PRİMER MEDİASTİNAL (TİMİK) BÜYÜK B HÜCRELİ LENFOMA

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Ondokuz Mayıs Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı
10 EYLÜL 2015

- Timus medullasında bulunan medüller B lenfositlerinden kaynaklanır.
- 1994 de REAL sınıflamasında DLBCL bir alt tipi olarak kabul edildi.

Mature B-cell Neoplasms

Chronic lymphocytic leukaemia /small lymphocytic lymphoma

B-cell prolymphocytic leukaemia

Splenic marginal zone lymphoma

Hairy cell leukaemia

Splenic lymphoma/leukaemia, unclassifiable

Lymphoplasmacytic lymphoma

Heavy chain diseases

Plasma cell neoplasms

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Nodal marginal zone lymphoma

Follicular lymphoma

Primary cutaneous follicle centre lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), NOS

T-cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the CNS

Primary cutaneous DLBCL, leg type

EBV positive DLBCL of the elderly

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

ALK positive large B-cell lymphoma

Plasmablastic lymphoma

Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease

Primary effusion lymphoma

Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

- Tüm Lenfomaların % 2-4
- DLBCL % 6-12
- 3. ve 4. dekatta daha sık
- Kadınlarda erkeklerden daha fazla 2:1

KLİNİK

- **Anterior Mediastinal kitle**

Supraklavikuler ve servikal lenf nodları tutulabilir
Uzak lenf nodları ve kemik iliği tutulumu nadirdir.

Vena kava süperior sendromu (%57)
Plevral efüzyon (%50)
Perikardiyal Efüzyon (%50)

Relaps ekstranodal olma eğilimindedir.
Karaciğer, GİS , Böbrekler, Overler, SSS.

153 PMBCL retrospektif İnceleme tanı anındaki semptom ve bulgular *

- LDH Yüksekliği (%77)
- B semptomları (%47)
- Pelevral ve Perikardiyal Efüzyon (%50)
- Evre I-II hastalık (%75)
- Bulky Hastalık (%74)

*Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience
K. J. Savage *, N. Al-Rajhi, N. Voss, C. Paltiel, R. Klasa, R. D. Gascoyne and J. M. Connors 2006

Morfoloji

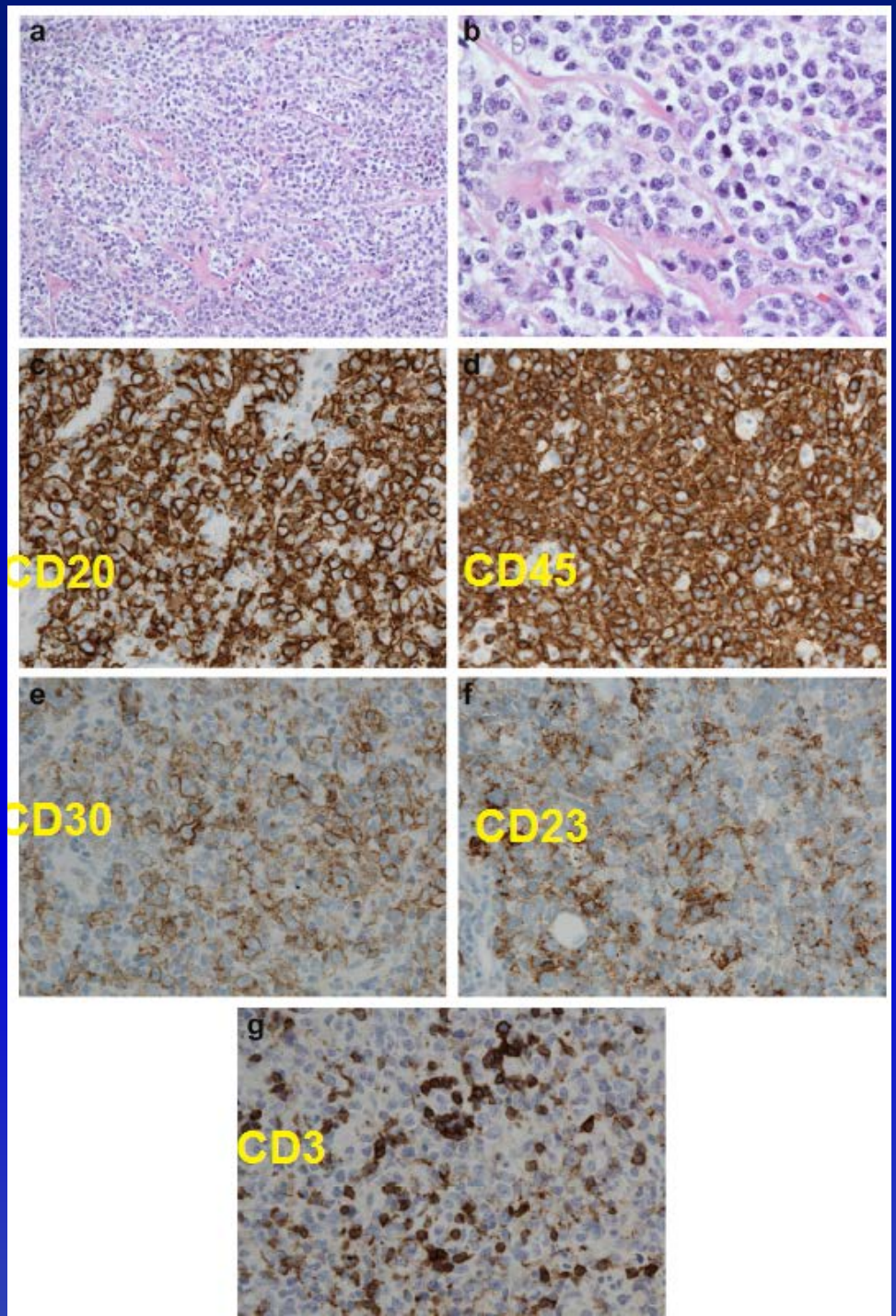
- Morfolojik spektrum olgudan olguya değişebilir.
- Tümör hücrelerini saran fibrozis vardır.
- Geniş şeffaf veya soluk stoplazma.
- Arada bazı hücreler pleomorfik olabilir multinükleer reed stenberg hücrelerine benzeyebilir.

