Composite Lymphoma

Lymphoma Tumor Board

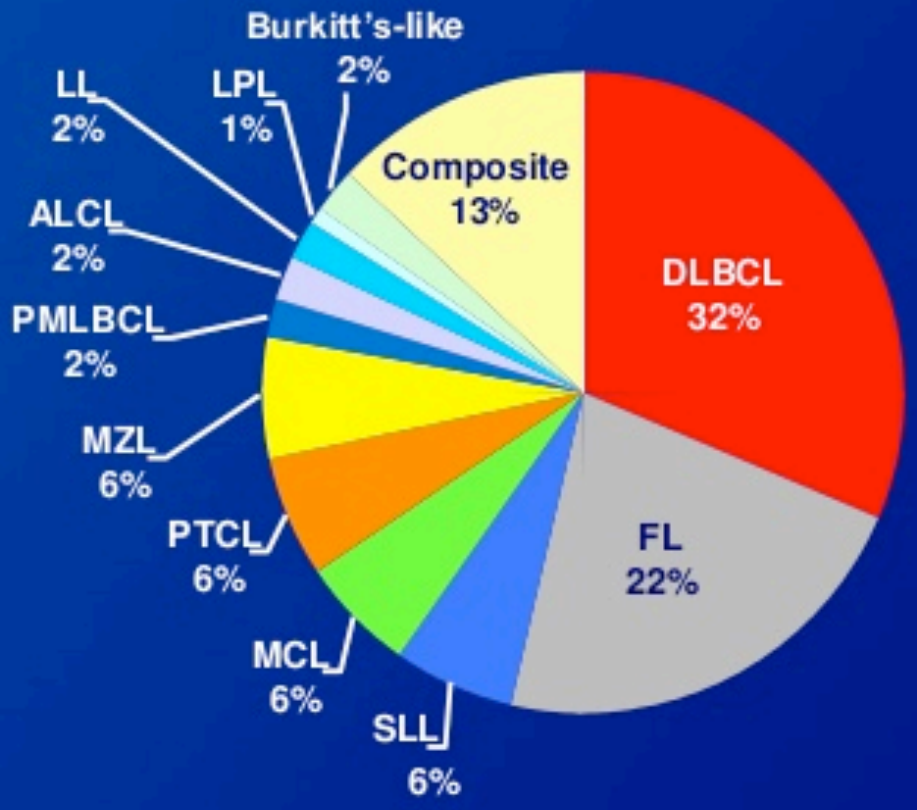
Friday, December 1, 2017

Background

- Rare: 1-4% of lymphomas, but may be underrecognized
- Two distinct lymphomas co-occurring in one patient
  - Metachronous
  - Synchronous
- Typically occur in the same organ
- Commonly comprise two subtypes of non-Hodgkin lymphoma, or the combination of a non-Hodgkin lymphoma and Hodgkin lymphoma
- No well-defined standard of care
- Tumors are often clonally related
  - In cases comprising the co-occurrence of non-Hodgkin with Hodgkin lymphoma, the malignant clones are thought to be derived from a common precursor, usually a germinal center B cell
- Lymph node or tissue biopsy remains mainstay of diagnosis

Relative Incidence of NHL Subtypes

>71,000 new cases in US in 2015



NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma.
Armitage & Weissenburger, 1998; ACS, 2015.

IDENTIFICATION OF COMMON GERMINAL-CENTER B-CELL PRECURSORS IN TWO PATIENTS WITH BOTH HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA

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Abstract

BACKGROUND: Hodgkin's disease and non-Hodgkin's B-cell lymphoma occasionally occur in the same patient. The identification of a common precursor of the two types of lymphoma would show definitively that Reed-Sternberg cells originate from B cells.

METHODS: We studied lymphomas from two patients, one with a composite lymphoma (classic Hodgkin's disease and a follicular lymphoma in the same lymph node) and the other with a T-cell-rich B-cell lymphoma that was followed by classic Hodgkin's disease. Single Reed-Sternberg cells and non-Hodgkin's lymphoma cells from frozen sections were micromanipulated. The rearranged immunoglobulin variable-region genes (V genes) of the heavy and light chains were amplified by the polymerase chain reaction from genomic DNA and sequenced.

RESULTS: In both patients, the Reed-Sternberg cells were related clonally to the non-Hodgkin's lymphoma B cells. The V genes carried somatic mutations (a hallmark of germinal-center B cells and their descendants). In both patients, some somatic mutations were shared by the Reed-Sternberg and non-Hodgkin's lymphoma cells, whereas other somatic mutations were found exclusively in one or the other cell type.

CONCLUSIONS: In two patients with classic Hodgkin's disease and non-Hodgkin's B-cell lymphoma, we identified a common B-cell precursor, probably a germinal-center B-cell, for both lymphomas. This finding suggests that the two types of lymphoma underwent both shared and distinct transforming events and provides proof of the B-cell derivation of Reed-Sternberg cells in classic Hodgkin's disease.

N Engl J Med. 1999 Apr 22;340(16):1239-47.

