5. HEMATOLOJİK ONKOLOJİ KONGRESİ
20-22 EYLÜL ACAPULCO RESORT HOTEL (K.K.T.C.)

Ekstranodal (Nazal) NK/T Hücreli Lenfoma

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20.09.2018

Ekstranodal (Nazal) NK/T Hücreli Lenfoma

- Lenfomalar; tüm kanserlerin %3'ü,
- Hematolojik kanserler arasında en sık gözlenen grup,
- Lenfomaların ~%75'ini non-Hodgkin, %25'ini Hodgkin lenfoma oluşturmaktadır*
- Ülkemizde oranlar % 80'e, % 20 olarak bulunmuştur.
- Periferik T hücre lenfomaları (PTCL), non-Hodgkin lenfomaların (NHL) yüzde 15'inden azını oluşturur.

* http://www.cancer.org/acs/groups/content/@nho/documents/document/ acspc-024113.pdf (Cancer Facts, erişim: 18.08.2013)

Epidemiyoloji

- Nazal tip NK / T hücreli lenfoma en sık Asya'da (Çin, Japonya, Kore, Hong Kong) ve Orta-Güney Amerika'daki (Peru ve Meksika) NHL'larının % 5-10 arasındadır.
- Tanıda medyan yaşı 52 *
- Ancak, çocukluk çağında nadir vakalar bildirilmiştir.
- Yaklaşık 2:1 erkek-kadın oranı vardır*

*Au WY, Weisenburger DD, Intragumtornchai T, et al. Blood 2009; 113:3931.

Table 1. Major Lymphoma Subtypes by Geographic Region

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
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.

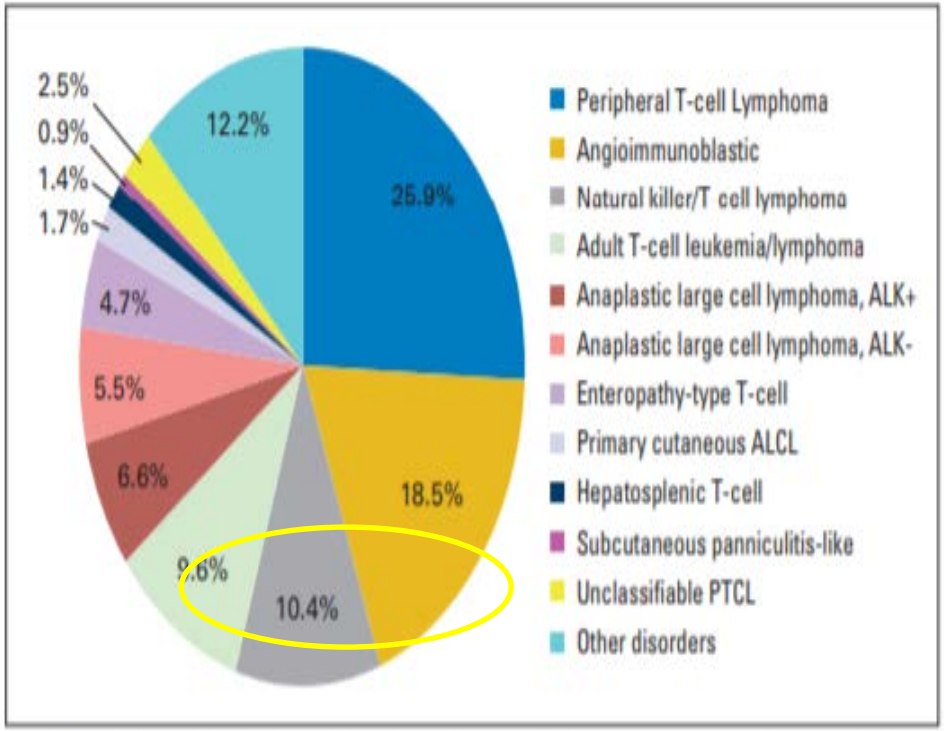

Fig 1. Distribution of 1,314 cases by consensus diagnosis. NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; PTCL, peripheral T-cell lymphoma.

Vose J[1], Armitage J, Weisenburger D; International T-Cell Lymphoma Project.J Clin Oncol. 2008 Sep 1;26(25):4124-30.

REAL Classification (1994)	→ Change	WHO Classification (2001)
Precursor cell lymphoma		***Precursor cell lymphoma***
Lymphoblastic lymphoma, T cell		Lymphoblastic lymphoma, T cell
B cell		B cell
Peripheral B-cell neoplasms		***Peripheral B-cell neoplasms***
B-chronic lymphocytic leukemia/small lymphocytic lymphoma/prolymphocytic leukemia	→	B-chronic lymphocytic leukemia/small lymphocytic lymphoma
	→	B-prolymphocytic leukemia
Lymphoplasmacytoid lymphoma	→	Lymphoplasmacytic lymphoma
Mantle cell lymphoma		Mantle cell lymphoma
Follicular center cell lymphoma	→	Follicular lymphoma
Marginal zone B-cell lymphoma		
– Extranodal	→	Extranodal marginal zone B-cell lymphoma of MALT type
– Nodal (*Provisional entity*)	→	Nodal marginal zone B-cell lymphoma
Splenic marginal zone B-cell lymphoma (*Provisional entity*)	→	Splenic marginal zone B-cell lymphoma
Hairy cell leukemia		Hairy cell leukemia
Diffuse large B-cell lymphoma		Diffuse large B-cell lymphoma
Burkitt lymphoma	→	Burkitt lymphoma (including Burkitt-like lymphoma)
High grade B-cell lymphoma, Burkitt-like (*Provisional entity*)	→	
Plasmacytoma/plasma cell myeloma		Plasmacytoma/plasma cell myeloma
Peripheral T and NK cell neoplasms		***Peripheral T and NK cell neoplasms***
T-cell chronic lymphocytic leukemia/ prolymphocytic leukemia	→	T-prolymphocytic leukemia
Large granular lymphocyte leukemia (T or NK cell)	→	T-cell granular lymphocytic leukemia
	→	Aggressive NK cell leukemia
Mycosis fungoides/Sezary syndrome		Mycosis fungoides/ Sezary syndrome
Peripheral T-cell lymphoma unspecified		Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma		Angioimmunoblastic T-cell lymphoma
Angiocentric lymphoma	→	Extranodal NK/T cell lymphoma, nasal and nasal-type
Intestinal T-cell lymphoma	→	Enteropathy-type T-cell lymphoma
Hepatosplenic $\gamma\delta$ T-cell lymphoma (*Provisional entity*)	→	Hepatosplenic $\gamma\delta$ T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma (*Provisional entity*)	→	Subcutaneous panniculitis-like T-cell lymphoma
Anaplastic large cell lymphoma, T/null cell	→	Anaplastic large cell lymphoma, T/null cell, primary systemic type
	→	Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
Adult T-cell lymphoma/leukemia (HTLV1+)		Adult T-cell lymphoma/leukemia (HTLV1+)

*Anaplastic large cell lymphoma, Hodgkin-like, considered a provisional entity in the REAL classification, has been deleted from the new WHO classification.

Mature T and NKcell neoplasms within the 2008 and revised 2016 WHO classification

2008 WHO classification	2016 revision	Comments
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia	- no major changes
T-cell large granular lymphocytic leukemias	T-cell large granular lymphocytic leukemias (T-LGL)	- *STAT3* and *STAT5B* mutations in a subset of cases
	Chronic lymphoproliferative disorder (LPD) of NK cells[a]	- new provisional entity - NK-cell counterpart of T-LGL
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	- no major changes
Systemic EBV$^+$ T cell lymphoproliferative disorder (LPD) of childhood	Systemic EBV$^+$ T cell lymphoma of childhood*	- change in nomenclature due to the fulminant clinical course and monoclonal proliferation - Hemophagocytic syndrome usually present
Hydroa vacciniforme-like lymphoma	Chronic active EBV infection[a] - systemic form - cutaneous form - Hydroa-vacciniforme-like LPD[a] - severe mosquito bite allergy[a]	- new category to encompass the EBV$^+$ T and NK-cell LPD in the pediatric age - can be monoclonal - change in nomenclature. Umbrella term that covers the entire spectrum of the disease - new subgroup.
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	- no major changes
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type	- no major changes
Enteropathy-associated T-cell lymphoma, type I	Enteropathy-associated T-cell lymphoma	- no major changes
Enteropathy-associated T-cell lymphoma type II	Monomorphic epitheliotropic intestinal T-cell lymphoma[a]	- change in nomenclature - lack association with celiac disease - mostly derived from γδ T cells - *STAT5B* mutations in 36% the cases - recurrent *SETD2* alterations
	Indolent T-cell LPD of the GI tract[a]	- new provisional entity
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	- no major changes
Subcutaneous paniculitis-like T-cell lymphoma	Subcutaneous paniculitis-like T-cell lymphoma	- no major changes
Mycosis fungoides	Mycosis fungoides	- no major changes
Sezary syndrome	Sezary syndrome	- no major changes
Primary cutaneous CD30+ LPD - Lymphomatoid papulosis (LyP) - anaplastic large cell lymphoma	Primary cutaneous CD30+ LPD - Lymphomatoid papulosis (LyP) - anaplastic large cell lymphoma	- new morphological subtypes
Primary cutaneous γδ T-cell lymphoma	Primary cutaneous γδ T-cell lymphoma	- needs to be distinguished from other γδ T-cell cutaneous disorders mainly LyP
Primary cutaneous CD8+ aggressive epdermotropic cytotoxic T-cell lymphoma	*Primary cutaneous CD8+ aggressive epdermotropic cytotoxic T-cell lymphoma*	- no major changes - differential diagnosis with LyP type D
	Primary cutaneous acral CD8$^+$ T-cell lymphoma[a]	- new provisional entity
Primary cutaneous CD4+ small/medium T-cell lymphoma	*Primary cutaneous CD4+ small/medium T-cell LPD*[a]	- change in nomenclature. Indolent disorder indistinguishable from clonal drug reactions
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	- molecular subgroups recognized
Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma - *Follicular T-cell lymphoma*[a] - *PTCL with TFH phenotype*[a]	- frequent *TET2*, *RHOA* and *IDH2* mutations - new subgroups with THF phenotype

Classification

Table 1 continued

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2018)

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-positive T-cell lymphoma of childhood
- Hydroa vacciniforme–like lymphoproliferative disorder
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma**
- *Primary cutaneous acral CD8-positive T-cell lymphoma**
- *Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK positive
- Anaplastic large-cell lymphoma, ALK negative
- *Breast implant–associated anaplastic large-cell lymphoma**

Hodgkin Lymphoma

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant Lymphoproliferative Disorders (PTLD)

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis-like PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

*Provisional entities are listed in italics.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2018 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2018;127:2375-2390.

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Did you mean: *extranodal nk/t cell lymphoma, nasal type* (1263 items)

Hematol Oncol. 2018 Aug 16. doi: 10.1002/hon.2547. [Epub ahead of print]

Extranodal lymphomas in the public health system in Chile. Analysis of 1251 patients from the National Adult Cancer Program.

Peña C[1], Russo M[2], Martinez V[3], Cabrera ME[4].