İmmünfenotip

- CD5, CD10 ve negatif
- CD19, CD 20, CD22, CD79a ve CD45 pozitif.
- CD30 zayıf pozitif.
- TRAF-1 ve nükleer c Rel pozitif.

MİKROSKOPİ

Hazırlanan kesitlerin tamamı tümör dokusundan ibaret olup, ince fibröz bantlarla ayrılmış diffüz infiltrasyon oluşturan iri hiperkromatik çekirdekli, bir kısmı veziküle çekirdekli, bir kısmı sentroblast morfolojisinde, bir kısmı da çentikli, dar eozinofilik sitoplazmalı hücrelerden oluşmaktadır.
Tümör hücreleri, CD 20, CD 79a, Pax-5 pozitif, bcl-2 negatiftir. CD 30 pozitif, ALK, Siklin D1 negatiftir.
CD 10 negatif, bcl-6 pozitif, MUM-1 pozitif boyanmış olup, nongerminal merkez orjinlidir.
Ki 67 proliferasyon indeksi % 90 civarındadır.
CD 3 ve CD 5 reaktif T hücrelerinde pozitif boyanmıştır.
Morfolojik ve immunohistokimyasal bulgular klinik ve radyolojik olarak toraks dışında başka bir yerde kitle yoksa Primer Mediastinal large B cell Lenfoma ile uyumludur.



V.R. Bhatt et al. / Cancer Treatment Reviews 41 (2015) 476–485

Genetik

- Tipik bir sitogenetik değişiklik yoktur.
- CIITA (major histocompatibility complex (MHC) class II transactivator CIITA (MHC2TA) genini içeren translokasyon (vakaların %40 ‘ında bulunmuştur.
- REL ve BCL11A (2p’de) amplifikasyon
- +9p24
- +2p15

Genetic alterations	Involved genes
2p14-p16gain	REL
9p24gain	JAK2, JMJD2C, RANBP6, PDL2, PDL1, SMARCA2
12q24 gain	ELK3, EPS8, IFNG[a]
12q11–q13	IGF1[a]
16p13 rearrangement	CIITA, SOCS1

Tanı Evreleme

- Örnekler Mediastinoskopi, perkutan biyopsi, anterior mediastinostomi ile alınabilir.
- Total eksizyon uygun değil.
- PET-CT veya BT
- Kemik İliği Biyopsi
  *Kemik iliği tutulumu veya uzak lenf nodu tutulumu olanlar genellikle başka lenfomanın mediastinal tutulumu
- Ann Arbor

Ayırıcı Tanı

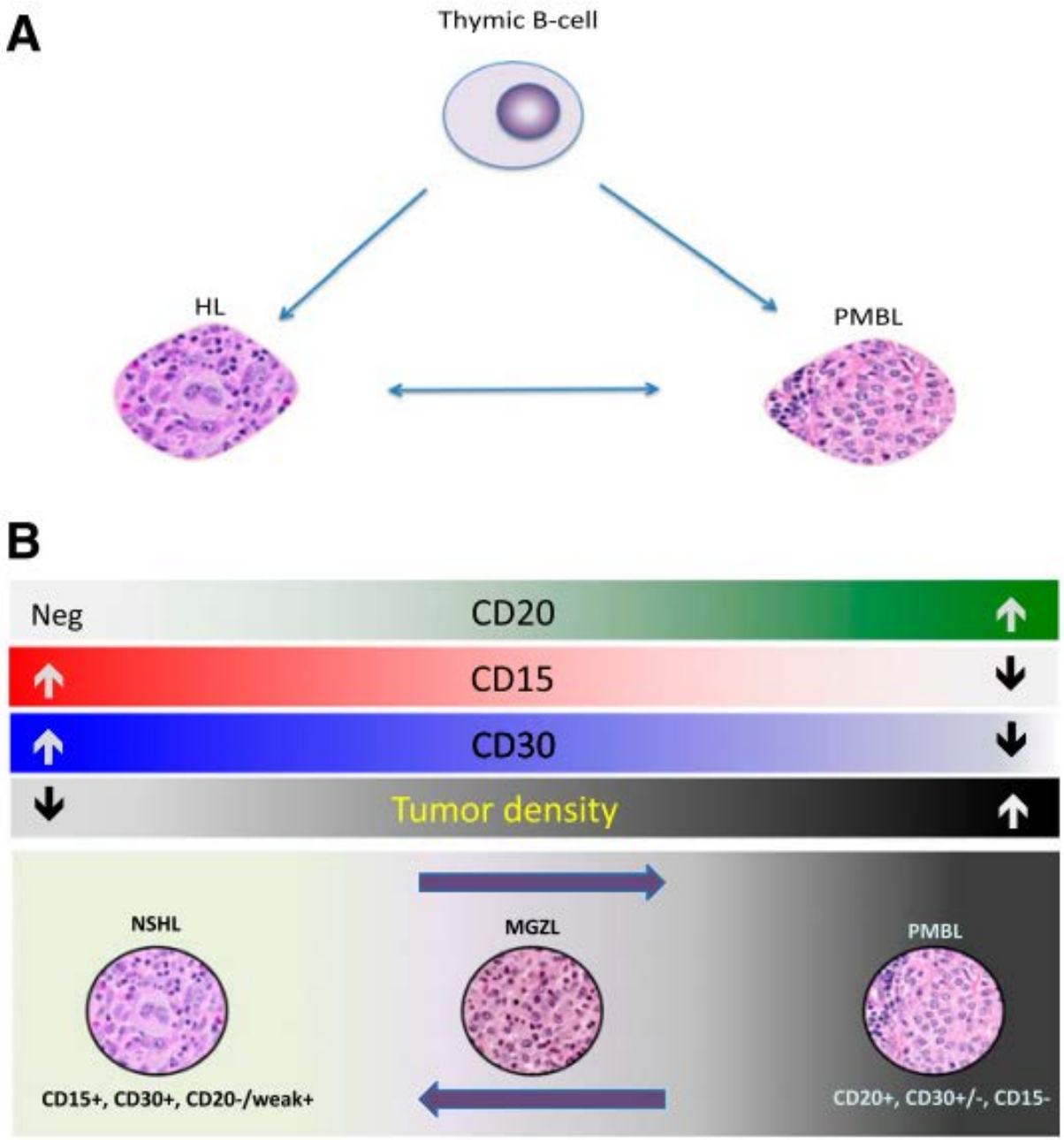
- Hodgkin Lenfoma
- Lenfoblastik lenfoma
- Anaplastik Büyük Hücreli Lenfoma
- B hücreli lenfoma sınıflandırılamayan, DBBHL ve KHL arası özellikler içeren
- Timoma
- Germ Hücreli Tümör
- Metastatik Tümör