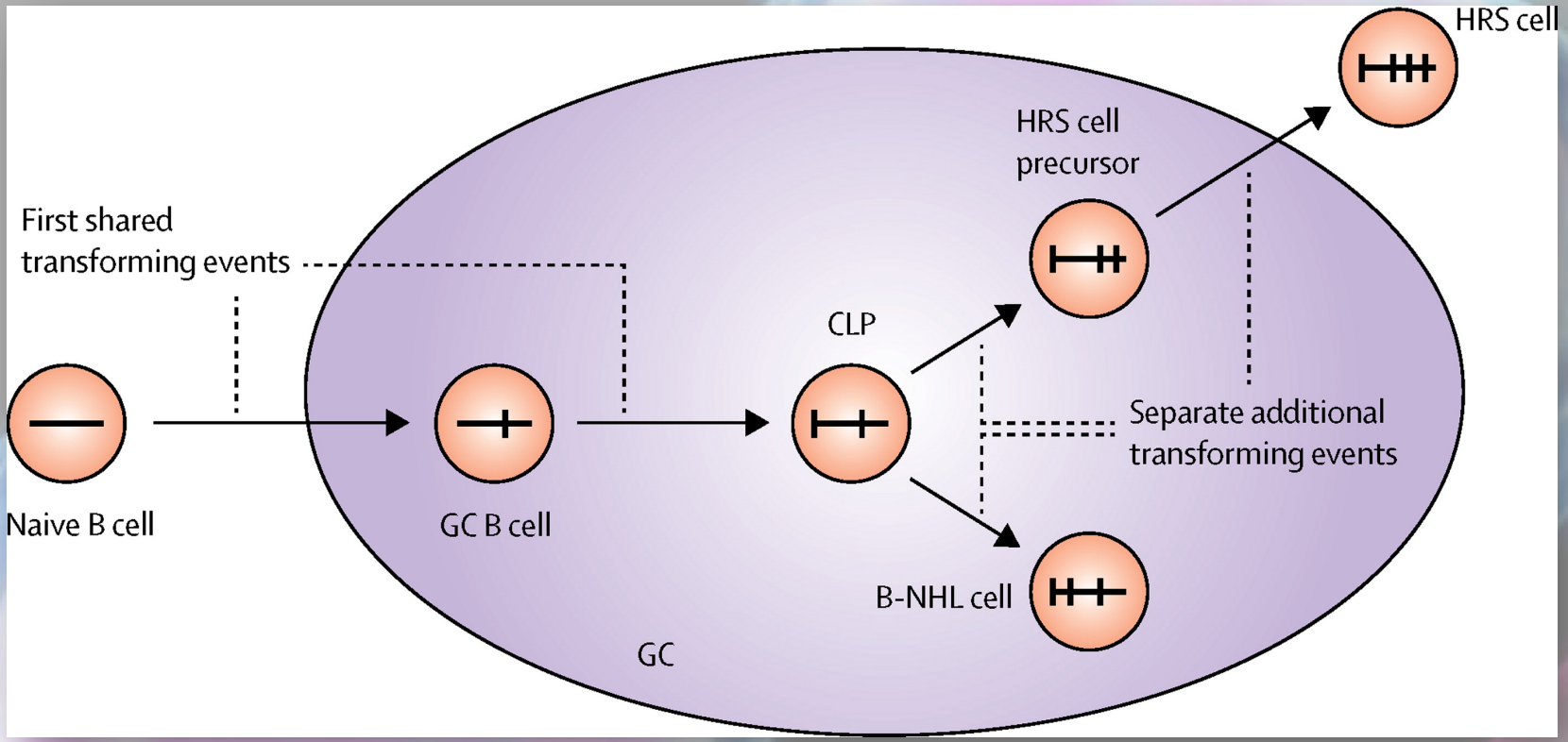

Figure 2: **Scenario for generation of clonally related composite lymphomas of a Hodgkin's lymphoma and a B-non-Hodgkin lymphoma**

Horizontal lines in the cells denote IgV genes, vertical lines V gene mutations. CLP=common lymphoma precursor. GC=germinal centre. NHL=non-Hodgkin lymphoma. HRS=Hodgkin and Reed-Sternberg.

The Lancet Oncology 2014 15, e435-e446DOI: (10.1016/S1470-2045(14)70153-6)