Author information

Abstract

The aim of the study was to describe the clinical and epidemiological characteristics, anatomic and histologic distribution, and treatment results of extranodal lymphomas (ENL), diagnosed and treated in the public health system in Chile. We included patients with ENL diagnosed from 1998 to 2014, in 17 cancer centers, registered prospectively in the database of the National Adult Cancer Program (PANDA) of the Ministry of Health. Treatment was based on the local protocols for each lymphoma subtype. ENL was documented in 1215 of 4907 non-Hodgkin lymphomas diagnosed in that period (25%). Median age was 59 years (range, 16-95) and 55% were female. The gastrointestinal tract (GI) was the most common location (38%), followed by head and neck (24%) and skin (15%). B-cell lymphomas accounted for78% of cases diffuse large B-cell lymphoma being the most common histologic subtype(68%) Mycosis fungoides/Sezary syndrome was the most significantly high prevalence of NK/T cell lymphoma nasal type, whilst the frequency of B-cell ENL and the anatomic distribution appeared similar, being GI the most commonly involved site.

1998 ve 2014 arasında 17 kanser merkezinde, toplam 4907 NHL hastanın 1215'i ENL (% 24.8)

KEYWORDS: Extranodal non Hodgkin lymphoma; National Adult Cancer Program Chile; gastrointestinal lymphoma

PMID: 30117170 DOI: 10.1002/hon.2547

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Figure 1. Extranodal sites involved in non Hodgkin lymphoma in Chile. 19 2014 (n=1215 cases).

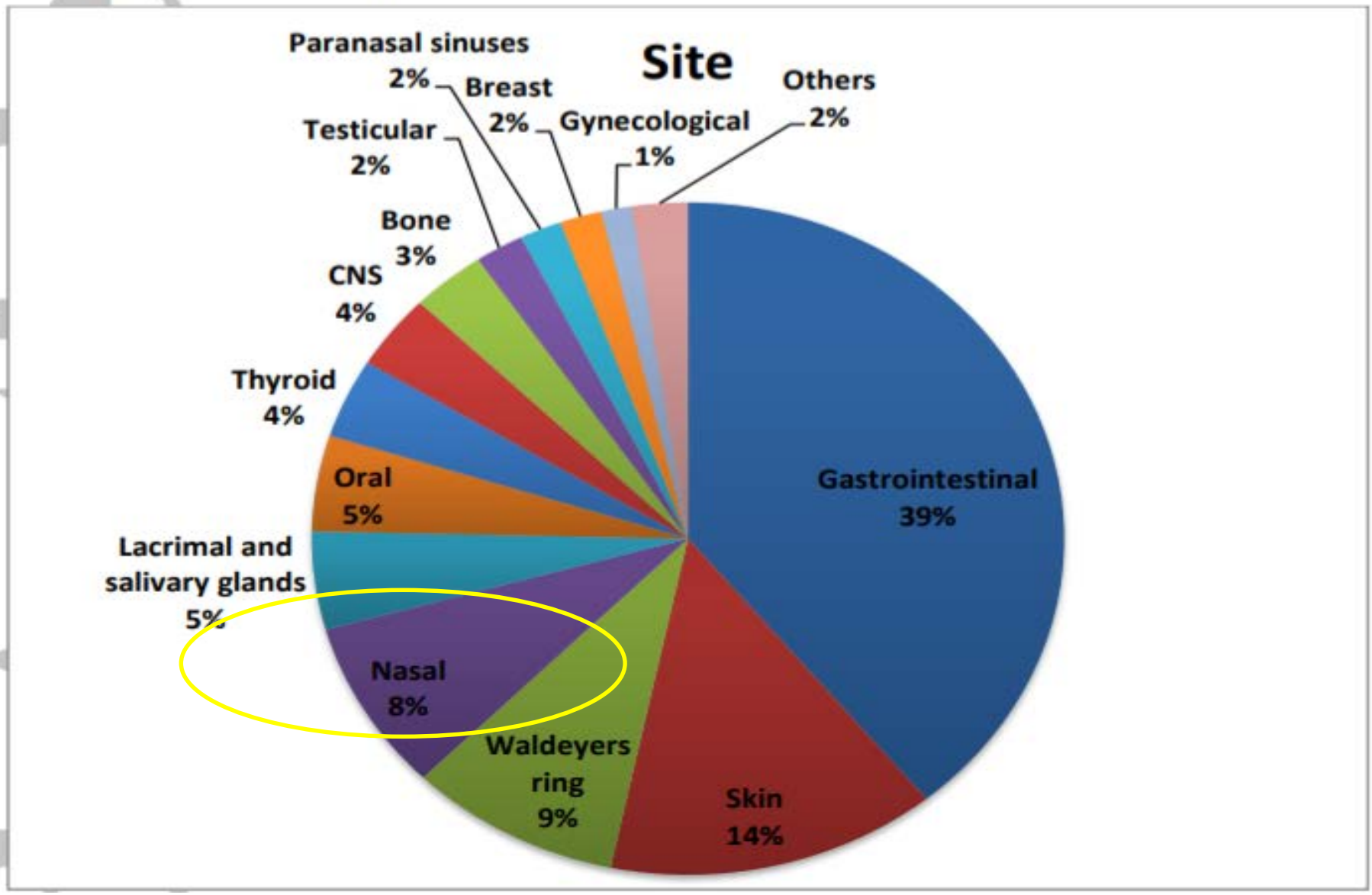
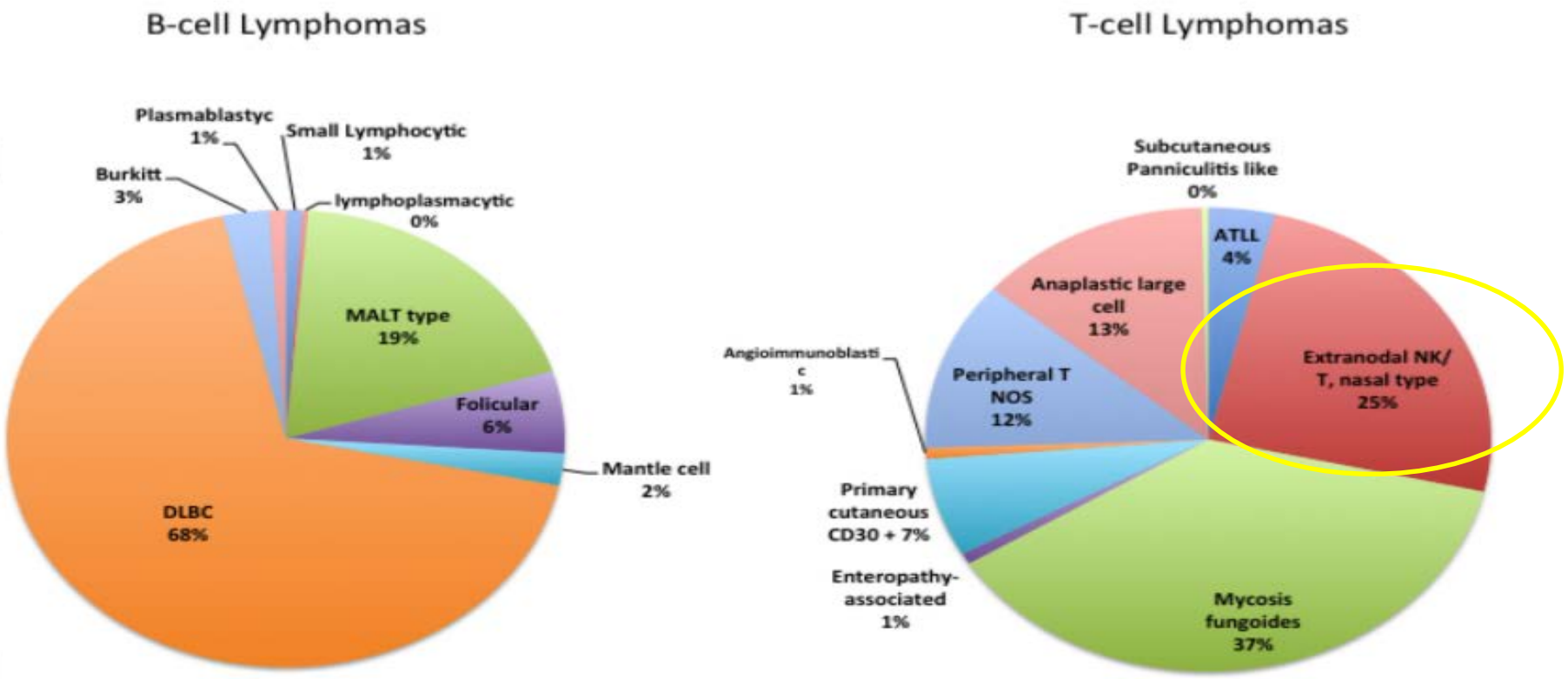


Figure 2. Histologic subtypes of 948 cases of B-cell and 267 cases of T-cell extranodal lymphomas.



DLBC: diffuse large B-cell lymphoma, Enteropathy associated T-cell lymphoma 0.8%, Angioimmunoblastic T-cell lymphoma 0.8%, subcutaneous panniculitis type 0.4%; ATLL, adult T-cell leukemia/lymphoma.

Ekstranodal NK / T hücreli lenfoma; nazal tip

- Eski adıyla anjiyosentrik lenfoma, "ölümcül orta hat granülomu olarak bilinmektedir.
- En sık yüzün orta hat yapılarından nazal kavite ve üst solunum yollarını tutarak çevre kıkırdak ve yumuşak dokuda destrüksiyon,
- Morfolojik görünüm, sık nekroz ve anjiyovasvazyon ile birlikte, doğal öldürücü (NK) hücre fenotipi ve Epstein-Barr virüsü (EBV) pozitifliği olan bir ekstranodal lenfomadır.
- Sitotoksik T hücrelerinden türetilmiş gibi görünmektedir.