Ayırıcı TANI

- Genç kadın , Mediastinal kitle
- PMBL hücreleri HL daki Reed Stenberg Hücreleri ile karışabilir.
- Skleroz
- İmmünfenotipleme ayırıcı tanıda yardımcı olabilir.

CD15, CD30 , PanB ve PanT antijeleri zayıf → HL

Pan B hüre antijenleri pozitif CD30 ve CD 15 zayıf pozitif → PMBBHL

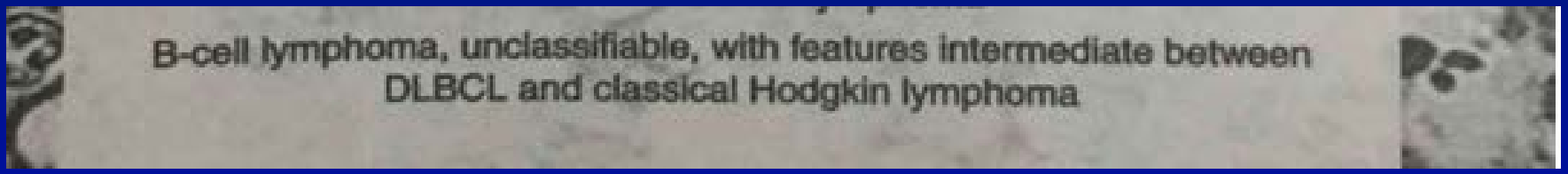

A
Thymic B-cell
HL
PMBL
B
Neg
CD20
CD15
CD30
Tumor density
NSHL
CD15+, CD30+, CD20-/weak+
MGZL
PMBL
CD20+, CD30+/-, CD15-

Ayırıcı TANI

- **Kompozit Lenfoma**: KHL + PMBBHL

- **Ardışık Lenfoma:** KHL sonrası gelişen tipik PMBBHL veya tersi

- **Gri Zon Lenfoma:** KHL ve PMBBHL arası örtüşen vakalar
  (morfolojik olarak NSHL 'ya benzeyen ancak CD30 yanısıra CD20 ve CD79a güçlü (+), CD15(-)'liği
- Morfolojik olarak PMBBL'ya benzeyen ancak CD20(-) , CD30 (+) CD15(+)



Klinik , morfolojik, immünfenotipik olarak DBBHL (özellikle Primer Mediastinal BHL) ve Klasik HL özelliklerinin üst üste bindiği B hücreli Lenfoma

Bu lenfoma daha çok mediastinal hastalıkla beraber olsada periferik lenf nodalarında da görülebilir.

CD20 (+), CD30(+), CD15(+/-), LCA (+/-)

Bu lenfomalar hem KHL dan hemden PMBHL dan daha agresiftir.

TEDAVİ

- Kurtarma Tedavileri etkili değil.
- İlk tedavi oldukça önemli.
- RÖ – RS

- Hangi rejim?
- Radyoterapi?
- YDK/AKHN?
- Relaps/Refrakter Hastalarda Tedavi?

Induction chemotherapy stategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients

haematologica 2002; 87:1258-1264
http://www.haematologica.org/2002_12/1258.htm

1. jenerasyon	3. jenerasyon
CHOP	MACOP-B
	VACOP-B
	Pro-MACECytaBOM
	DA-EPOCH

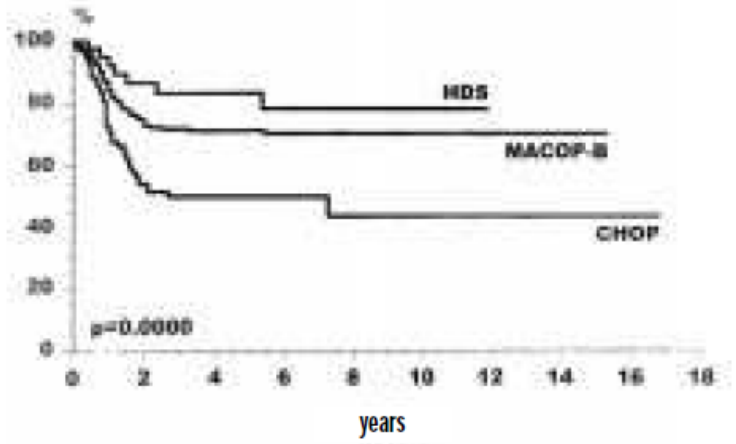


Figure 3. OS curves of the three main chemotherapy sub-groups.

