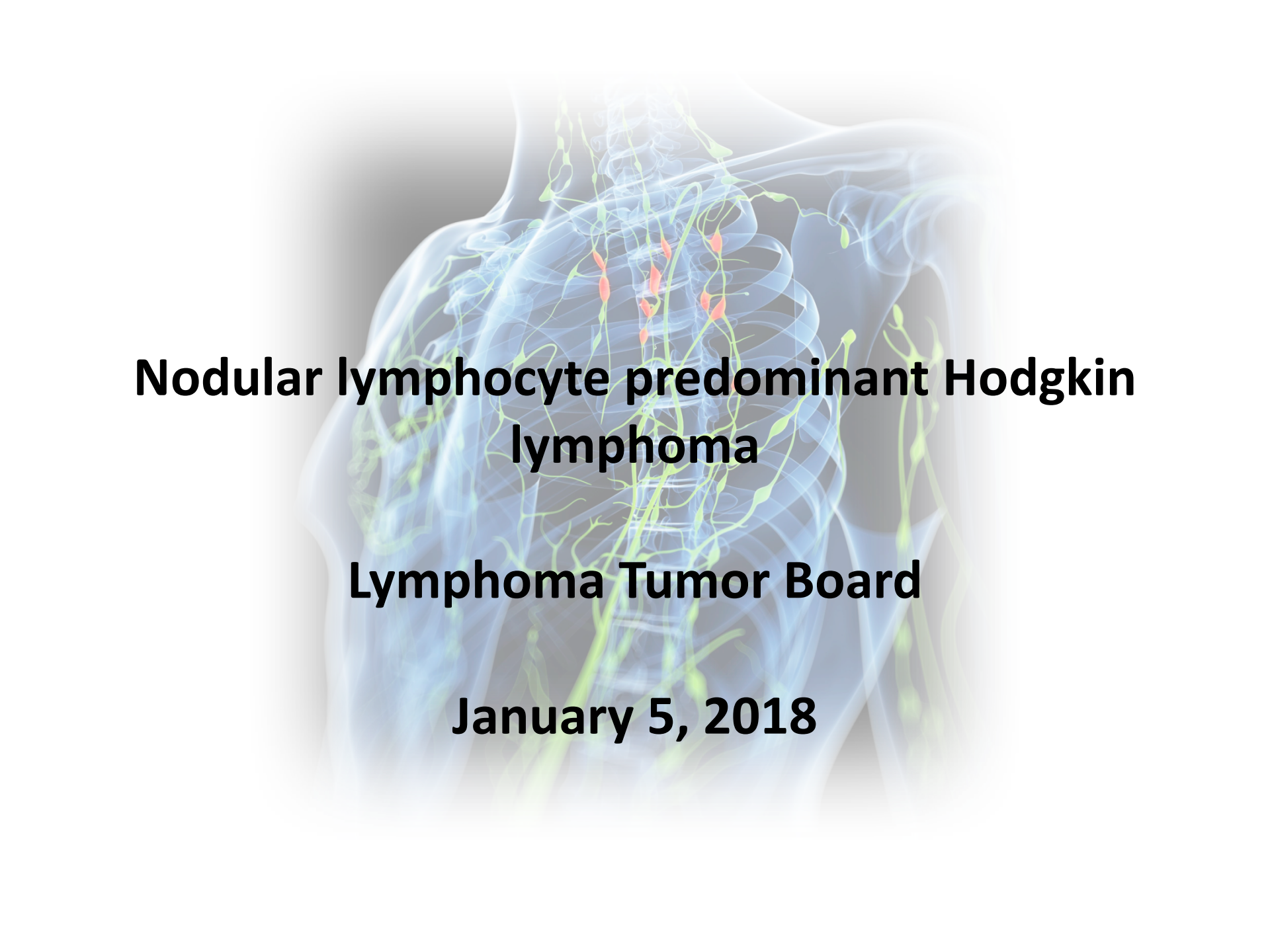


Nodular lymphocyte predominant Hodgkin lymphoma

Lymphoma Tumor Board

January 5, 2018

Etiology

Etiology - Hodgkin Lymphoma

Infectious agents

- EBV, may be involved in the pathogenesis. In as many as 50% of cases, the tumor cells are EBV-positive.
- Patients with HIV infection have a higher incidence of Hodgkin lymphoma compared with the population without HIV infection.