Pathogenesis

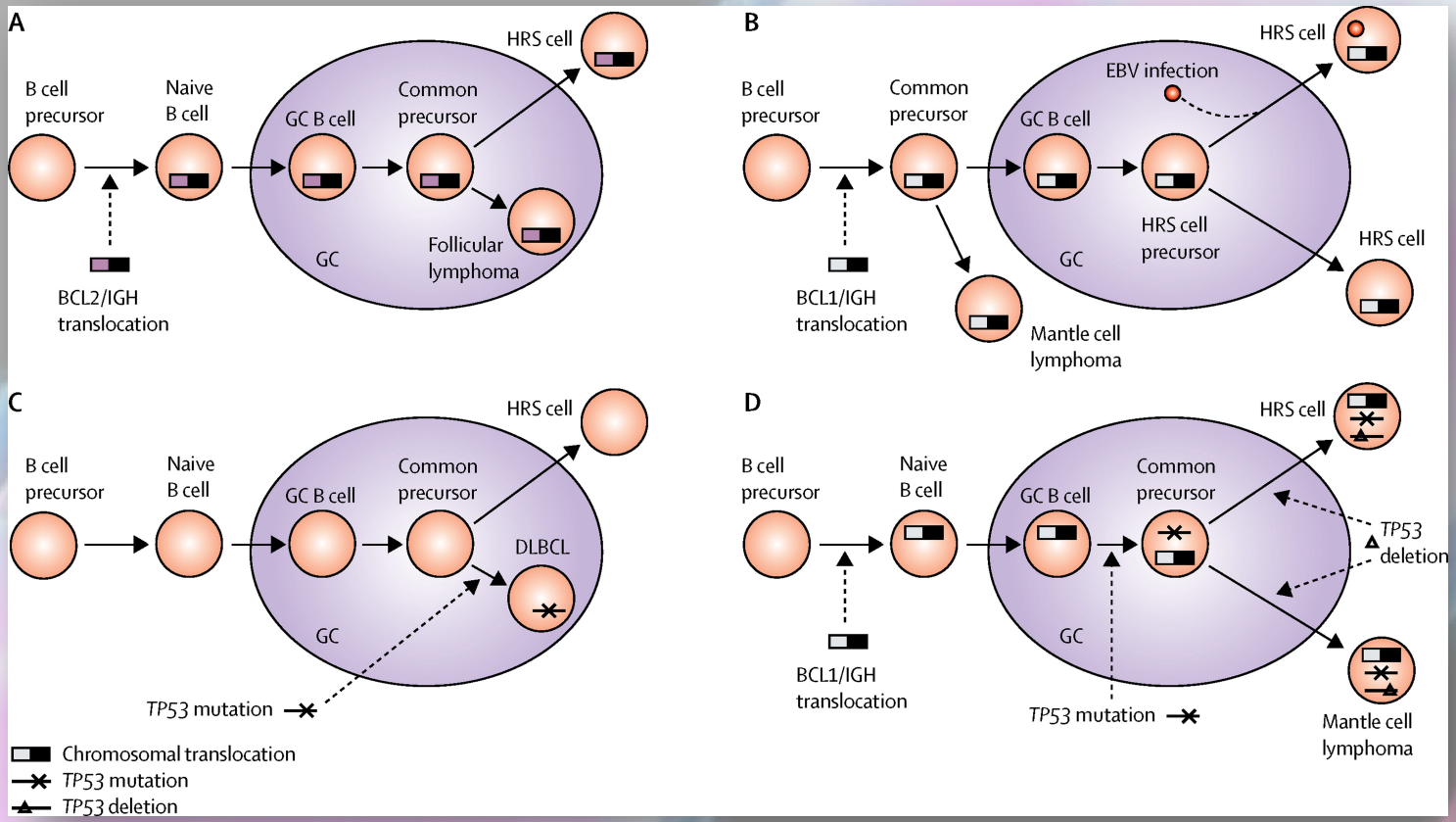

Figure 3: **Transforming events during composite lymphoma pathogenesis**

Several composite and sequential clonally related Hodgkin's lymphomas and B-non-Hodgkin lymphomas were studied for shared and distinct transforming events. (A) *BCL2*/IgH chromosomal translocations.[22,54] (B) Chromosomal translocations with EBV infection.[54] (C) *TP53* mutation.[54] (D) Chromosomal translocation with *TP53* mutation and *TP53* deletion on the other allele.[25] GC=germinal centre. HRS=Hodgkin Reed–Sternberg. DLBCL=diffuse large B-cell lymphoma. EBV=Epstein–Barr virus.

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Pathology (1)

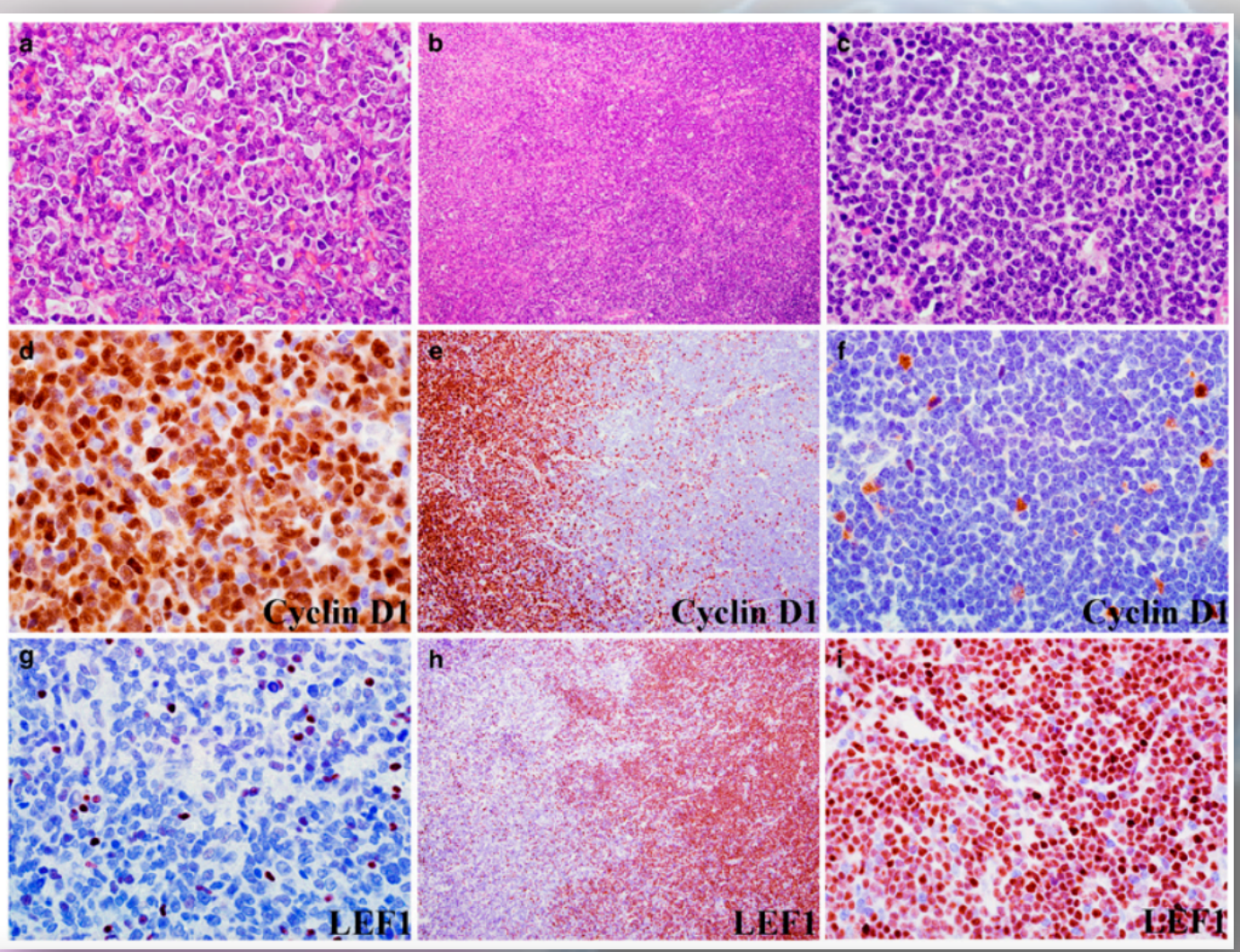

Figure 6: Composite lymphoma composed of small lymphocytic lymphoma and mantle cell lymphoma, pleomorphic type. Middle (b, e, h): low-power view of the lymph node biopsy (× 100); left (a, d, g): high-power view of the mantle cell lymphoma component (× 600); right (c, f, i): high-power view of the small lymphocytic lymphoma component (× 600). (a–c) Two distinct areas composed of large pleomorphic cells on the left and small lymphocytes on the right (H&E stain). (d–f) Immunostaining for cyclin D1 showed nuclear positivity in the large cell component on the left, consistent with mantle cell lymphoma. The small cell component on the right was negative. (g–i) Immunostaining for LEF1 demonstrated nuclear positivity in the small cell component (small lymphocytic lymphoma) on the right, but negative in the large cell component (mantle cell lymphoma) on the left.