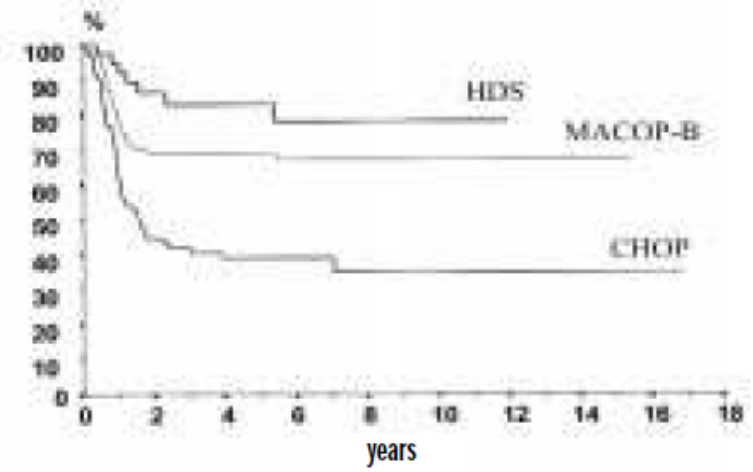


Figure 4. PFS curves of the three main chemotherapy sub-groups.

Number of patients	High IPI (%)	CHTH	RTH	OS	PFS
426 (105/277/44)	21	CHOP(-like)//3rd-generation//HDT/SCT	Yes in 84 % pts	10-y 65 % (44/71/ 77 %)	10-y 62 % (35/67/78 %)
138 (43/95)	22	CHOP//MACOP-B(VACOP-B)	Yes in 75.5 % pts in CR	N/D	5-y EFS 39.5 %/75.7 %
141(56/68/17)	28	CHOP(-like)//NHL-15//HDT/SCT	Yes (only in 23 %)	10.9-y 66 % (51/84/78 %)	10.9-y 50 % (34/60/60 %)
153 (63/47/18*)	N/D (only aaiPI)	CHOP(-like)//MACOP-B(VACOP-B)//R-CHOP	Depending on recommendations	5-y 75 % (71/87/81 %)	5-y 69 % (N/D)
68(42/26)	26 %	CHOP/3rd generation	Yes in 87 %	5-y 61 % (50/91 %)	5-y 52 % (33/83 %)
54	N/D	R-CHOP/ICE	No	3-y 88 %	3-y 78 %
15	N/D	GMALL B-ALL/NHL	Yes in 67 %	5-y 100 %	5-y 93.3 %

Rituximab ÖNCESİ

- RÖ dönem de standart tedavi:
  VACOP-B or MACOP-B + consolidative mediastinal involved field radiation therapy (IFRT)

RİTUXİMAB SONRASI

[Ref]	Year (data collection)	Type of study	Number of patients	High IPI (%)	Chemotherapy	RTH	OS	PFS (EFS, TTP)
[45••]	2011 (N/D)	Prospective randomized	87 (43/44)	0	CHOP/R-CHOP (-like)	Yes in 67/71 %	3-y 83 % (78/89 %)	3-y EFS 65 % (52/87 %)
[41•]	2012 (N/D)	Multicenter	111 (76/45)	22/29	CHOP/R-CHOP	Yes in 52/76 % CR pts	5-y (69/89 %)	5-y EFS (47/80 %)
[58•]	2012 (N/D)	Population study	176 (80/96)	N/D	CHOP/R-CHOP	Yes variable (PET-guided****)	5-y (70/88 %)	5-y TTP (65/78 %)
[7••]	2013 (1986-2012)	Multicenter	345(44/187/45/57)	48	CHOP//R-CHOP//R-DA-EPOCH//2/3rd generation regimens//HDT+SCT	Yes in 42 % pts	4-y 87 % (67/90/100/91/92 %)	4-y PFS 70 % (40/71/100/83/76 %)
[46•]	2013 (1996-2011)	Single center	63	33	R-CHOP	Yes in 77 % pts	5-y 79 %	5-y PFS 68 %
[64]	2013	Single center	79	52 (aaIPI>1)	CHOP/R-CHOP	Yes in 76 % pts	5-y 62 % (48/84 %)	5-y PFS 59 % (44/77 %)

original article

Annals of Oncology 22: 664–670, 2011
doi:10.1093/annonc/mdq418
Published online 19 August 2010

Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study

M. Rieger[1]*, A. Österborg[2], R. Pettengell[3], D. White[4], D. Gill[5], J. Walewski[6], E. Kuhnt[7], M. Loeffler[8], M. Pfreundschuh[9] & A. D. Ho[1], for the MabThera International Trial (MInT) Group

[1]Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; [2]Departments of Oncology, Haematology, Karolinska University Hospital, Stockholm, Sweden; [3]St George's University of London, UK; [4]Dalhousie University, Halifax, Nova Scotia for the NCIC Clinical Trials Group, Kingston, Ontario, Canada; [5]Department of Haematology, Princess Alexandra Hospital, Queensland, Australia; [6]Department of Lymphoma, Maria Sklodowska-Curie Institute and Oncology Centre, Warszawa, Poland; [7]Clinical Trial Centre Leipzig, University of Leipzig, Leipzig; [8]Institute of Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig; [9]Saarland University Medical School, Homburg, Germany