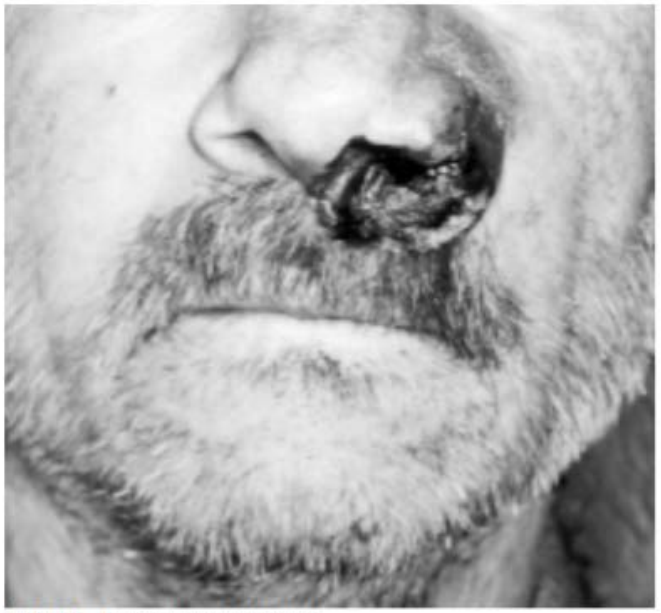
KBB İhtisas Dergisi
2002;9(6):425-428

OLGU SUNUMU

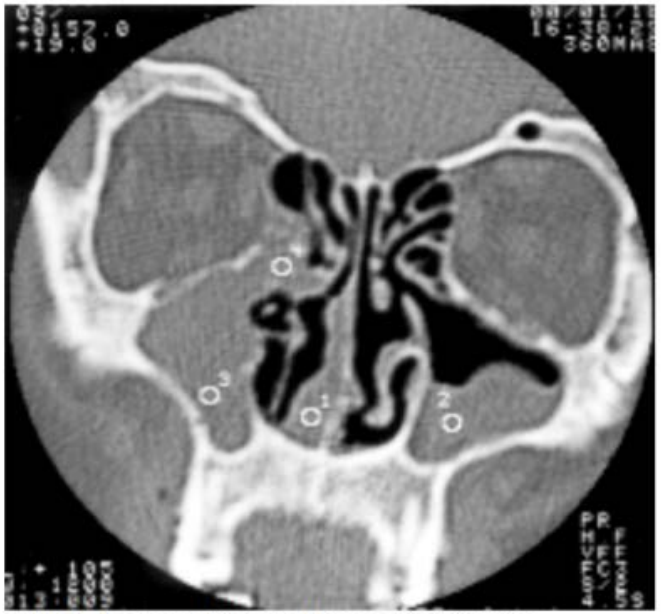
Sinonazal lenfoma: Olgu sunumu

A case of sinonasal lymphoma

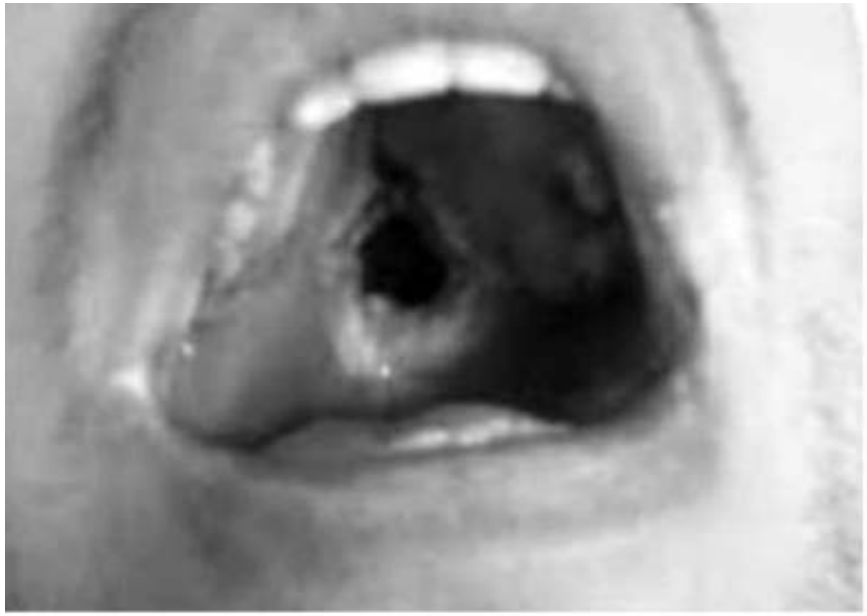
landı. Enfeksiyonun tedavisi için antibiyoterapiye başlandı. Bilgisayarlı tomografide sol maksiller sinüsü ve burun yan duvarında kemik destrüksiyonu yaparak sol nazal kaviteyi dolduran, yaklaşık 5x8 cm'lik kitle belirlendi (Şekil 2). Kitlenin malign olabileceği düşünüldü. Ancak, biyopsi sonucunda kısmen granülamatöz özellikte nonspesifik aktif kronik iltihap, lamellar kemikte osteomyelit, yaygın nekroz, nekroz içinde kitle oluşturan flemantoz mikroorganizmaların görülmesi öncelikle nokardiyoz tanısını düşündürdü ve kesin tanı için mikrobiyolojik inceleme önerildi. Kültür sonucunda metisiline duyarlı *Staphylococcus aureus* üremesi üzerine, biyopsinin tekrarına karar verildi. İkinci biyopsinin sonucu periferik T-hücreli lenfoma (mikst orta ve büyük hücreli) CD4 (+) olarak belirlendi. Onkoloji polikliniğine sevk edilen hastaya siklofosfamid, adriamisin, vinkristin ve prednisolondan oluşan protokol ile kemoterapi uygulanmaya başlandı. Kemoterapinin ikinci küründe hasta yaşamını yitirdi.



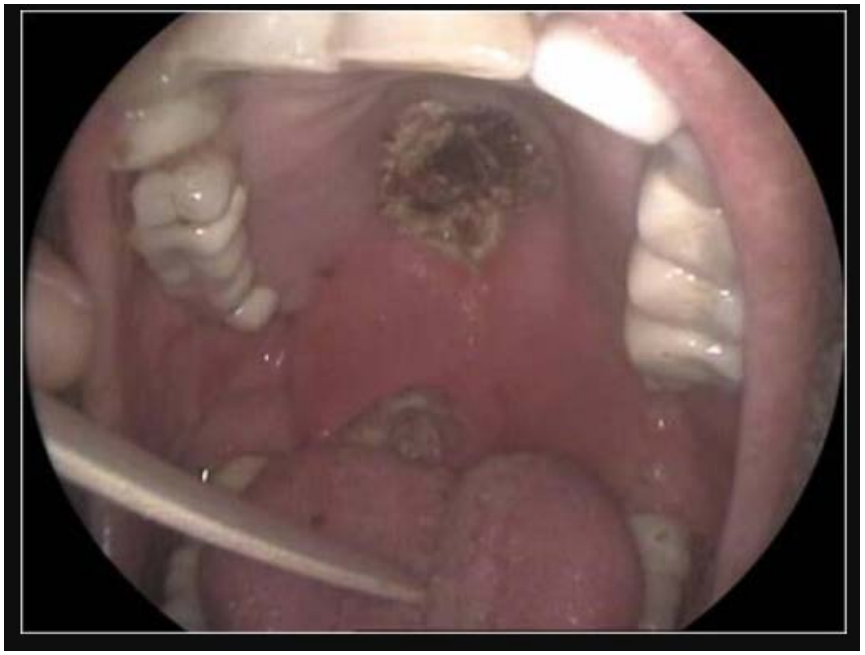
Şekil 1 - Lezyonun görünümü.

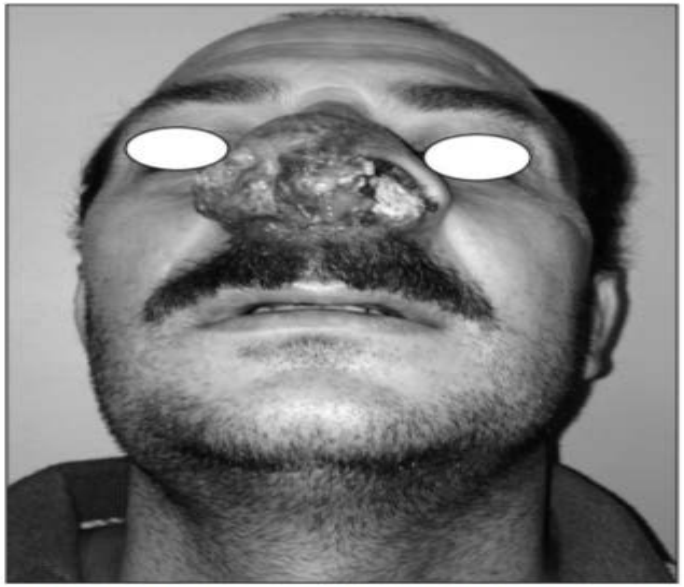


Şekil 2 - Lezyonun bilgisayarlı tomografi görüntüsü.

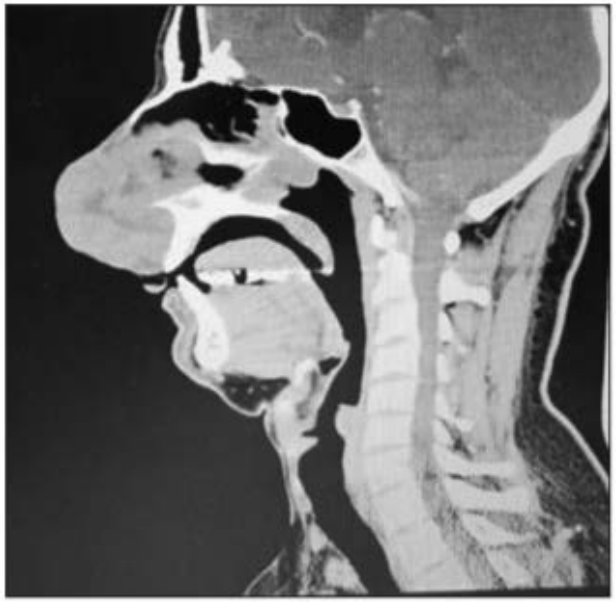


Şekil 1. *Sert ve yumuşak damak bileşkesinde 3x2 cm çapında destrüksiyona neden olan, yara kenarları nekrotik orta hat lezyonu.*





RESİM 1: Nazal tip bölgesini ekspanse eden, nazal kaviteyi dolduran yer yer ülserasyon gösteren kitle-alttan görünüm.



RESİM 3: Paranasal sinüs bilgisayarlı tomografi (PNS BT) sagital kesitlerde nazal tip bölgesini ekspanse eden, nazal kaviteyi dolduran vejetan kitle.

Patogenez

- Hemen hemen tüm olgularda monoklonal epizomal EBV-DNA ve EBV ile kodlanmış küçük nükleer RNA'lar (EBER'ler) bulunur.
- Bu tümörlerin yüksek bir yüzdesi, p53 tümör baskılayıcı proteinini aşırı ifade eder ve yaklaşık dörtte biri p53 mutasyonunun kanıtlarını gösterir*
- p53'ün doğru bir hedefi olan siklin bağımlı kinaz inhibitörü p21, p53 mutasyon durumundan bağımsız olarak bu tümörlerde aşırı eksprese edilir*
- p21 aşırı ekspresyonunun EBV enfeksiyonu ile ilişkili olabileceği varsayılmaktadır*

*Quintanilla-Martinez L, Kremer M, Keller G, et al. Am J Pathol 2001; 159:2095.

Klinik özellikler;

- Hastalar, burun tıkanıklığı, burun kanaması semptomları ve / veya burun, sinüs veya damağı içeren yıkıcı bir kitle ile sonuçlanan lokalize hastalığa sahiptirler.
- Üst hava yolu, waldeyer halkası, gastrointestinal sistem, deri, testis, akciğer, göz veya yumuşak dokuların tutulumuna bağlı semptomlar*
- Lenf düğümleri ikincil olarak yer alabilir, ancak nadiren birincil tutulum yeridir**
- Kemik iliği tutulumu % 10 ve B semptomları % 35 görülür***

*Au WY, Weisenburger DD, Intragumtornchai T, et al. Blood 2009; 113:3931.
**Chan JK, Sin VC, Wong KF, et al.Blood 1997; 89:4501.
***Li YX, Liu QF, Fang H, et al.Clin Cancer Res 2009; 15:2905.