Pathology (2)

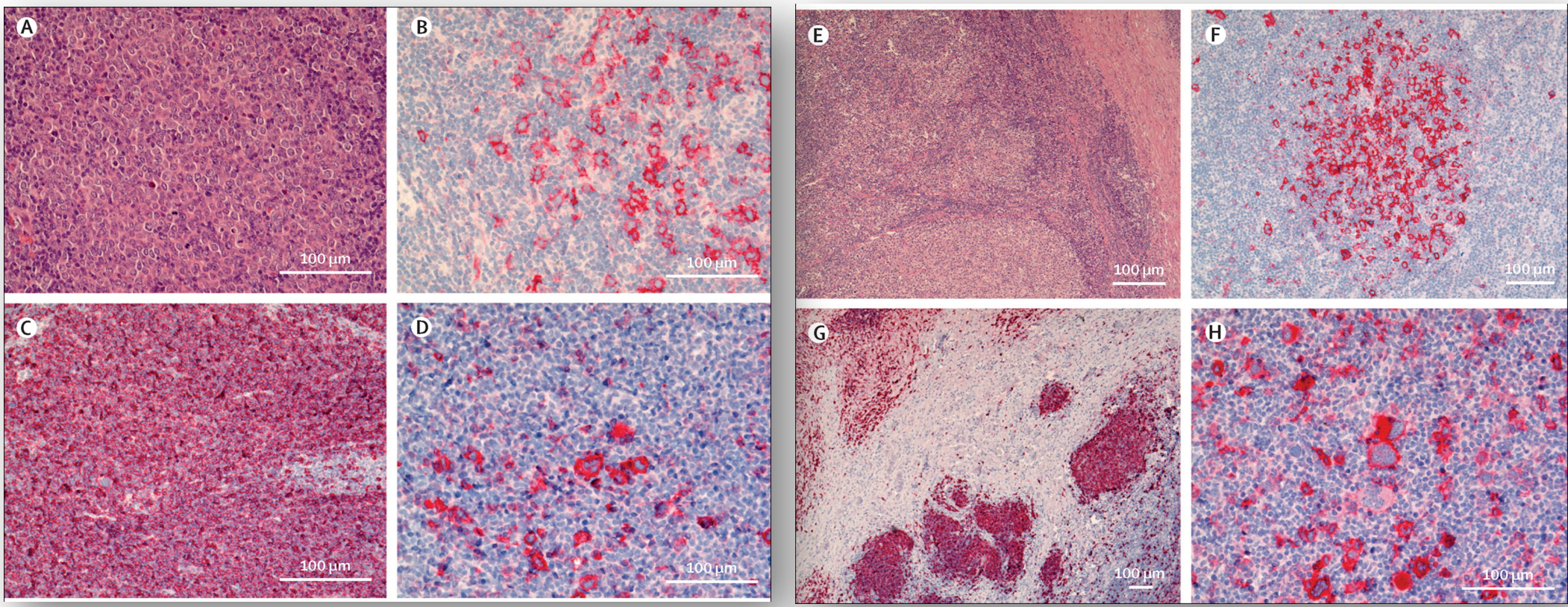

Figure 1: **Histology and immunohistochemistry of composite lymphomas**
DLBCL=diffuse large B-cell lymphoma. HRS=Hodgkin's and Reed–Sternberg. CD20 and CD30 were visualised by immunostaining. (A) and (B) Composite lymphoma of a DLBCL and a classic Hodgkin's lymphoma of nodular sclerosis type. 20× magnification. (A) Haematoxylin and eosin staining show DLBCL features. (B) CD30-positive HRS cells. (C) and (D) Composite lymphoma of a DLBCL and a classic Hodgkin's lymphoma. 20× magnification. (C) CD20-positive DLBCL cells. (D) CD30-positive HRS cells. (E) and (F) Composite lymphoma of a follicular lymphoma and a classical Hodgkin's lymphoma. (E) Follicular lymphoma, sclerotic band on the right side of the picture, haematoxylin and eosin staining, 4× magnification. (F) CD30-positive HRS cells. 10× maginification. (G) and (H) Composite lymphoma of a follicular lymphoma and a classical Hodgkin's lymphoma. (G) CD20-positive neoplastic follicles of the follicular lymphoma. In the middle of the picture, a pale CD20-negative area composed of a Hodgkin's lymphoma infiltrate is visible. 4× magnification. (H) CD30-positive HRS cells (from pale area of picture G). 20× magnification.