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www.jcma-online.com

Original Article

Rituximab induction therapy, survival benefits, and the increasing selection of radiotherapy as the postinduction treatment in patients with primary mediastinal large B-cell lymphoma

Sheng-Hsiang Yang [a,b,c], Liang-Tsai Hsiao [a,b,*], Tzeon-Jye Chiou [b,d], Ching-Fen Yang [b,e], Yuan-Bin Yu [a,b], Chun-Yu Liu [a,b], Jyh-Pyng Gau [a,b], Jin-Hwang Liu [a,b], Po-Min Chen [a,b], Cheng-Hwai Tzeng [a,b]

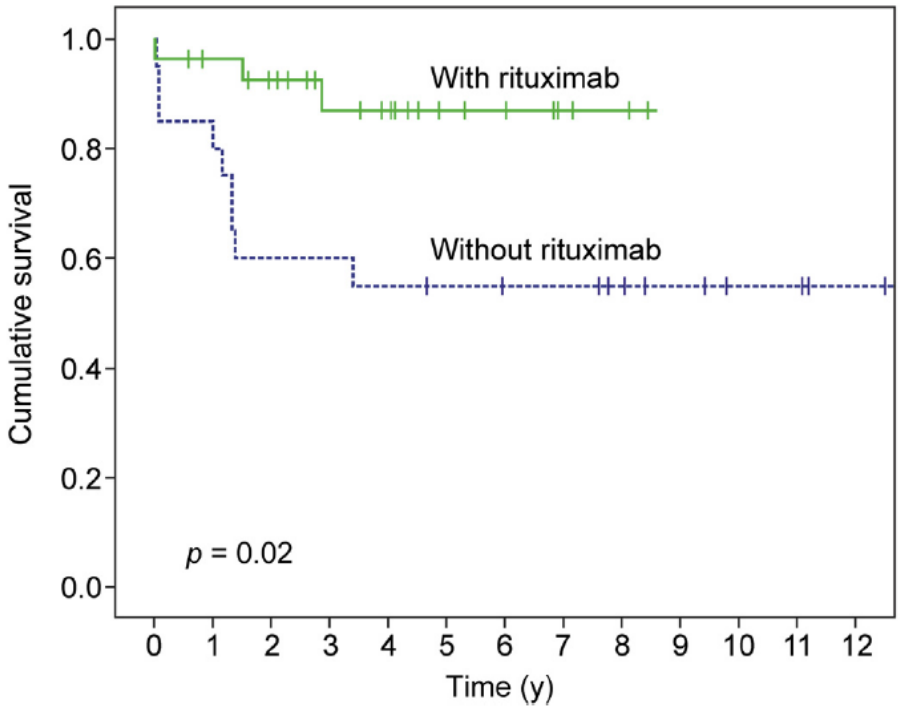


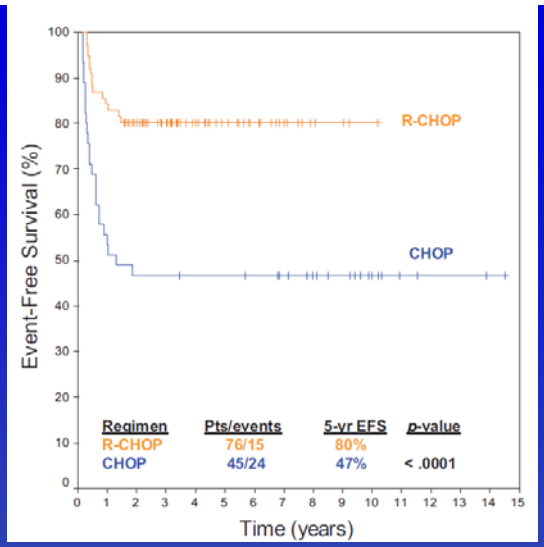
Fig. 1. The overall survival of patients with primary mediastinal large B-cell lymphoma, according to the use of rituximab induction.

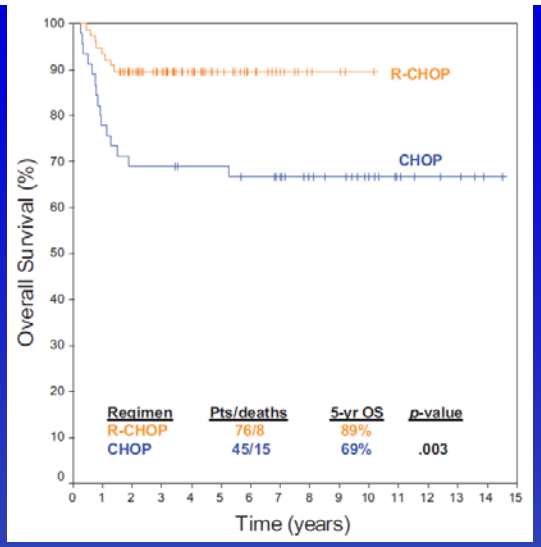
The Oncologist®

Lymphoma

Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone with or Without Radiotherapy in Primary Mediastinal Large B-Cell Lymphoma: The Emerging Standard of Care

	R-CHOP with or without RT		CHOP with or without RT	
	n	%	*n*	%
All patients (*n*)	76	100	45[a]	100
Early deaths	1/76	1	1/45[a]	2
Early treatment failures	7/75	9	13/44[a]	30
Completed (immuno)chemo and responded	68		29[a]	
Received RT	52/68	76	14/29	48
Median RT dose (range), Gy	36 (20–46)		38 (23–50)	





