II	45	82
III/IV	10	18
IPI		
1	29	53
2	16	29
3	8	15
4	2	3
Involved sites		
Nasal cavity/nasopharynx	48	87
Other	7	13

Response rate after the GOLD regimen.

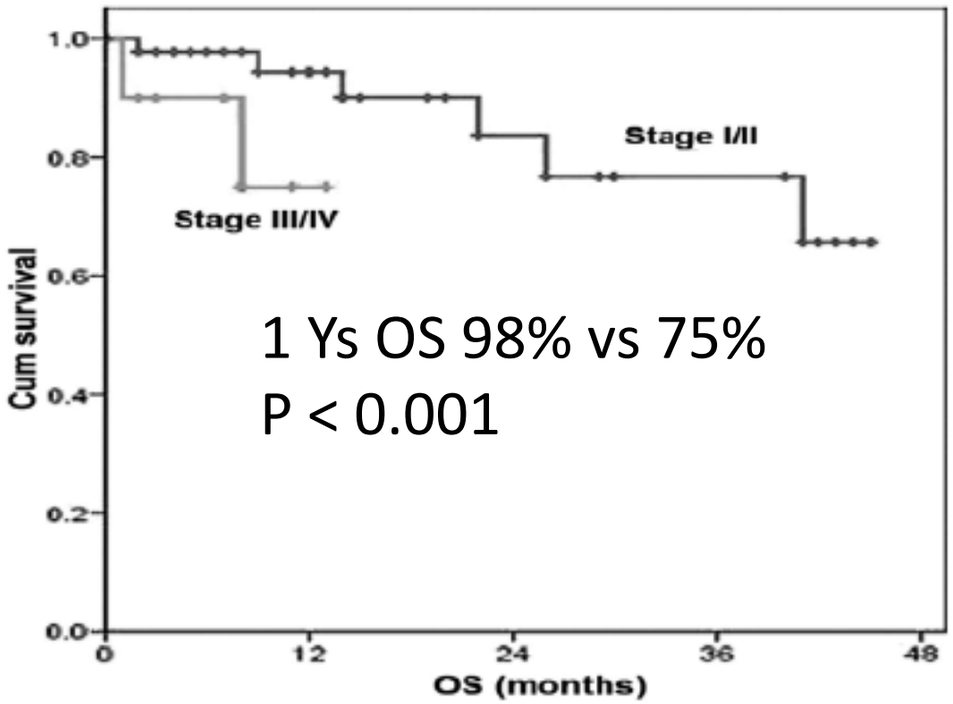
Type of response	Patient no.	Percentage
Complete response	34	62
Partial response	16	29
Stable disease	2	4
Progressive disease	3	5