Cytogenetics – ALCL/DLBCL example

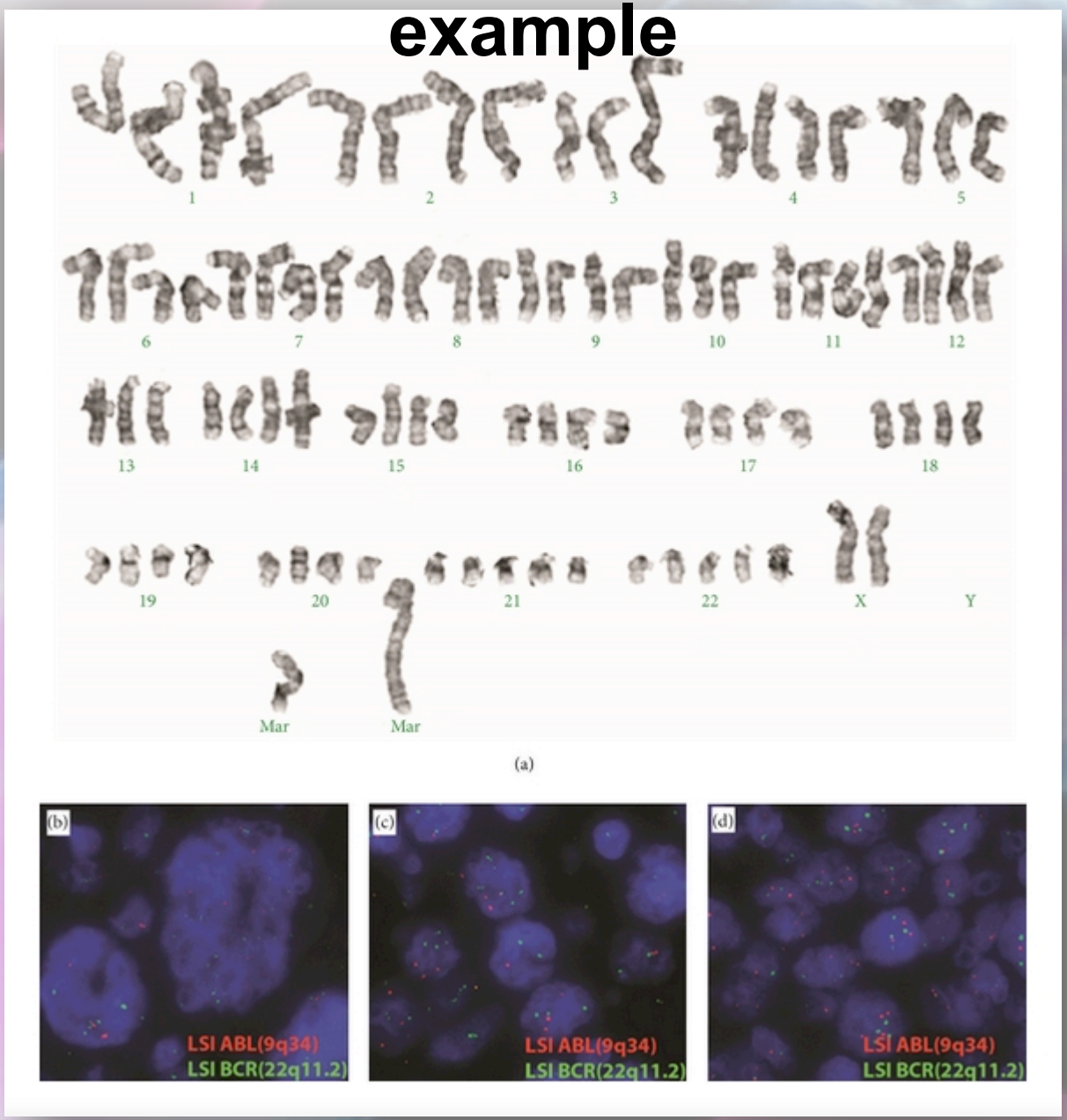

Figure 3: Conventional cytogenetics and FISH analysis of the lymphoma. (a) Representative karyotype showing complex numerical and structural abnormalities. (b) and (c) FISH analysis using LSI ABL (9q34, red) and LSI BCR (22q11.2, green) dual color probes shows approximately 3–8 signals for chromosome 9 (red) and chromosome 22 (green) in anaplastic large cell lymphoma-like area. (d) FISH analysis using the same probes shows approximately 4 signals for chromosome 9 (red) and chromosome 22 (green) in conventional diffuse large B-cell lymphoma area.

	Clonal relation	Description
Classic Hodgkin's lymphoma		
Follicular lymphoma[15]	Yes	Shared and distinct V gene mutations
Follicular lymphoma[19]	Yes	Shared and distinct V gene mutations
CLL[19]	Yes	Shared and distinct V gene mutations; initial CLL diagnosis 5 years earlier
CLL[20]	No	..
CLL[20]	No	..
CLL[30]	No	..
DLBCL[16]	Unknown	Two different V_H genes rearranged to the same D_HJ_H joint; receptor revision in one clone, or separate development from a common pro-B cell
DLBCL[18]	Yes	..
DLBCL[23]	Yes	Shared and distinct V gene mutations
CLL & anaplastic DLBCL[27]	Yes	Three lymphomas in one lymph node; identical V_H mutation pattern
MCL[25]	Yes	Only shared mutations
MCL[26]	Yes	HRS cells with IgV gene mutations, mantle cell lymphoma unmutated
MCL[29]	No	..
MCL[29]	No	..
T-cell NHL[28]	No	..
Low-grade B-cell NHL[30]	Yes	..
Low-grade B-cell NHL[30]	Yes	..
High-grade B-cell NHL[30]	No	..
Cutaneous T cell LPD[31]	Yes	Hodgkin's lymphoma in lymph node; T-cell origin of both lymphomas
Nodular lymphocyte predominant Hodgkin's lymphoma		
DLBCL[32]	Yes	..
TCRBCL[33]	Yes	..
Classic Hodgkin's lymphoma[34]	Yes	Clonality based on two identically sized VκJκ joints, not on sequencing
Classic Hodgkin's lymphoma[35]	Yes	Shared mutations (short sequence)

MCL=mantle cell lymphoma. CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. LPD=lymphoproliferative disorder. NHL=non-Hodgkin lymphoma. TCRBCL=T-cell-rich B-cell lymphoma. HRS=Hodgkin and Reed-Sternberg cells. LP=lymphocyte predominant cells. *Only cases in which at least the HRS or LP cells were microdissected for molecular analysis are considered.