Original Contribution

Rituximab Combined With MACOP-B or VACOP-B and Radiation Therapy in Primary Mediastinal Large B-Cell Lymphoma: A Retrospective Study

Pier Luigi Zinzani,[1] Vittorio Stefoni,[1] Erica Finolezzi,[2] Ercole Brusamolino,[3]

Treatment	Number of Patients	CR (%)	PR (%)	NR (%)	CR + PR (%)
After 6 Cycles of MACOP-B/VACOP-B Plus Rituximab	45	20 (44)	24 (54)	1 (2)	44 (98)
After MACOP-B/VACOP-B Plus Rituximab (12 Cycles)	42	26 (62)	15 (36)	1 (2)	41 (98)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D.,

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Prospective NCI Cohort (N=51)	Retrospective Stanford Cohort (N=16)	P Value between Study Cohorts
Female sex — no. (%)	30 (59)	9 (56)	1.00
Age — yr			0.04
Median	30	33	
Range	19–52	23–68	
Bulky tumor, ≥10 cm			0.57
Patients — no. (%)	33 (65)	9 (56)	
Maximal diameter range — cm	5–18	7–18	
Stage IV disease — no. (%)	15 (29)	7 (44)	0.36
Elevated lactate dehydrogenase level — no. (%)	40 (78)	11 (69)	0.51
Extranodal site — no. (%)	27 (53)	3 (19)	0.02
Pleural effusion — no. (%)	24 (47)	10 (62)	0.39
CD20+ malignant cells — no. (%)	51 (100)	16 (100)	1.00
BCL6+ malignant cells — no. (%)	33/37 (89)	ND	ND

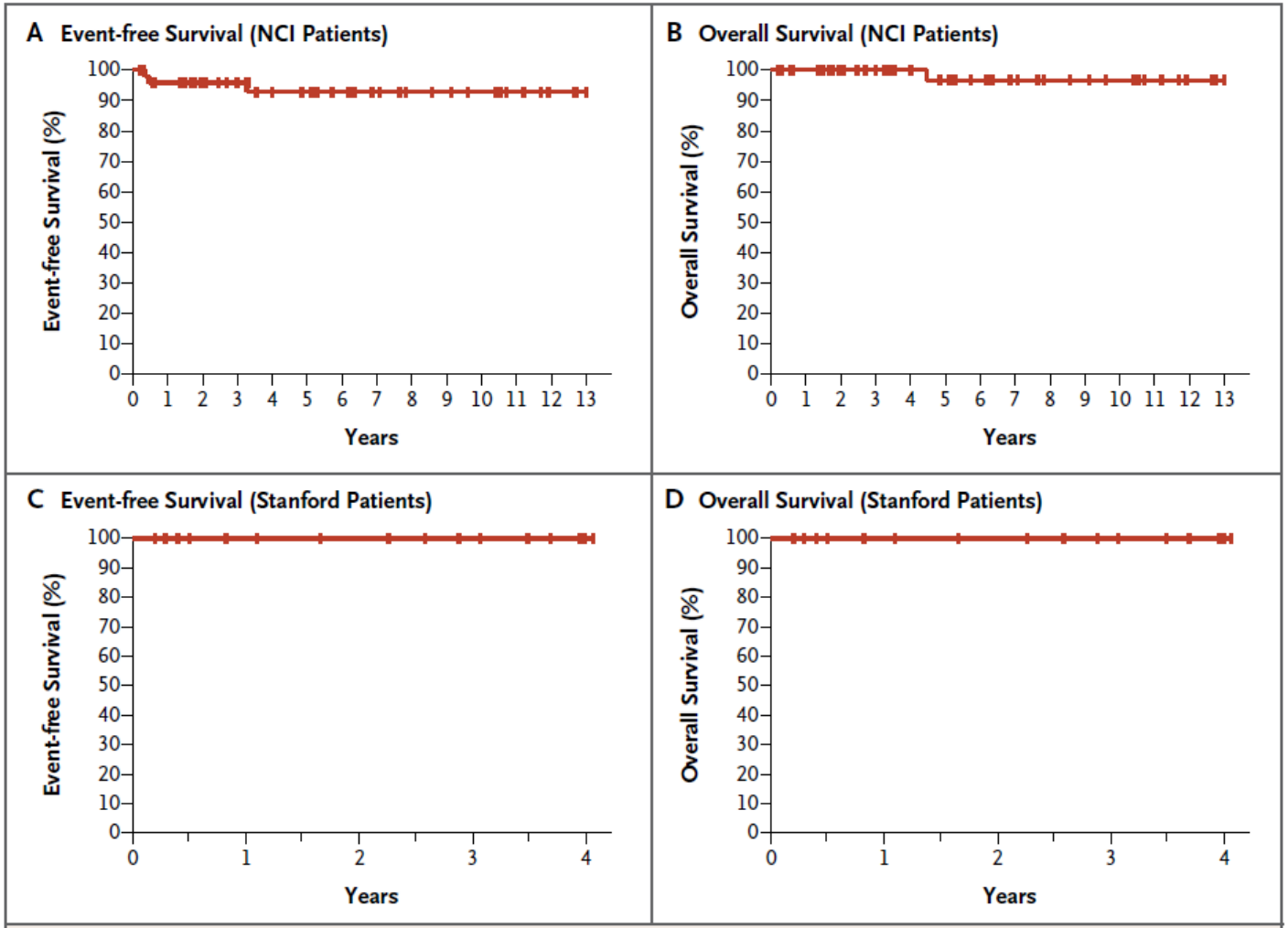


Figure 1. Kaplan–Meier Estimates of Event-free and Overall Survival of Patients with Primary Mediastinal B-Cell Lymphoma Receiving DA-EPOCH-R, According to Study Group.