Variable Clinical Presentations of Nasal and Waldeyer Ring Natural Killer/T-Cell Lymphoma

Ye-Xiong Li,[1] Qing-Feng Liu,[1] Hui Fang,[1] Shu-Nan Qi,[1] Hua Wang,[1] Wei-Hu Wang,[1] Yong-Wen Song,[1] Jiade Lu,[3] Jing Jin,[1] Shu-Lian Wang,[1] Yue-Ping Liu,[1] Ning Lu,[2] Xin-Fan Liu,[1] and Zi-Hao Yu[1]

Abstract

Purpose: To determine the clinical characteristics, prognosis, and treatment outcome for patients with nasal natural killer (NK)/T-cell lymphoma (N-NKTL) and Waldeyer ring NK/T-cell lymphoma (WR-NKTL).

Experimental Design: A total of 145 patients with N-NKTL and 95 patients with WR-NKTL were compared.

Results: Compared with N-NKTL, WR-NKTL exhibited distinct differences in clinical features with a propensity for nodal involvement, more advanced stages, low elevated lactate dehydrogenase, intermediate chemosensitivity, and a favorable prognosis. Compared with patients with WR-NKTL, patients with N-NKTL were associated with a lower overall response (54% versus 89%) and higher persistent or progressive disease after initial chemotherapy (46% versus 11%; $P = 0.000$). The 5-year overall survival and progression-free survival rates were 67% and 56% for N-NKTL and 65% and 47% for WR-NKTL, respectively. Patients with stage II WR-NKTL showed favorable prognosis compared with those with stage II N-NKTL. Compared with radiotherapy alone, patients with early-stage WR-NKTL that received radiotherapy and chemotherapy showed a superior progression-free survival and improved overall survival. In contrast, the addition of chemotherapy to radiotherapy did not provide any survival benefit for patients with early-stage N-NKTL.

Conclusions: N-NKTL and WR-NKTL represent heterogeneous groups with variable clinical features, responses, prognosis, and treatment options.

Table 1. Clinical characteristics and treatment of patients with N-NKTL and WR-NKTL

Characteristics	All patients (n = 240), n (%)	N-NKTL (n = 145), n (%)	WR-NKTL (n = 95), n (%)	P (N-NKTL vs WR-NKTL)
Sex				
Male	163 (68)	94 (65)	69 (73)	0.205
Female	77 (32)	51 (35)	26 (27)	
Age (y)				
Median (range)	42 (7-79)	43 (11-72)	38 (7-79)	
≤60	222 (93)	137 (94)	85 (89)	0.15
>60	18 (7)	8 (6)	10 (11)	
Ann Arbor stage				
I	134 (56)	117 (81)	17 (18)	<0.001
II	82 (34)	25 (17)	57 (60)	
III	13 (5)	0 (0)	13 (14)	
IV	11 (5)	3 (2)	8 (8)	
Cervical nodal involvement				
Present	98 (41)	24 (17)	74 (78)	<0.001
Absent	142 (59)	121 (83)	21 (22)	
Nodal involvement				
Present	101 (42)	25 (17)	76 (80)	<0.001
Absent	139 (58)	120 (83)	19 (20)	
Involvement of adjacent organ				
Present	148 (62)	91 (63)	57 (60)	0.667
Absent	92 (38)	54 (37)	38 (40)	
B symptoms	83 (35)	50 (34)	33 (35)	0.968
Elevated LDH level	84 (35)	66 (46)	18 (19)	0.008
Eastern Cooperative Oncology Group score				
0	55 (23)	32 (22)	23 (24)	0.172
1	162 (68)	95 (66)	67 (71)	
2	17 (7)	12 (8)	5 (5)	
3	6 (2)	6 (4)	0 (0)	
IPI				
0	122 (50)	67 (46)	55 (58)	0.017
1	90 (37)	64 (44)	26 (27)	
2	24 (10)	14 (10)	10 (11)	
3	2 (1)	0 (0)	2 (2)	
4	2 (1)	0 (0)	2 (2)	
Treatment for stage I-II	n = 216	n = 142	n = 74	
CMT	145 (67)	89 (63)	56 (76)	
Radiotherapy	61 (28)	47 (33)	14 (19)	
Chemotherapy	10 (5)	6 (4)	4 (5)	
Treatment for stage III-IV	n = 24	n = 3	n = 21	
CMT	13 (54)	2 (67)	11 (52)	
Chemotherapy	11 (46)	1 (33)	10 (48)	

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Clinical Investigation: Lymphoma

Immunophenotypic and Clinical Differences Between the Nasal and Extranasal Subtypes of Upper Aerodigestive Tract Natural Killer/T-Cell Lymphoma

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Received Oct 8, 2013, and in revised form Dec 1, 2013. Accepted for publication Dec 4, 2013.

Summary

There are few data available

Purpose: To investigate, in a large cohort of patients, the immunophenotypic and clinical differences of nasal and extranasal extranodal nasal-type natural killer/T-cell lymphoma of the upper aerodigestive tract (UADT-NKTCL) and examine the relevance of the immunophenotype on the

UADT-NKTCL have significantly different clinical features, immunophenotypes, and prognosis. Lower expression of CD56 and Ki-67 are associated with a relatively favorable prognosis

dicted poorer survival for extranasal UADT-NKTCL but not for nasal UADT-NKTCL.
Conclusions: Patients with nasal and extranasal UADT-NKTCL have significantly different clinical features, immunophenotypes, and prognosis. Extranasal UADT-NKTCL should be considered as a distinct subgroup apart from the most commonly diagnosed prototype of nasal UADT-NKTCL.

- Nazal (181) ve ekstranazal (50) ENKL'nin klinik sonuçlarını karşılaştırılmıştır*
- Nazal NK / T hücreli lenfoma ile karşılaştırıldığında, ekstranazal NK / T hücresi lenfoması biraz farklı immünofenotipe sahipti.
- B semptomları nazal grupta (% 37'ye karşılık % 54) daha düşüktü.

Table 1 Immunophenotypic and clinical features of nasal and extranasal UADT-NKTCL

Characteristic	All patients	Nasal UADT-NKTCL	Extranasal UADT-NKTCL	*P*, nasal vs extranasal
Immunophenotype*				
CD3ε+	217 (93.9)	169 (93.4)	48 (96.0)	.490
CD56+	191 (82.7)	159 (87.8)	32 (64.0)	<.001
Gram-B+ (n=220)	205 (93.1)	166 (96.5)	39 (81.3)	.001
TIA-1+ (n=213)	190 (89.2)	144 (86.2)	46 (100)	.008
EBER+ (n=205)	181 (88.3)	137 (86.7)	44 (93.6)	.196
Ki-67 ≥50% (n=198)	116 (58.6)	95 (62.5)	21 (46.7)	.065
Sex, male	158 (68.4)	120 (66.3)	38 (76.0)	.192
Age (y)				
Median	41	41	38	
Range	11-85	11-85	11-81	.727
≤60 y	202 (87.4)	159 (87.8)	43 (86.0)	
Ann Arbor stage				<.001
I	167 (72.3)	145 (80.1)	22 (44.0)	
II	58 (25.1)	32 (17.7)	26 (52.0)	
III-IV	6 (2.6)	4 (2.2)	2 (4.0)	
Cervical nodal involvement	60 (26.0)	33 (18.2)	27 (54.0)	<.001
B symptoms	93 (40.3)	66 (36.5)	27 (54.0)	.025
Elevated LDH level	54 (23.4)	39 (21.5)	15 (30.0)	.211
ECOG score				.026
0-1	221 (95.7)	176 (97.2)	45 (90.0)	
≥2	10 (4.3)	5 (2.8)	5 (10.0)	
IPI				.256
0-1	216 (93.5)	171 (94.5)	45 (90.0)	
2-4	15 (6.5)	10 (5.5)	5 (10.0)	

Abbreviations: EBER = Epstein-Barr virus-encoded RNA; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; UADT-NKTCL = extranodal nasal-type NK/T-cell lymphoma of the upper aerodigestive tract.

Values are number (percentage) unless otherwise noted.

* Complete immunophenotypic analysis was not available for some cases owing to limited biopsy material, background staining, extensive necrosis, failure of some antibodies, or other reasons.

Histology, immunophenotype, and genetic features of the peripheral T cell lymphomas

Entity	Histology	Immunophenotype	Genetic features
Angioimmunoblastic T cell lymphoma	Polymorphous infiltrate of small to large atypical lymphocytes with prominent arborizing high endothelial venules. Expanded populations of follicular dendritic cells can be detected with CD21 staining.	Express CD3 and CD4; sometimes express BCL-6 and CD10. May lose a subset of pan-T cell antigens (ie, CD2, CD3, CD5, CD7).	TCR genes are rearranged in 75 to 90%; immunoglobulin heavy chains are rearranged in 25%. Epstein-Barr virus and human herpes virus-6 genomes may be present in reactive B cells.
Enteropathy-associated T cell lymphoma*	Tumor cells are of variable size and morphology. The adjacent "normal" mucosa often demonstrates signs of celiac disease.	Typically express CD3 and do not express CD4; most cases also CD8 negative. Large cells within the tumor infiltrate are frequently CD30 positive.	TCR beta gene is clonally rearranged. Many patients have an HLA haplotype associated with celiac disease. 50 to 60% have complex segmental amplification of the 9q34 region.
Extranodal NK/T cell lymphoma; nasal type	Polymorphous lymphoid infiltrate of variable morphology that invades the vascular walls, often producing extensive fibrinoid necrosis.	Express CD2, cytoplasmic CD3, CD56, and cytotoxic granule proteins, and are negative for surface CD3.	Clonal Epstein-Barr virus genomes are virtually always present. TCR and immunoglobulin genes are usually germline, consistent with a natural killer cell origin.
Hepatosplenic T cell lymphoma*	Malignant cells accumulate within the sinusoids of the liver, spleen, or bone marrow.	Express CD2, surface CD3, CD7, and CD16, and do not express CD4, CD5, or CD8. Express gamma/delta TCR or alpha/beta TCR.	Cytogenetics demonstrating isochrome 7q supports the diagnosis, but is not essential.
Subcutaneous panniculitis-like T cell lymphoma*	Subcutaneous infiltrate of atypical lymphocytes involving the fat lobules, but typically sparing the septae, overlying dermis, and epidermis.	Express CD3, CD8, and the alpha/beta TCR, but are negative for CD4, CD56, and TCR gamma. Strong expression of the cytotoxic granule proteins. Expression of CD2, CD5, and/or CD7 is variable.	Clonal TCR rearrangements are present.
Anaplastic large cell lymphoma T/null cell type	Composed of large cells with horseshoe-shaped or embryoid nuclei, prominent nucleoli, and abundant cytoplasm. Often shows a cohesive growth pattern.	Homogeneous and strong expression of CD30 in a membrane and golgi pattern. Usually express one or more T cell antigens (ie, CD2, CD3, CD5, CD7).	Two distinct subtypes: ALK positive (detected by immunostains or molecular genetics) and ALK negative.
Peripheral T cell lymphoma; not otherwise specified	Mixture of small and large atypical cells.	Varies greatly from case to case, but always demonstrates expression of one or more of the pan-T antigens (ie, CD2, CD3, CD5, CD7). Roughly half of cases lose a T cell antigen (ie, CD2, CD3, CD5, CD7).	While the majority have cytogenetic abnormalities, none is specific.