Guo HQ, Liu L, Wang XF, Lin TY,et al. Mol Clin Oncol. 2014 Nov;2(6):1172-1176

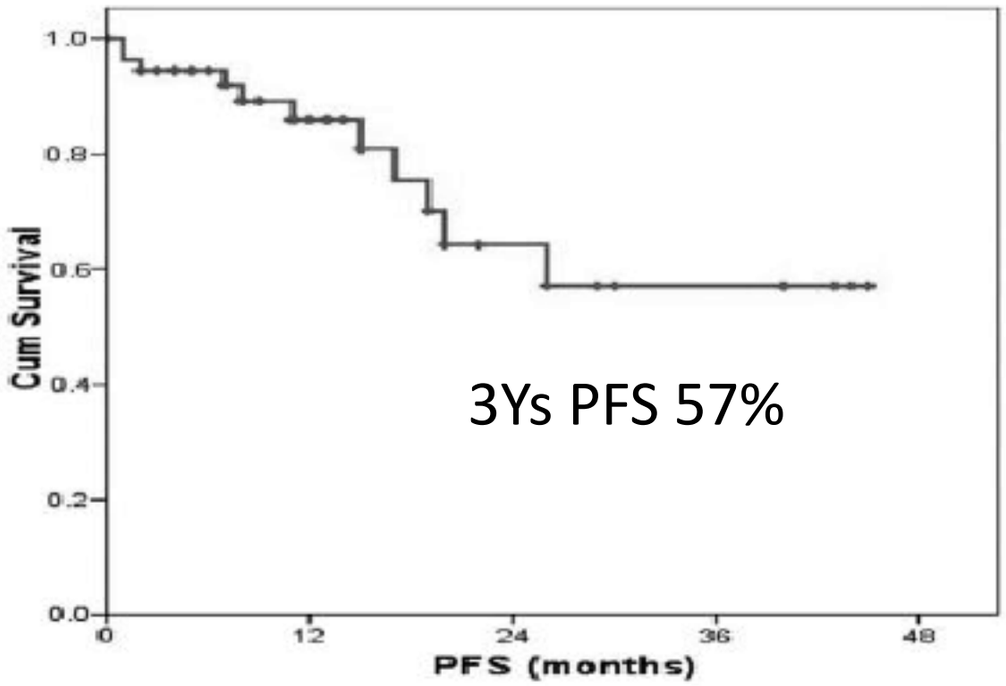
GOLD 方案



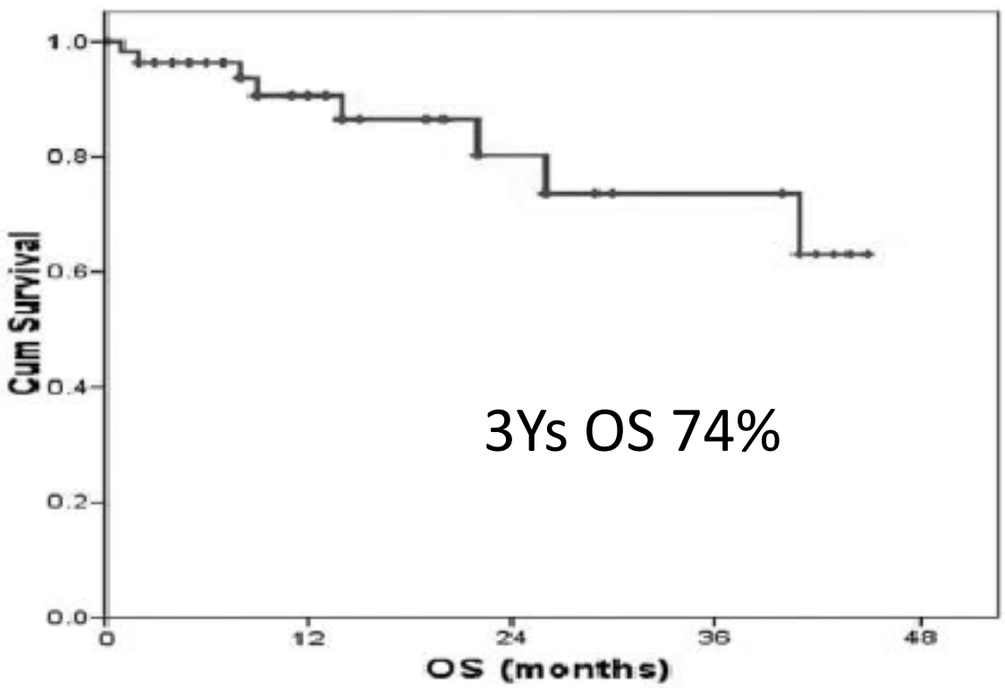
1 Ys PFS 87% vs 66%
P < 0.001



1 Ys OS 98% vs 75%
P < 0.001



3Ys PFS 57%



3Ys OS 74%

Guo HQ, Liu L, Wang XF, Lin TY,et al. Mol Clin Oncol. 2014 Nov;2(6):1172-1176

GOLD 方案

- GOLD的方案治疗ENKL获得很高的ORR（91%），CR率62%，PR率29%
- 3年 OS 74%，PFS 57%
- Ann Arbor分期是预后的重要影响因素，III/IV期患者的OS/PFS明显低于I/II期患者

Guo HQ, Liu L, Wang XF, Lin TY,et al. Mol Clin Oncol. 2014 Nov;2(6):1172-1176

同步/序贯化放疗（重点解决 I/II 期）

Disease	No.	Treatment	ORR	CR	OS	PFS	Adverse effects		
							Mucositis	Leucopenia	TRM
Relapsed/refractory	19	AspaMetDex	78%	61%	2 y: 40%	2 y: 40%	NR	Grade 3/4: 44%	0%
Newly diagnosed, relapsed/ refractory, any stage	87	SMILE ± sandwiched RT (50 Gy)	81%	66%	5 y 50%	4 y DFS: 64%	NR	Grade 3/4: 67%	5.7%
Newly diagnosed, stage I/II nasal	18	RT (median 50 Gy)	78%	78%	5 y: 30%	5 y: 30.5%	NR	NR	NR
Newly diagnosed, stage I/II nasal	31	RT (median 50 Gy)	100%	97%	5 y: 66%	5 y: 61%	NR	NR	NR
Newly diagnosed, stage I/II nasal	17	CHOP + RT (45 Gy)	58%	58%	3 y: 59%	NR	NR	NR	NR
Newly diagnosed, stage I/II nasal	27	Concurrent RT (50 Gy) + 2/3DeVIC	81%	77%	2 y: 78%	2 y: 67%	Grade 3/4: 30%	Grade 3/4: 93%	0%
Newly diagnosed, stage I/II nasal	30	Concurrent RT (50 Gy) + cisplatin + VIPD	86%	83%	3 y: 85%	3 y: 85%	Grade 1/2: 11%	Grade 3/4: 14%	6.6%
Newly diagnosed, stage I/II nasal	26	LVP + sandwich RT (56 Gy)	89%	81%	2 y: 89%	2 y: 81%	Grade 3: 23%	Grade 3: 3%	0%
Newly diagnosed, stage I/II nasal	27	GELOX + sandwiched RT (56 Gy)	96%	74%	2 y: 96%	2 y: 86%	Grade 3: 15%	Grade 3/4: 33.3%	0%
Newly diagnosed, stage IV, or relapsed/refractory	38	SMILE	79%	45%	1 y: 55%	1 y: 53%	NR	Grade 3/4: 100%	5.3%

Concurrent

Sequential

Blood. 2013;121(25):4997-

NCCN 指南

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