DA-EPOCH-R was administered to 51 patients in a prospective trial at the National Cancer Institute (NCI), and to 16 patients in a retrospective trial at Stanford University. In the prospective NCI cohort, the event-free survival rate was 93% (Panel A) and the overall survival rate was 97% (Panel B) at a median follow-up of 63 months. In the retrospective Stanford cohort, the event-free and overall survival rates were both 100% (Panel C and Panel D, respectively) at a median follow-up of 37 months.

Table 4. Rituximab-based immunochemotherapy in the treatment of primary mediastinal large B-cell lymphoma

Regimen. study	*n* of patients	RT[b]	3-yr FFP/EFS[a]	3 yr OS[a]
R-CHOP-21				
R-CHOP, Novoselac et al. (2007) [37] (initial abstract, 2004)	10	++	100%	100%
R-CHOP, Vassilakopoulos et al. (2005) [38] (abstract, initial report)	15	+++	100%	93%
R-CHOP, Savage et al. (2006) [7]	18	++	NG	82%
R-CHOP, Ahn et al. (2010) [39]	21	++	79%	83%
R-CHO(E)P, Trneny et al. (2008) [40] and Rieger et al. (2011) [41], aaIPI ≤1; R-CHO(E)P, 43%; R-MACOP-B, 7%	44	++	78%	89%
R-CHOP, Vassilakopoulos et al. (2010) (present study)	76	++	81%	89%
More aggressive regimens				
da-EPOCH-R, Dunleavy et al. (2005) [48] and Dunleavy et al. (2008) [49] (abstract)	40	−/+	93%	100%
R-C_{1000}HOP-14 × 4 plus ICE × 3, Moskowitz et al. (2010) [46] (abstract)	54	no	78%[c]	88%[c]
R-CHOP-14, Schneider et al. (2010) [47] (abstract)	23	+++	91%	96%
R-VACOP-B, Avigdor et al. (2007) [44] (abstract)	21	no	84%	~96%
R-MACOP-B, Zinzani et al. (2009) [43]	45	++	84%	80%

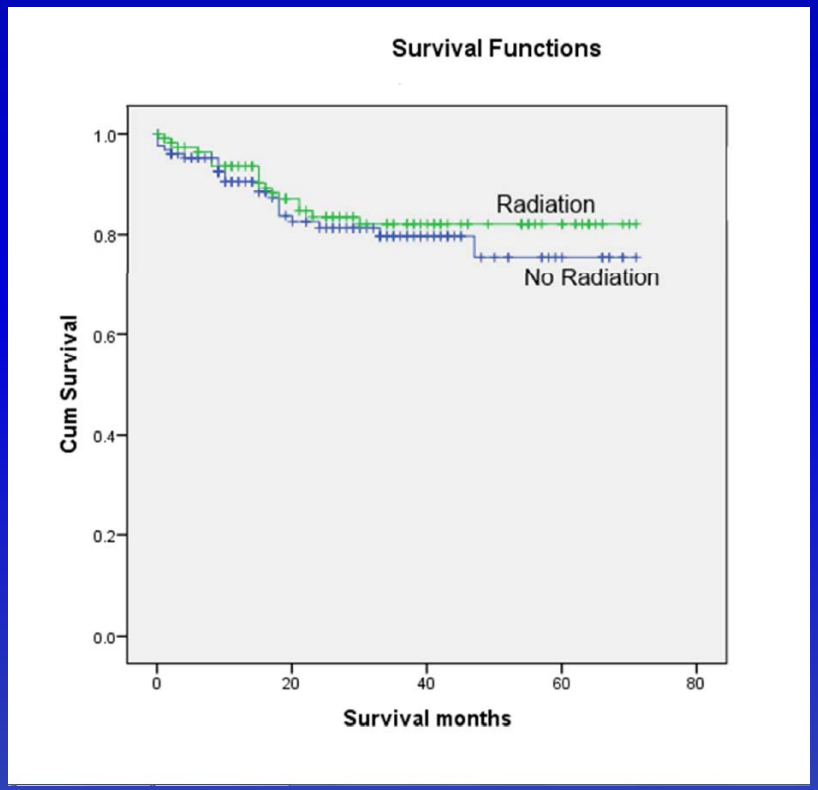
RADYOTERAPİ

- RÖ dönemde 1. jenerasyon ve 3. jenerasyon ilaçlardan sonra konsolidasyon amaçlı kullanılmış ve sağkalımı olumlu etkilemiştir.
- RS radyoterapinin potansiyel uzun dönem toksisitelerinden dolayı tartışmalı hala gelmiştir.

Role of radiation therapy in primary mediastinal large B-cell lymphoma in rituximab era:

Smith Giri, MBBS,* Vijaya Raj Bhatt, MBBS,* Ranjan Pathak, MBBS, R. Gregory Bociek, MD, MS, Julie M. Vose, MD, MBA, James O. Armitage, MD

- The five year OS was similar between patients treated with versus without RT (82.5% vs. 78.6%,p=0.47).



YDK/AKHM nin YERİ

- Büyük çalışma yok.
- OS avantajı sağlamadan PFS iyileşme sağlıyor.
- 5 yıllık PFS oranları 1. remisyonda AKHN yapılması ile artıyor.
- ASCT nin başarısı Kemosensitif olanlarda 3 kat yüksek.