TCR: T cell receptor.

Hastanın değerlendirmesi:

- İlk değerlendirmede kesin ***histolojik alt tip, hastalığın derecesi*** ve ***tutulum yerleri*** ile ***performans durumu*** belirlenmelidir.
- Tanı kesinleştikten sonra, tedavi öncesi değerlendirme hem hastalığın evresini hem de bireyin tedavi seçenekleri üzerinde etkili olması muhtemel ko-morbid hastalıkları belirlenir.
- Öykü ve fizik muayeneye ek olarak, ENKL'li hastalarda aşağıdaki ön tedavi çalışmalarını yapılmalıdır.

WORKUP

ESSENTIAL:

- History and physical exam with attention to node-bearing areas (including Waldeyer's ring), testicles, and skin
- ENT evaluation of nasopharynx
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate[h]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET/CT scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of Prognostic Index of Natural Killer Lymphoma (PINK)[i]
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenedione
- EBV viral load[j] by quantitative PCR
- Concurrent referral to RT for pre-treatment evaluation

USEFUL IN SELECTED CASES:

- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)
- Discussion of fertility and sperm banking
- HIV testing

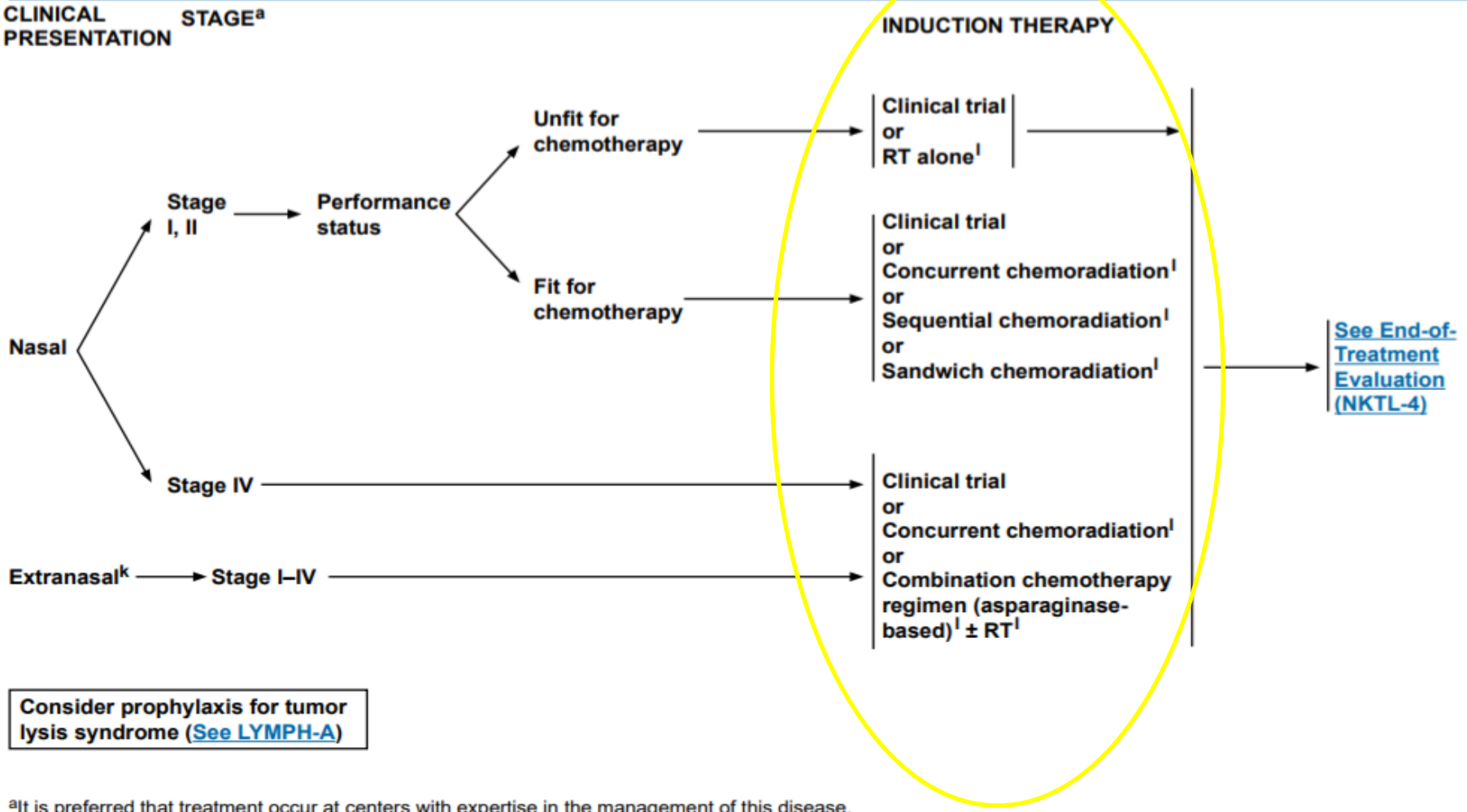
→ See Induction Therapy (NKTL-3)

[h]BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemophagocytosis may be present.
[i]See Prognostic Index of Natural Killer Lymphoma (PINK) (NKTL-A).
[j]EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

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

İndüksiyon tedavisi

- Ekstranodal NK / T hücreli lenfoma, nazal tip (ENKL) hastaların tedavisi hastalığın evresine göre belirlenir.
- Bu yaklaşım, Ulusal Kapsamlı Kanser Ağı (NCCN) ve Avrupa Tıbbi Onkoloji Derneği tarafından açıklananla büyük oranda uyumludur.
- ENKL tanısı konduğunda, sonraki tedavi ve prognoz hastalığın evresine dayanır.



Consider prophylaxis for tumor lysis syndrome (See LYMPH-A)

[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[k]In rare circumstances of stage I_E primary cutaneous NK/T-cell lymphoma, IFRT for solitary skin lesions can be considered.
[l]See Suggested Treatment Regimens (NKTL-B).

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

İndüksiyon tedavisi

- Hastaların yaklaşık % 70-80'i, başlangıçta radyoterapi± kemoterapiye iyi yanıtlı lokalize hastalık ile başvurmaktadır.
- Bu hastalarda 3-5 yıllık bir ortalama genel sağkalım var iken,
- İleri evre hastalar, kemoterapiye yetersiz yanıt ve yaklaşık 4 aylık konvansiyonel kemoterapi ile medyan sağkalımı gösterirler.

Lokalize hastalık

- Lokalize ENKL'li hastalar eşzamanlı/ardışık/kombine modalite tedavisi (CRT) ile tedavi edilir.*
- Lokalize hastalığı olan çoğu hasta için, 50 Gy radyoterapi ve azaltılmış dozda (2/3doz) DeVIC (deksametazon, etoposid, ifosfamid, karboplatin) ile eşzamanlı tedavi ile CMT önerilmekte.**
- Kabul edilebilir alternatif bir CRT rejimi haftalık cisplatin ile 40 Gy RT'dir, bunu VIDL (etoposid, ifosfamid, deksametazon, L-asparaginaz) takip eder.***

*Chim CS, Ma SY, Au WY, et al. Blood 2004; 103:216.
**Li YX, Liu QF, Fang H, et al. Clin Cancer Res 2009; 15:2905.
***Kanavaros P, Lescs MC, Brière J, et al. Blood 1993; 81:2688.

Lokalize hastalık

- Yeni tanı evre I-II hastalığı olan 33 hastada eşzamanlı lokalize RT (50 Gy) ve 3xDeVIC tedavisi verilen faz I / II çalışmasında (2/3 doz DeVIC),*
- Tedavi edilen 27 hastanın 5 yıllık genel sağkalım oranı (OS) ve progresyonsuz sağkalım (PFS) sırasıyla % 70 ve % 63, toplam yanıt oranı (ORR) %81 (toplamda%77) gösterdi.*¸**
- En yaygın nonhematolojik toksisite radyasyona bağlı şiddetli (derece 3/4) mukozit (% 30) idi.**

* Yamaguchi M, Tobinai K, Oguchi M, et al. J Clin Oncol 2009; 27:5594.
** Yamaguchi M, Tobinai K, Oguchi M, et al. J Clin Oncol 2012; 30:4044.

Yaygın hastalık

- Evre III veya evre IV hastalar, Evre II hastalık ve üst aero-sindirim sistemi dışında tutulumlu hastalar da yaygın hastalık olarak tedavi edilmelidir.
- Yaygın hastalık SMILE (deksametazon, metotreksat, ifosfamid, L-asparajinaz, etoposide) ile tedavi edilir.
- Yetmiş yaş üstü veya düşük lenfosit sayısı (<500 / mikroL) veya ağır organ disfonksiyonu olan hastalar (grade 3/4 sitopeni, karaciğer veya böbrek yetmezliği) muhtemelen SMILE'ı tolere edemezler.*
- Bu hastalıklar için, komorbiditeler ve genel uygunluk temelinde, daha az yoğun bir L-asparajinaz içeren kemoterapi, doz azaltılmış DeVIC veya gemsitabin içeren kemoterapi ile tedavi edilir.

*Yamaguchi M, Kwong YL, Kim WS, et al. J Clin Oncol 2011; 29:4410.

Yaygın hastalık

- Relaps/refrakter ve yeni tanı almış ENKL'si olan ve 6xSMILE (ort:üç kür) ile tedavi edilen 87 hastanın retrospektif analizi;
- Hastalık % 44 oranında lokalize (evre I / II) idi .
- ORR yüzde 81 (tam %66) idi ve yeni tanı ile relaps / refrakter hastalık için benzerdi .
- 31 aylık ortalama bir takipte, tahmini 5 yıllık OS ve 4 yıllık hastalıksız sağkalım sırasıyla %50 ve % 64 bulundu.*
- Sepsise bağlı 5 ölümün çoğu şiddetli nötropeni dahil olmak üzere; ciddi trombositopeni; ve nefrotoksisite ile ilişkili idi.*

*Kwong YL, Kim WS, Lim ST, et al. Blood 2012; 120:2973.