Table 1: **Composite Hodgkin's and non-Hodgkin lymphomas for which the clonal relations was clarified***

	Clonal relation	Description
Classic Hodgkin's lymphoma		
TCRBCL[15]	Yes	HL developed 3 years after TCRBCL; shared and distinct V gene mutations
Follicular lymphoma[21]	Yes	Follicular lymphoma developed two years after HL; shared and distinct V_H gene mutations
Follicular lymphoma[22]	Yes	HL diagnosed 4 years after follicular lymphoma
SMZL[24]	Yes	HL developed 15 years after SMZL; both lymphomas had unmutated V_H region genes
DLBCL[44]	No	DLBCL diagnosed 12 years after initial HL diagnosis
Small non-cleaved cell B-cell NHL[40]	No	B-cell NHL developed 6 years after HL
MALT lymphoma and anaplastic DLBCL[41]	No	MALT lymphoma 4 years before and DLBCL 2 years after HL; NHL clonally related to each other
marginal zone & T-cell NHL[43]	No	T-cell NHL first diagnosed 30 years before the other lymphomas, which occurred concurrently
PMBCL[47]	Yes	HL developed after PMBCL
PMBCL[47]	Yes	PMBCL developed after HL
PMBCL[48]	Yes	PMBCL developed after HL; confirmation of clonal relationship mainly based on shared chromosomal lesions
CLL[17]	No	HL developed 4 years after CLL
CLL[17]	No	HL developed 5 years after CLL
CLL[39]	Yes	HL developed 4 years after CLL
CLL[39]	Yes	HL developed 8 years after CLL
CLL[39]	No	HL developed 10 years after CLL
CLL[45]	No	HL diagnosed 10 years after CLL
Lymphomatoid papulosis and cutaneous T-cell lymphoma[46]	Yes†	HL developed 4 years after lymphomatoid papulosis and was followed 10 years later by a cutaneous T-cell lymphoma
Nodular lymphocyte predominant Hodgkin's lymphoma		
DLBCL[32]	Yes	DLBCL developed 34 months after NLPHL
TCRBCL[42]	Yes	TCRBCL developed 4 years after NLPHL; shared and distinct V gene mutations

CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. HL=Hodgkin's lymphoma. PMBCL=primary mediastinal B-cell lymphoma. SMZL=splenic marginal zone lymphoma. TCRBCL=T-cell-rich B-cell lymphoma. NHL=non-Hodgkin lymphoma. HRS=Hodgkin and Reed–Sternberg cells. LP=lymphocyte predominant cells. *Only cases in which at least the HRS or LP cells were microdissected for molecular analysis are considered. †Although HRS cells were not microdissected for molecular analysis, this case is included, because at time of diagnosis of Hodgkin's lymphoma no T-cell malignancy as a potential source for contamination in the PCR analysis was evident in the patient.

Table 2: **Clonal relation between Hodgkin's and non-Hodgkin lymphomas developing consecutively in a patient***

	Type and presence of transforming event	Description
Classical HL; DLBCL[18]	EBV positive; EBV negative	..
Classical HL; follicular lymphoma[22]	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; MCL[25]	t(11;14), BCL1/IgH, *TP53* deletion and mutation; t(11;14), BCL1/IgH, *TP53* deletion and mutation	Identical translocation, identical *TP53* point mutation, but presumably distinct deletion of other *TP53* allele
Classical HL; MCL[26,54]	t(11;14), BCL1/IgH, subclone EBV positive; t(11;14), BCL1/IgH, EBV negative	Identical translocation, HRS cell subclone with distinct V_H mutations EBV positive
Classical HL; NLPHL[35]	EBV positive; EBV negative	..
Classical HL; CLL[39]	EBV positive; EBV negative	HL developed after CLL
Classical HL; CLL[39]	EBV positive; EBV negative	HL developed after CLL
Classical HL; follicular lymphoma[54]	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; follicular lymphoma[54]	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; DLBCL[54]	*TP53* mutations negative; *TP53* mutations positive	..

HRS=Hodgkin and Reed–Sternberg cells. EBV=Epstein-Barr virus. Ig=immunoglobulin. HL=Hodgkin's lymphoma. DLBCL=diffuse large B-cell lymphoma. MCL=mantle cell lymphoma. CLL=chronic lymphocytic leukaemia. NLPHL=nodular lymphocyte predominant Hodgkin's lymphoma.

Table 3: **Shared and distinct genetic lesions and viral infections in clonally related composite or consecutive Hodgkin's lymphoma and B-cell non-Hodgkin lymphoma**

Treatment - Principles

- Overall therapeutic strategy needs to consider both disease components
- Current first-line chemotherapy protocols are based on alkylating agents
- Indolent lymphomas: 6 cycles of bendamustine and rituximab induce remissions in 90% of patients
    - Remission can be prolonged by using anti-CD20 maintenance therapy
- Aggressive lymphomas: alkylating agents combined with anthracyclines, glucocorticoids, and other agents
- $CD20^+$ B-cell lymphomas: alkylating agents are combined with antibodies directed against CD20
- DLBCL: 6 to 8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is standard of care
- $CD20^-$ lymphomas: treatment is tailored to size of tumor mass
    - ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or BEACOPP for more advanced stages (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)

Maintenance rituximab following induction R-CHOP chemotherapy in patients with composite or discordant, indolent and aggressive, B-cell non-Hodgkin lymphomas

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Key words: composite lymphoma, discordant lymphoma, transformed lymphoma, maintenance rituximab, R-CHOP

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Treatment – Patient Characteristics

Table 1. Baseline patients' characteristics according to diagnosis: composite (COM) *versus* discordant (DIS) lymphoma.