YANIT DEĞERLENDİRME

- Tedavi bitiminden 1 ay sonra mutlaka klinik ve laboratuvar
- KT sonra 6-8 hafta sonra PET-CT
- RT bitiminden 3 ay sonra PET-CT

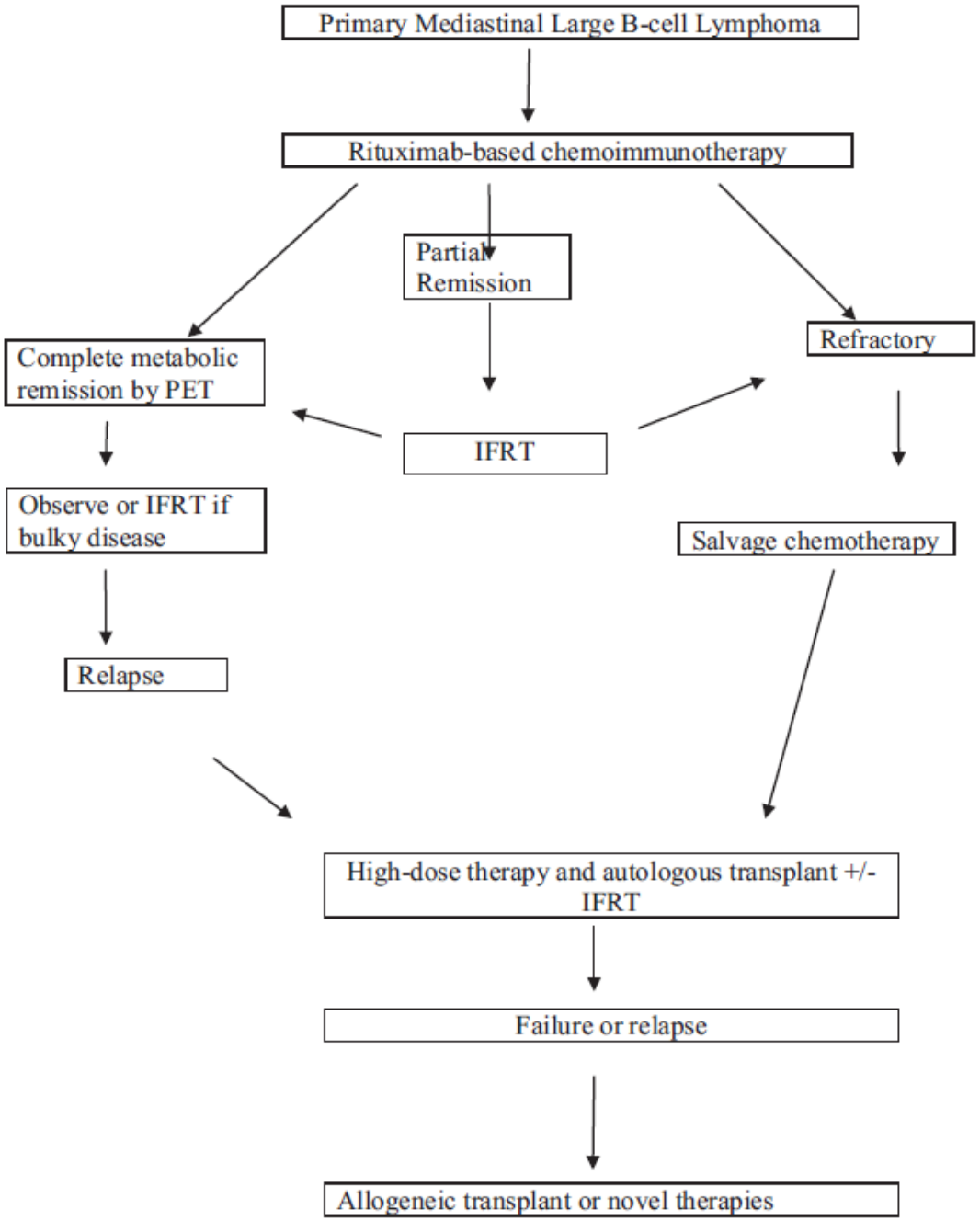
- Gençlerde timik hiperplazi nedeni ile PET yanlış pozitivite olabilir.
- Rezidü lezyon için görüntüleme takibi ve biyopsi
- Tedaviye geçilmeden mutlaka biyopsi alınmalıdır.

RELAPS HASTALIK

- Genellikle ilk 2 yıl içinde
- Ekstranodal tutulum ile relaps sık
- Tedavi için standart yok
- Kurtarma Rejimi-R ------ Kemosensitif ise YDT

YENİ TEDAVİLER

REL	IKK-β inhibitor, HSP90 inhibitor, bortezomib
JAK2, JMJD2C, RANBP6, PDL2, PDL1, SMARCA2	JAK inhibitor, PD/PDL antibody, ?JMJD2C inhibitor
ELK3, EPS8, IFNG[a]	
IGF1[a]	
CIITA, SOCS1	JAK inhibitors


Primary Mediastinal Large B-cell Lymphoma
Rituximab-based chemoimmunotherapy
Partial Remission
Complete metabolic remission by PET
Refractory
IFRT
Observe or IFRT if bulky disease
Salvage chemotherapy
Relapse
High-dose therapy and autologous transplant +/- IFRT
Failure or relapse
Allogeneic transplant or novel therapies

ÖZET

- Özel bir BHL alt grubudur.
- Küçük mediastinal biyopsiler tanı açısından güçlük oluşturur.
- İmmünohistokimyasal boyama CD30, CD15, CD20, CD3, CD45, PAX5 içermelidir.
- R-DA EPOCH günümüzde en akılcı tedavi rejimi

- Sabrınız için teşekkür ederim.....