Induction treatment with SMILE and consolidation with ASCT for newly diagnosed stage IV extranodal natural killer/T-cell lymphoma patients

- SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) ve ardından OKIT
- Evre IV 27 hasta, medyan 45 (17-65) yaş
- Yanıt:CR: 9 hasta, ORR % 59 (16/27)
- 5 hastada grade IV febril nötropeni ve ölüm !!!!
- 11 hastaya OKİT yapılabildi, OKİT sonrası 4 hastada nüks var
- Medyan PFS 5.1 ay
- Tedavi öncesi Epstein-Barr virus (EBV) DNA titresi tek bağımsız genel sağkalım ile ilişkili olumsuz etken

Kim SJ et al.Ann Hematol. 2015 Jan;94(1):71-8

DDGP versus SMILE in Newly Diagnosed Advanced Natural Killer/T-Cell Lymphoma: A Randomized Controlled, Multicenter, Open-label Study in China

- Evre III-IV, PS: 0-2,
- Randomize, primer sonlanım PFS
- 6xDDGP (dexamethasone,cisplatin,gemcitabine,pegasparaginase) vs 6x SMILE
- 42 hasta randomize edildi
- 1 yıl PFS % 86 vs % 38, P = 0.006
- 2 yıl OS % 74% vs. % 45, P = 0.027
- Yanıt: CR % 71 vs % 29; ORR % 95 vs % 67

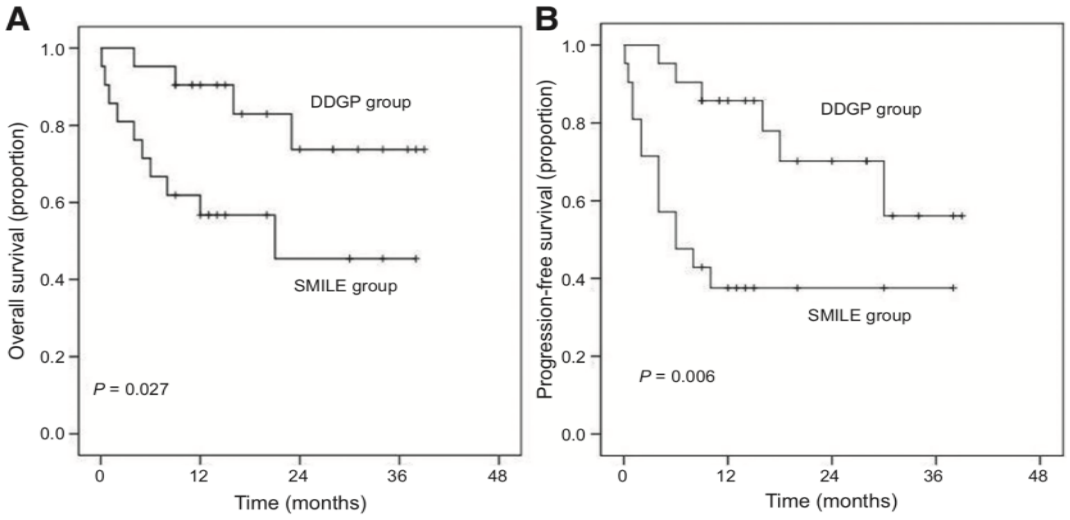


Figure 1.
A, overall survival is shown for all patients, showing that the DDGP group has a better OS than the SMILE group ($P = 0.027$). **B,** progression-free disease is shown for all patients, showing that the DDGP group has a better PFS than the SMILE group ($P = 0.006$).

Li X et al, Clin Cancer Res Nov 2016, 5223-8

Yaygın hastalık

- Yeni tanı evre IV veya relaps / refrakter ENKL'si olan 41 hastaya ort. 6xGDP (gemsitabin, deksametazon, sisplatin) kemoterapisi verilmiş.
- % 83'lük bir ORR (% 42'si tamamlamış) ve 16 aylık bir median takipten sonra bir yıllık PFS oranı % 55 olarak bildirilmiştir.*
- Hastaların% 34'ünde grade 3/4 nötropeni gelişmiştir.

*Wang JJ, Dong M, He XH, et al. Medicine (Baltimore) 2016; 95:e2787.

Merkezi sinir sistemi profilaksisi

- Merkezi sinir sistemi (CNS) profilaksisi kullanımı tartışmalıdır.
- CNS tutulum riski, tanı anında klinik faktörlere ve kemoterapi rejimi ve radyasyon tedavisine bağlı olarak değişebilir.
- RT-DeVIC veya SMILE kemoterapisi ile tedavi edilirken genellikle CNS profilaksisi uygulanmaz.
- Diğer uzmanlar, sistemik intravenöz metotreksat kullanımını desteklemektedir.

Konsolidasyon tedavisi

- ENKL‘ li hastaların kötü sonuçları, konsolidasyon tedavisi olarak hematopoetik hücre transplantasyonuna (HCT) ilgi göstermiştir.
- HCT'nin konsolidasyon tedavisi olarak rolü tartışmalı olsa da, indüksiyon tedavisinden sonra kısmi remisyon (PR) elde eden hastaların otolog ve allojenik HCT'nin risklerini ve yararları tartışmalıdır.
- Ayrıca tam remisyona (CR) ulaşan ileri evre ENKL'li hastalara da HCT önerilir.

Autologous Hematopoietic Stem Cell Transplantation in Extranodal Natural Killer/T Cell Lymphoma: A Multinational, Multicenter, Matched Controlled Study

Jeeyun Lee,[1] Wing-Yan Au,[2] Min Jae Park,[1] Junji Suzumiya,[3] Shigeo Nakamura,[4] Jun-Ichi Kameoka,[5] Chikara Sakai,[6] Kazuo Oshimi,[7] Yok-Lam Kwong,[2] Raymond Liang,[2] Harry Yiu,[8] Kam-Hung Wong,[8] Hoi-Ching Cheng,[8] Baek-Yeol Ryoo,[9] Cheolwon Suh,[10] Young Hyeh Ko,[11] Kihyun Kim,[1] Jae-Won Lee,[12] Won Seog Kim,[1] Ritsuro Suzuki[13]

- HSCT zamanında ve tam remisyonda (CR) bulunan hastalarda, 5 yıllık sağkalım oranları, kontrol grubuna kıyasla, anlamlı olarak daha yüksekti (% 87.3 %67,8, P =0 .027).
- Buna karşılık, CR olmayan hastalara yönelik HSCT veya HSCT olmayan tedavi süreleri alt grup analizinde, HSCT grubunda kontrol grubuna göre 1 yıllık sağkalımı uzatmıştı (% 66.7 karşı %28,6) P = .141).

non-CR patients at the time of HSCT or non-HSCT treatment, disease-specific survival rates were not significantly prolonged in the HSCT group compared with the control group (1-year survival rate, 66.7% for HSCT vs 28.6% for non-HSCT; $P = .141$). The impact of HSCT on the survival of all patients was significantly retained at the multivariate level with a 2.1-fold (95% CI = 1.2- to 3.7-fold) reduced risk of death ($P = .006$). HSCT seems to confer a survival benefit in patients who attained CR on postremission consolidation therapy. These findings suggest that, in particular, patients in CR with high NKIPI risk scores at diagnosis should receive full consideration for HSCT.

Biol Blood Marrow Transplant 14: 1356-1364 (2008) © *2008 American Society for Blood and Marrow Transplantation*

KEY WORDS: NK/T-cell lymphoma, autologous hematopoietic stem cell transplantation, chemotherapy

Lee J, Au WY, Park MJ, et al. Biol Blood Marrow Transplant 2008; 14:1356.

Table 1. Patient and Treatment Characteristics

	All Patients	HSCT	Controls	*P* Value
Total cases, n (%)	154 (100)	47 (30.5)	107 (69.5)	
Median age, years (range)	47 (17 to 80)	42 (17 to 62)	52 (17 to 80)	
Age, years, n (%)				
≤ 60	122 (79.2)	45 (95.7)	77 (72.0)	.001
> 60	32 (20.8)	2 (4.3)	30 (28.0)	
Sex, n (%)				
Male	111 (72.1)	34 (72.3)	77 (72.0)	.962
Female	43 (27.9)	13 (27.7)	30 (28.0)	
Performance status, n (%)				
ECOG 0-1	139 (90.3)	43 (91.5)	96 (89.7)	.733
ECOG 2-4	15 (9.7)	4 (8.5)	11 (10.3)	
Ann Arbor stage, n (%)				
Limited (I-II)	118 (77.1)	31 (66.0)	87 (82.2)	.038
Advanced (III-IV)	36 (23.5)	16 (34.0)	20 (17.8)	
LDH (n = 150), n (%)				
≤ Upper limit of normal	77 (51.3)	23 (51.1)	54 (51.4)	.972
> Upper limit of normal	73 (48.7)	22 (48.9)	51 (48.6)	
IPI risk group (n = 151), (%)				
Low/low-intermediate	127 (84.1)	37 (82.2)	90 (84.9)	.680
High-intermediate/high	24 (15.9)	8 (17.8)	16 (15.1)	
B symptoms, n (%)				
Positive	97 (63.0)	27 (57.4)	70 (65.4)	.345
Negative	57 (37.0)	20 (42.6)	37 (34.6)	
Anatomic category, n (%)				
UNKTL	141 (91.6)	42 (89.4)	99 (92.5)	.516
EUNKTL	13 (8.4)	5 (10.6)	8 (7.5)	
NKIPI risk group (n = 145), n (%)				
Low risk (group 1-2)	80 (55.2)	23 (54.8)	57 (55.3)	.949
High risk (group 3-4)	65 (44.8)	19 (45.2)	46 (44.7)	
Primary treatment, n (%)				
Anthracycline-based chemotherapy ± RT	125 (81.2)	41 (87.2)	84 (78.5)	
Non-anthracycline-based chemotherapy ± RT	15 (9.7)	3 (6.4)	12 (11.9)	.600
RT only	13 (8.4)	3 (6.4)	10 (10.2)	
Surgical excision + RT	1 (0.6)	0 (0.0)	1 (0.8)	
Disease status at treatment, n (%)				
CR1	61 (39.6)	14 (29.8)	47 (43.9)	
CR2	34 (22.1)	13 (27.7)	21 (19.6)	.232
PR/NR/PD	59 (38.3)	20 (42.6)	39 (36.4)	

NKIPI indicates natural killer/T cell lymphoma International Prognostic Index; UNKTL, upper aerodigestive NK/T cell lymphoma; EUNKTL, extra-upper aerodigestive NK/T cell lymphoma; RT, radiotherapy; CR1, first complete response; CR2, second complete response; PR, partial response; NR, no response; PD.