Characteristics	Composite N=58	Discordant N=40	P
Age			
≤ 60 years	29 (50%)	11 (28%)	0.026
> 60 years	29 (50%)	29 (72%)	
Sex			
Male	30 (52%)	25 (63%)	0.291
Female	28 (42%)	15 (38%)	
Performance status			
0 – 1	47 (81%)	22 (55%)	0.006
≥ 2	11 (19%)	18 (45%)	
Lactate dehydrogenase			
Normal	35 (64%)	14 (35%)	0.006
Elevated	20 (36%)	26 (65%)	
Ann Arbor Stage			
I/II	13 (22%)	0	<0.001
III/IV	45 (78%)	40 (100%)	
Number of extranodal sites			
< 2	48 (83%)	18 (45%)	<0.001
≥ 2	10 (17%)	22 (55%)	
IPI			
Low	17 (29%)	3 (8%)	
Low-intermediate	18 (33%)	7 (18%)	<0.001
High-intermediate	17 (31%)	11 (27%)	
High	3 (6%)	19 (47%)	
Largest tumor mass			
< 10 cm	40 (49%)	29 (73%)	0.706
≥ 10 cm	18 (31%)	11 (27%)	
Type of indolent NHL			
Follicular	53 (91%)	15 (37%)	<0.001
Low grade, NOS	0	25 (63%)	
Marginal zone	4 (7%)	0	
Lymphoplasmacytic	1 (2%)	0	
Bone marrow involvement			
Indolent NHL	13 (22%)	34 (85%)	<0.001
DLBCL	5 (9%)	2 (5%)	
Negative	40 (69%)	4 (10%)	
Response to R-CHOP			
Complete	47 (81%)	30 (75%)	0.474
Partial	11 (19%)	10 (25%)	
Maintenance rituximab			
No	18 (31%)	25 (63%)	0.002
Yes	40 (69%)	15 (37%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

Kansara *et al.*, Haematologica 2016; 101:e413

Treatment - Patient Characteristics (2)

Table 2. Baseline patients' characteristics according to maintenance rituximab.

Characteristics	Pre-policy R-CHOP only N=43	Post-policy R-CHOP + MR N=55	P
Age			
≤ 60 years	19 (44%)	21 (38%)	0.548
> 60 years	24 (56%)	34 (62%)	
Sex			
Male	27(63%)	28 (51%)	0.240
Female	16 (37%)	27 (49%)	
Performance status			
0 – 1	25 (58%)	44 (80%)	0.019
≥ 2	18 (42%)	11 (20%)	
Lactate dehydrogenase			
Normal	21/42 (50%)	28/53 (53%)	0.784
Elevated	21/42 (50%)	25/53 (47%)	
Ann Arbor Stage			
I/II	5 (12%)	8 (15%)	0.673
III/IV	38 (88%)	47 (85%)	
Extranodal sites			
< 2	25 (61%)	38 (70%)	0.395
≥ 2	16 (39%)	16 (30%)	
IPI			
Low	9/42 (21%)	13/53 (24%)	0.401
Low-intermediate	11/42 (26%)	15/53 (27%)	
High-intermediate	10/42 (23%)	18/53 (33%)	
High	13/42 (30%)	9/53 (16%)	
Largest tumor mass			
< 10 cm	31 (72%)	38 (69%)	0.434
≥ 10 cm	12 (28%)	17 (31%)	
Diagnosis			
Composite NHL	18 (42%)	40 (73%)	0.002
Discordant NHL	25 (58%)	15 (27%)	
Type of indolent NHL			
Follicular	23 (53%)	44 (80%)	0.021
Low grade, NOS	17 (40%)	8 (14%)	
Marginal zone	3 (7%)	2 (4%)	
Lymphoplasmacytic	0	1 (2%)	
Bone marrow involvement			
Indolent NHL	27 (56%)	20 (36%)	0.027
DLBCL	3 (7%)	4 (7%)	
Negative	13 (30%)	31 (56%)	
Response to R-CHOP			
Complete	36 (84%)	41 (75%)	0.272
Partial	7 (16%)	14 (25%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

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Treatment Outcome – PFS and OS