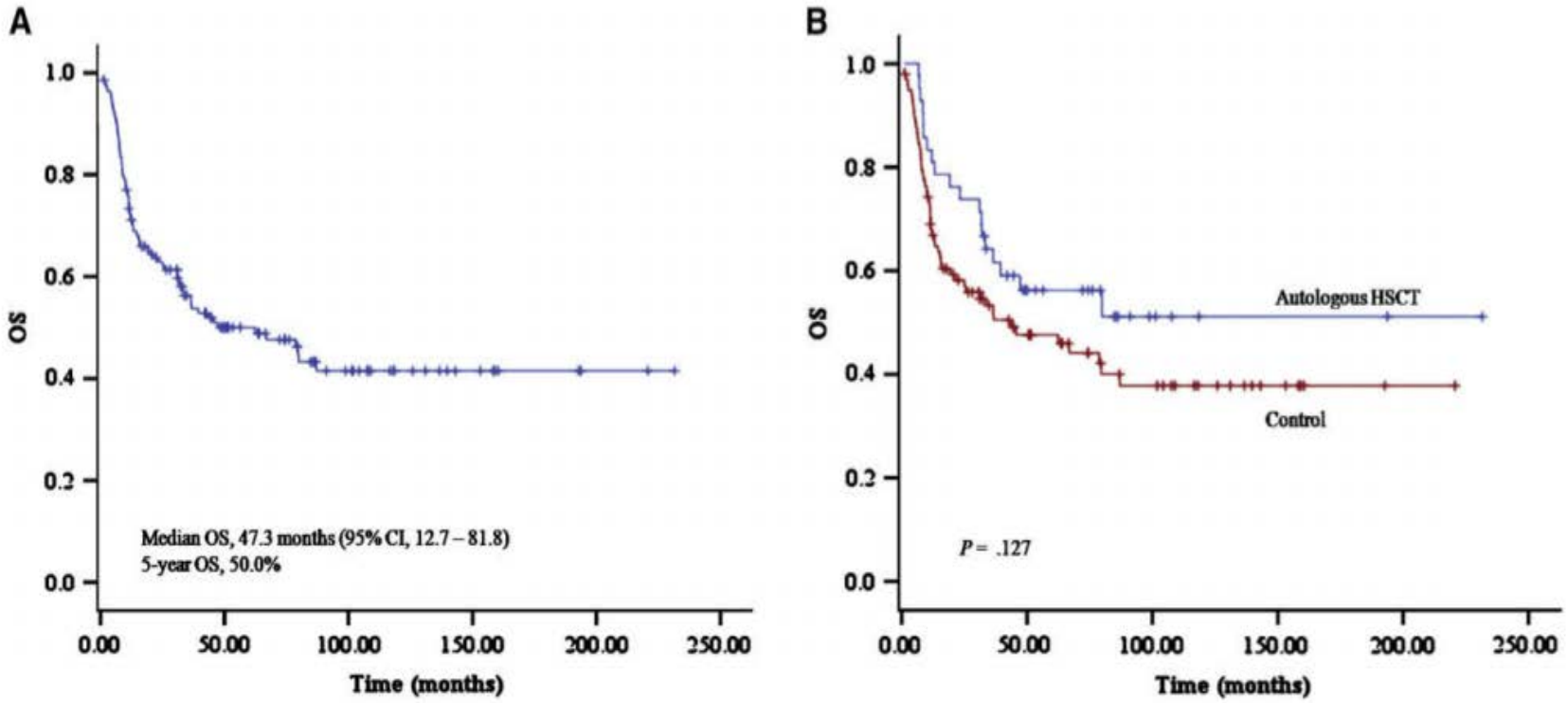


Figure 1. Survival of all patients (A) and survival according to HSCT (B).

Otolog için kullanılan hazırlık rejimleri;

- CBV (etoposid, karmustin ve Cy; n: 4),
- BEAM (karmustin, etoposid, sitarabin ve melfalan (Mel); n: 12),
- MCEC (ranimustin, Cy, etoposid ve karboplatin; n: 8),
- BEAC (karmustin, etoposide, sitarabin),

SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (asparaginase-based)[b,c]
- **AspaMetDex (pegaspargase, methotrexate, and dexamethasone)**
- **Modified-SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage**
- **P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin)**

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

Sequential chemoradiation
- **For Stage I, II, modified-SMILE x 2–4 cycles followed by RT 45–50.4 Gy**

Sandwich chemoradiation[c]
- **P-GEMOX x 2 cycles followed by RT 56 Gy followed by P-GEMOX x 2–4 cycles**

Radiation therapy alone (unfit for chemotherapy)
- **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.**

[a]See references for regimens NKTL-B 2 of 2.
[b]See Asparaginase Toxicity Management in the NCCN Guidelines for Acute Lymphoblastic Leukemia.
[c]Pegaspargase-based regimens are preferred. However, there are no data to recommend one particular regimen over another. Treatment should be individualized based on patient's tolerance and comorbidities. P-GEMOX is an option for selected patients who cannot tolerate intense chemotherapy.

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

EVIDENCE BLOCKS FOR THE TREATMENT OF EXTRANODAL NK/T-CELL LYMPHOMAS

Regimen	Nasal Type			Extranasal	
	Induction Therapy		Relapsed/Refractory Disease	Induction Therapy (Stage I–IV)	Relapsed/Refractory Disease
	Stage I–III	Stage IV			
AspaMetDex	—				
AspaMetDex + RT	—		—		—
Modified–SMILE x 4–6 cycles	—				
Modified–SMILE x 4–6 cycles + RT	—		—		—
P–GEMOX	—				
P–GEMOX + RT	—		—		—
RT and DeVIC x 3 cycles			—		—
RT and cisplatin followed by VIPD x 3 cycles			—		—
Modified-SMILE x 2–4 cycles followed by RT		—	—	—	—
P–GEMOX x 2 cycles followed by RT followed by P-GEMOX x 2–4 cycles		—	—	—	—
Pembrolizumab	—	—		—	

Prognoz

- ENKL agresif lenfoma olup tedavi olmaksızın hayatta kalma aylar içinde ölçülür.
- Prognoz büyük ölçüde tanıdaki hastalığın evresi ile ilişkilidir.
- Evre I ENKL'li hastaların % 60'ından fazlası kemoterapi ile veya kemoterapi olmadan radyasyon tedavisi (RT) ile tedaviyi takiben uzun süreli remisyonda kalırken,
- Evre II ila IV hastalığı olan hastalar diğer ekstranodal bölgelerde sık relaps ile daha kötü prognoza sahiptir.*

*Liu QF, Wang WH, Wang SL, et al. Int J Radiat Oncol Biol Phys 2014; 88:806.

Prognoz

- Uluslararası Prognostik İndeks (IPI) - ENKL olan hastalar için IPI'nin değeri sınırlıdır, çünkü hastaların büyük çoğunluğu favorable alt gruba girmektedir.*
- Kemoterapi ve/veya radyoterapi ile tedavi edilen (antrasiklin-temelli olmayan) 527 hastanın uluslararası bir çalışması, Prognostic index of natural killer lymphoma (PINK-E) modelinin gelişmesine yol açmıştır.**

* Kim TM, Park YH, Lee SY, et al.Blood 2005; 106:3785.
** Kim SJ, Yoon DH, Jaccard A, et al. Lancet Oncol 2016; 17:389.

PTCL: Sağkalım ve IPI

	5-yıl OS		
	%	IPI 0/1	IPI 4/5
PTCL-NOS	32%	50%	11%
AITL	32%	56%	25%
ALCL, ALK+	70%	90%	33%
ALCL, ALK-	49%	74%	13%
ATLL	14%	28%	7%
NKTCL, nasal	42%	57%	0
NKTCL, extranasal	9%	17%	0
Enteropathy-type	20%	29%	14%
Hepatosplenic	7%	0	0
Subcutaneous panniculitis-like	64%	60%	0

J Clin Oncol 2008;26:4124-4130

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA (PINK)[a]

RISK FACTORS	
Age >60 y	
Stage III or IV disease	
Distant lymph-node involvement	
Non-nasal type disease	
	Number of risk factors
Low	0
Intermediate	1
High	≥2

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)[a]

RISK FACTORS	
Age >60 y	
Stage III or IV disease	
Distant lymph-node involvement	
Non-nasal type disease	
Epstein-Barr virus DNA	
	Number of risk factors
Low	0-1
Intermediate	2
High	≥3

3 yıllık OS

%81,
%55
%28 olarak

[a]Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 2018;17:389-400.

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

Prognoz

- Primer RT ile tedavi edilen 69 hastanın (58 EI/11 EII) prospektif gözlemsel bir çalışmasında, tedavi öncesi yüksek plazma EBV DNA seviyeleri (> 500 kopya / mL) olan hastaların üç yıllık progresyonsuz sağkalım (PFS) %52'ye karşı %79) ve OS (% 66'ye karşı %97) daha düşük bulunmuştur.*
- Saptanabilir EBV DNA'sı olan hastalar ile karşılaştırıldığında, tedaviden sonra tespit edilemeyen EBV DNA'sı olan hastalar üç yıl içinde tahmini PFS oranları % 51'e karşılık% 78 *P*=0,028 ve OS %70'e karşı % 92;*P*=0,031 anlamlı derecede daha yüksekti. *

*Wang ZY, Liu QF, Wang H, et al. Blood 2012; 120:2003.

Relaps/refrakter hastalıkta tedavi;

- Lokalize hastalığı olan hastaların yaklaşık %25'i ve yayılmış hastalıkları olan hastaların %80'i remisyona ulaşamayacak veya nüksedeceklerdir.
- Bu hastaların tedavisi ile ilgili çok az veri bulunmaktadır.
- Genel yaklaşım, tam veya kısmi remisyon elde etme umuduyla ikinci basamak kombinasyon kemoterapi rejimini uygulamak olmuştur.
- Bu tedavilere yanıt veren hastalara otolog veya allojenik hematopoietik hücre transplantasyonu (HCT) önerilmelidir.
- Kurtarma tedavisi olarak L-asparaginaz içeren birkaç rejim umut verici sonuçlar verdi.

Relaps/refrakter hastalıkta tedavi;

- Allojeneik HCT ile tedavi edilen yaygın/refrakter ENKL'si olan 12 (5 kord kanı) hastanın 10 myeloablatif (MAC), 2 indirgenmiş yoğunlukta (RIC) retrospektif analizi*:
- Ortanca 13 aylık (1-168) takipte, 7 hasta remisyonda yaşıyor, 5 hasta ölmüş ve 1 hastada tedaviye bağlı ölüm olmuştur.
- Transplantta progres olan tüm hastalar öldü; transplant sırasında tam yanıt (CR) veya kısmi yanıt (PR) olan 8 hastanın 7'si uzun süreli sağ kalanlardı ve hastalar, hastalık nüksü olmadan canlıydı.

*Ennishi D, Maeda Y, Fujii N, et al.Leuk Lymphoma 2011; 52:1255.

Relaps/refrakter hastalıkta tedavi;

- Allogeneik HCT uygulanan <60 yaş, 18 hastalık (14 MAC/4 RIC) bir analizde (9 CR1,7 CR2,1 PR, 1 ilerleyici hastalık),*
- Ortanca 20.5 aylık takipte 5 yıllık OS% 57, 5 yıllık PFS% 51 idi.
- SMILE rejiminin pre-HSCT kullanımı, en önemli pozitif prognostik göstergedir ve bu da belirgin bir şekilde daha iyi OS ve EFS ile sonuçlanmıştır (P<0.01).
- Akut GVHD'nin OS'de belirgin bir negatif etkisi vardı (P=0.03)
- CR1 ve CR2 hastalarının benzer sağkalımları vardı, ancak remisyona alınmayan tüm hastalar öldü.

*Tse E, Chan TS, Koh LP, et al.Bone Marrow Transplant 2014; 49:902

Relaps/refrakter hastalıkta tedavi;

- **PD-1 blokajı:** Pembrolizumab ile tedavi, 5 L-asparaginaz içeren rejimler ve 2 allojenik HCT uygulanan sonrasında nüks eden ENKL'li 7 hastanın tamamında remisyonlar (klinik, radyolojik [PET / CT], morfolojik ve / veya moleküler remisyon) sağladı.*
- İki hasta PR ve 5 hastada CR elde edildi;
- Yedi kür (2-13) pembrolizumab sonrası 6 (aralık, 2-10) aylık bir medyan takibinin ardından, 5 CR hastasının tümü hala remisyonda idi.
- Pembrolizumab ile PD1 blokajı, L-asparaginaz rejimleri başarısız NK / T hücreli lenfomalar için güçlü bir stratejidir.

*Kwong YL, Chan TSY, Tan D, et al.Blood 2017; 129:2437.

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Extranodal NK/T-Cell Lymphoma, nasal type

NCCN Guidelines Index
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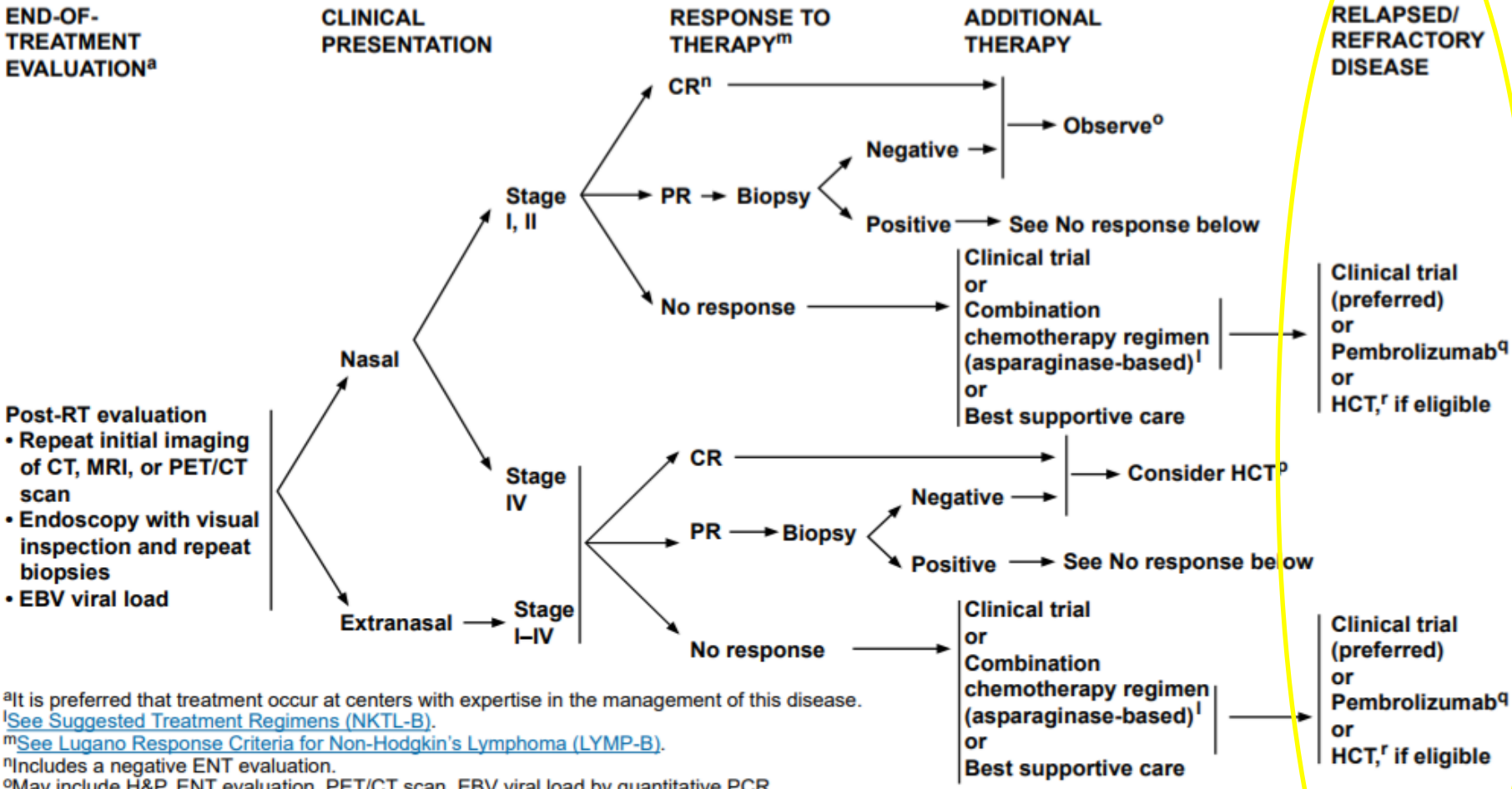
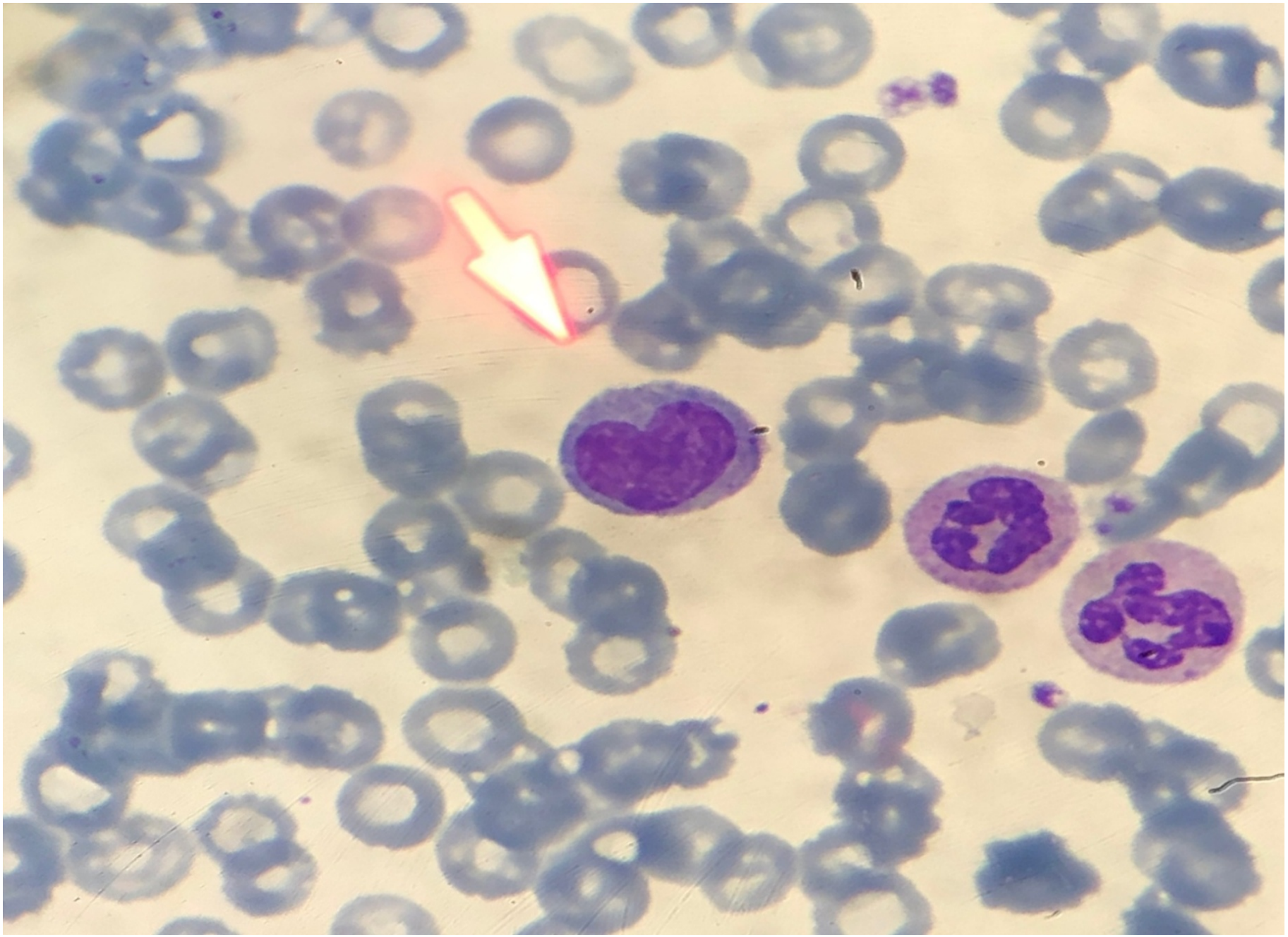


[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[l]See Suggested Treatment Regimens (NKTL-B).
[m]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).
[n]Includes a negative ENT evaluation.
[o]May include H&P, ENT evaluation, PET/CT scan, EBV viral load by quantitative PCR.
[p]There are no clear data to suggest whether allogeneic or autologous HSCT is preferred and treatment should be individualized.
[q]Clinical trial is the preferred relapsed/refractory option. In the absence of a clinical trial, pembrolizumab is an appropriate option.
[r]Allogeneic preferred, if donor available.

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



Özet/öneriler;

- ENKL tedavisi hastalığın derecesine göre belirlenir.
- Lokalize hastalıkta, tek başına 50 Gy dozda RT ve/veya azaltılmış dozda (2/3doz); DeVIC (deksametazon, etoposid, ifosfamid, karboplatin) ile eşzamanlı kombine tedavi önerilir.
- L-asparaginase içeren; SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide) veya AspaMetDex (L-asparaginase, methotrexate, dexamethasone)
- Antrasiklin içerikli tedavilerin etkinliği yok

Özet/öneriler;

- Yaygın ENKL hastalar veya üst aero-digestif dışı evre II dışı hastalar için, CHOP kemoterapisinden ziyade L-asparaginaz içeren bir kombine KT önerilir.
- Bu hastaların çoğu SMILE (deksametazon,metortreksat, ifosfamid, L-asparajinaz,etoposid) kemoterapisi ile tedavi edilir.
- Yaygın ENKL'si olan ve SMILE'yi tolere edemeyen yaşlı hastalar için daha az yoğun L-asparajinaz içeren kemoterapi, doz azaltılmış DeVIC veya gemsitabin içeren kemoterapi ile tedavi edilmeli.

Özet/öneriler;

- Lokalize hastalığı olan hastaların yaklaşık % 25'i ve tanı anında dissemine hastalıklı hastaların % 80'i remisyona ulaşamayacak veya nüksedeceklerdir.
- Tam veya kısmi remisyon için ikinci basamak kombinasyon kemoterapi rejimini uygulanmalıdır.
- İkinci basamak kemoterapi ile tam veya kısmi remisyona giren hastalar için, HCT ile konsolidasyon öneririz.
- Otolog ve allojenik HCT arasındaki bir seçim hastanın performans durumuna ve organ fonksiyonuna ve bir donörün varlığına bağlıdır.

Özet/öneriler;

- Genel olarak SMILE kemoterapi ile tedavi edilirken CNS profilaksisini uygulamıyoruz.
- İndüksiyon tedavisinden sonra kısmi yanıt veren hastalara hematopoietik hücre transplantasyonu (HCT) ile konsolidasyon önerilir.
- Konsolidasyon tedavisi olarak otolog ve allojenik HCT arasındaki bir seçim hastanın performans durumu ve organ fonksiyonuna ve bir donörün kullanılabilirliğine bağlıdır.
- Ayrıca, tam cevaba (CR) yol açan ileri veya relaps / refrakter ENKL'li hastalara da HCT sunuyoruz .
- Tam remisyon elde eden lokalize ENKL olan hastalarda rutin HCT önerilmiyor.

SMILE chemotherapy

- 2 g/m2 intravenous (IV) methotrexate on day 1,
- 500 mg/m2 ifosfamide and 100 mg/m2 etoposide followed by 40 mg IV dexamethasone on days 2–4 and
- 6,000 U/m2 IV Escherichia coli Lasparaginase on days 8, 10, 12, 14, 16, 18 and 20 days