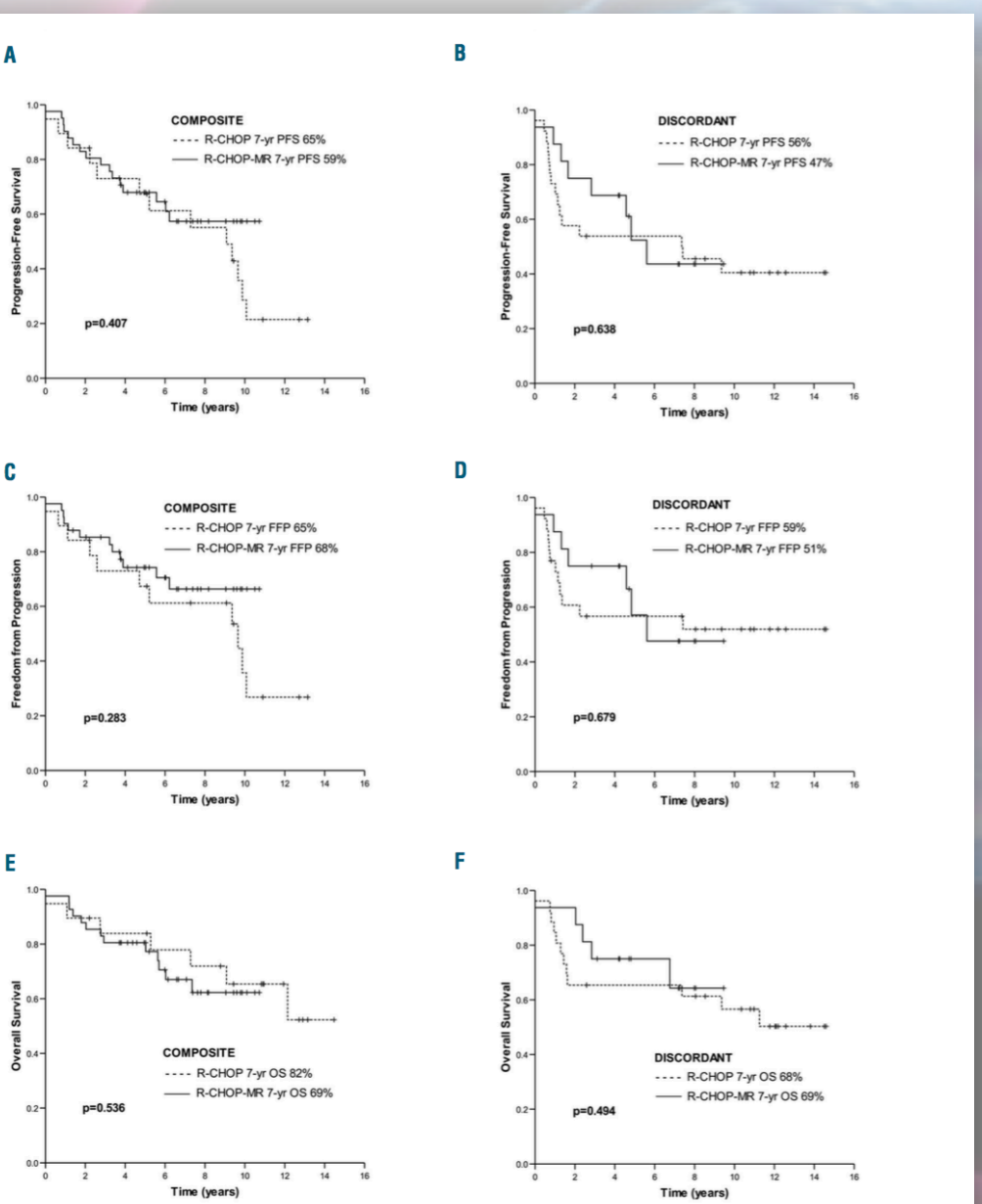

Figure 1. Outcomes according to maintenance rituximab. Progression-free survival: (A) composite lymphoma (COM), (B) discordant lymphoma (DIS); freedom from progression: (C) COM, (D) DIS; overall survival: (E) COM, (F) DIS.

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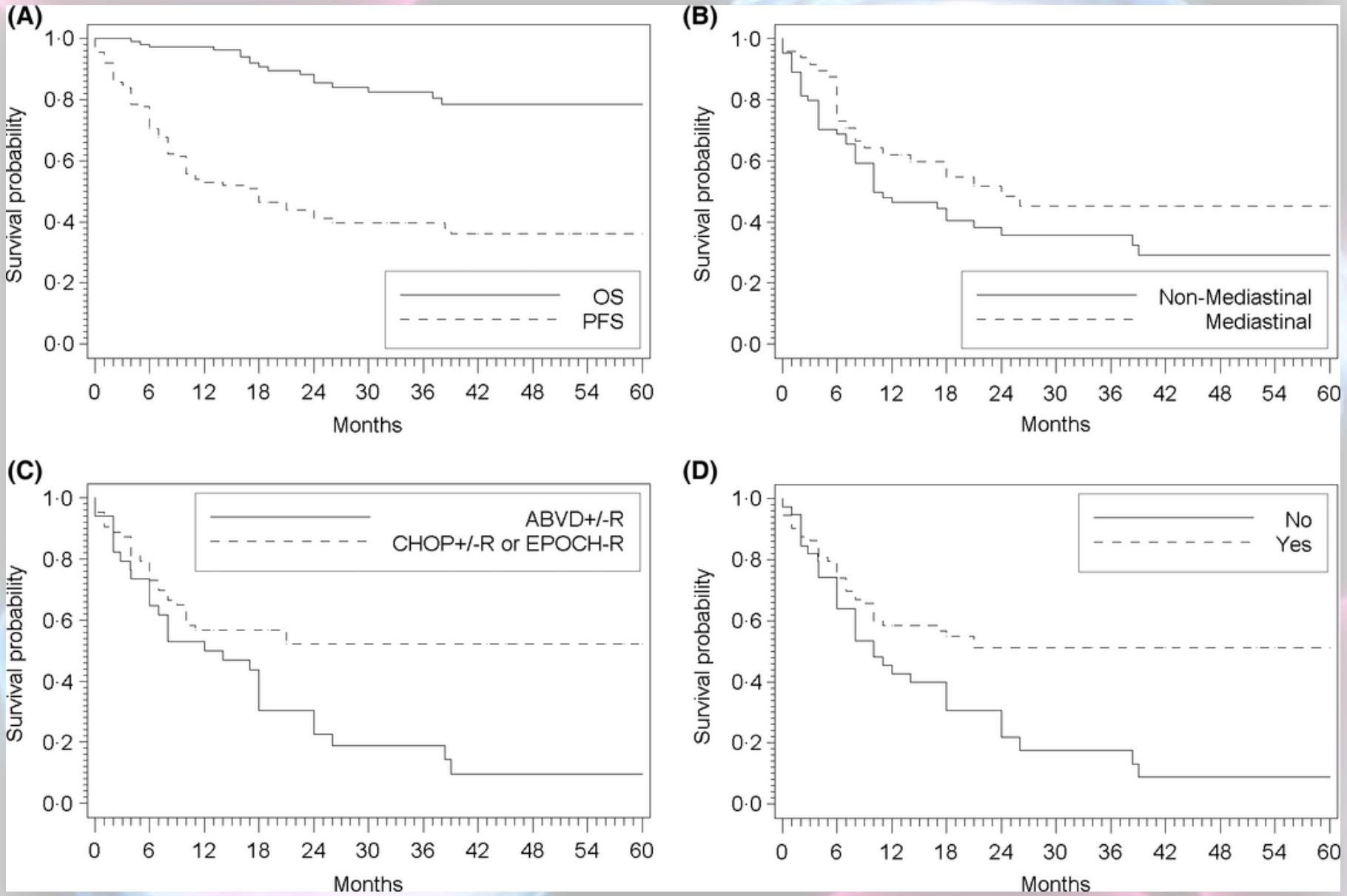
How I manage patients with grey zone lymphoma



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