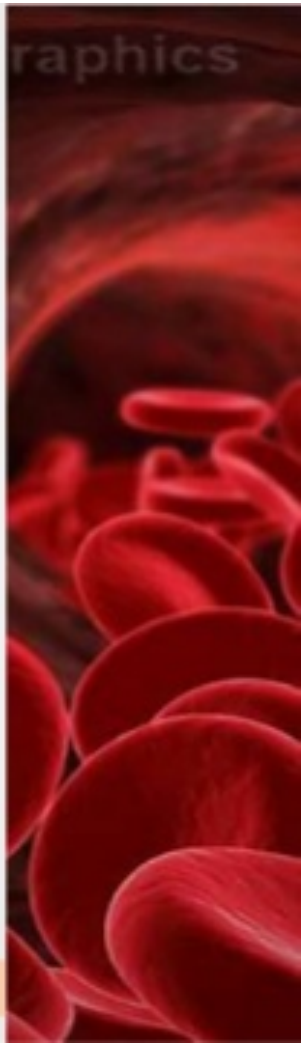
Genetic predisposition

- Approximately 1% of patients with Hodgkin lymphoma have a family history of the disease.

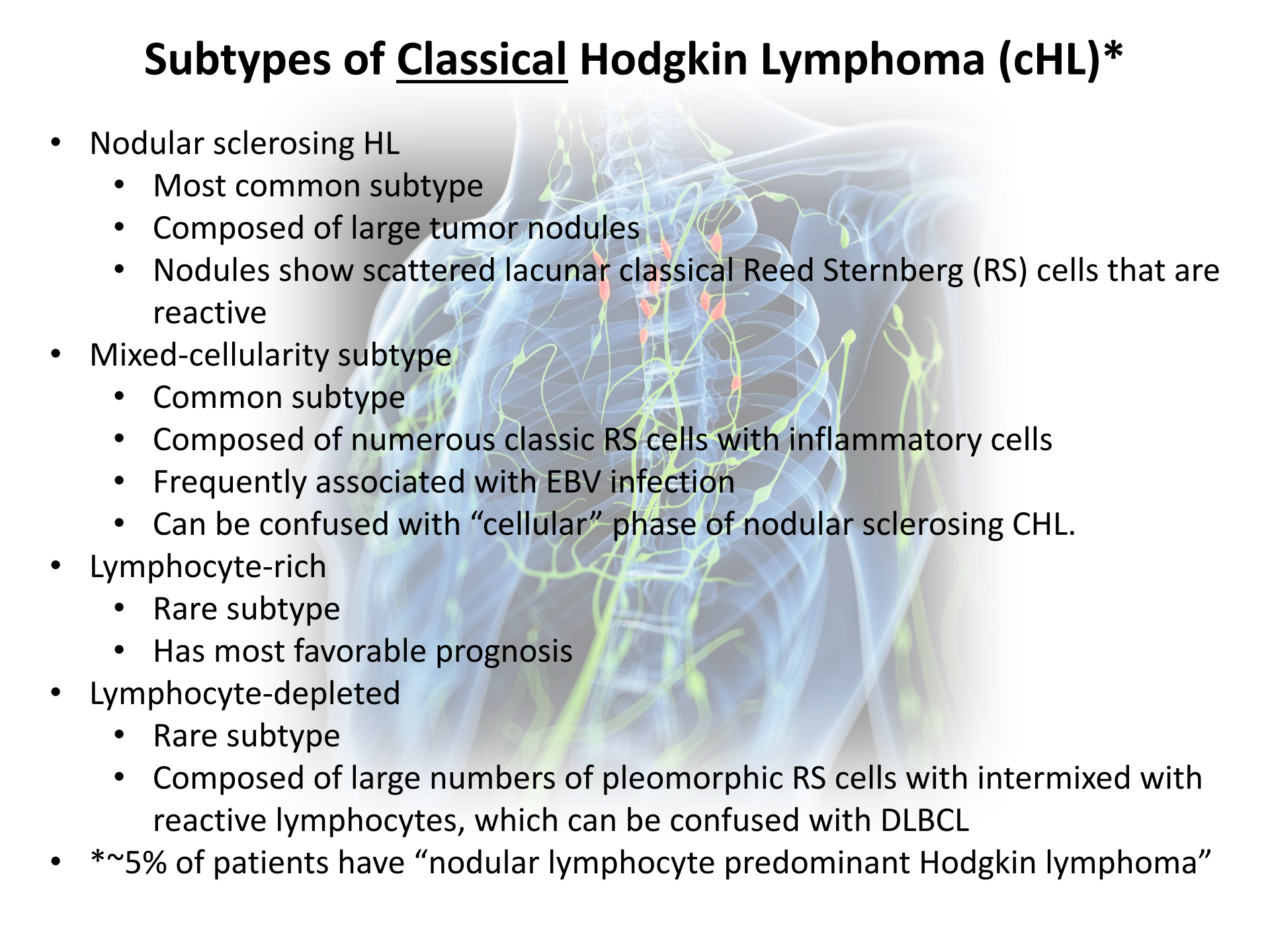
UV radiation exposure

- May have a protective effect against lymphomagenesis through mechanisms that may be independent of vitamin D

Source: http://emedicine.medscape.com/article/201886-overview#aw2aab6b2b3



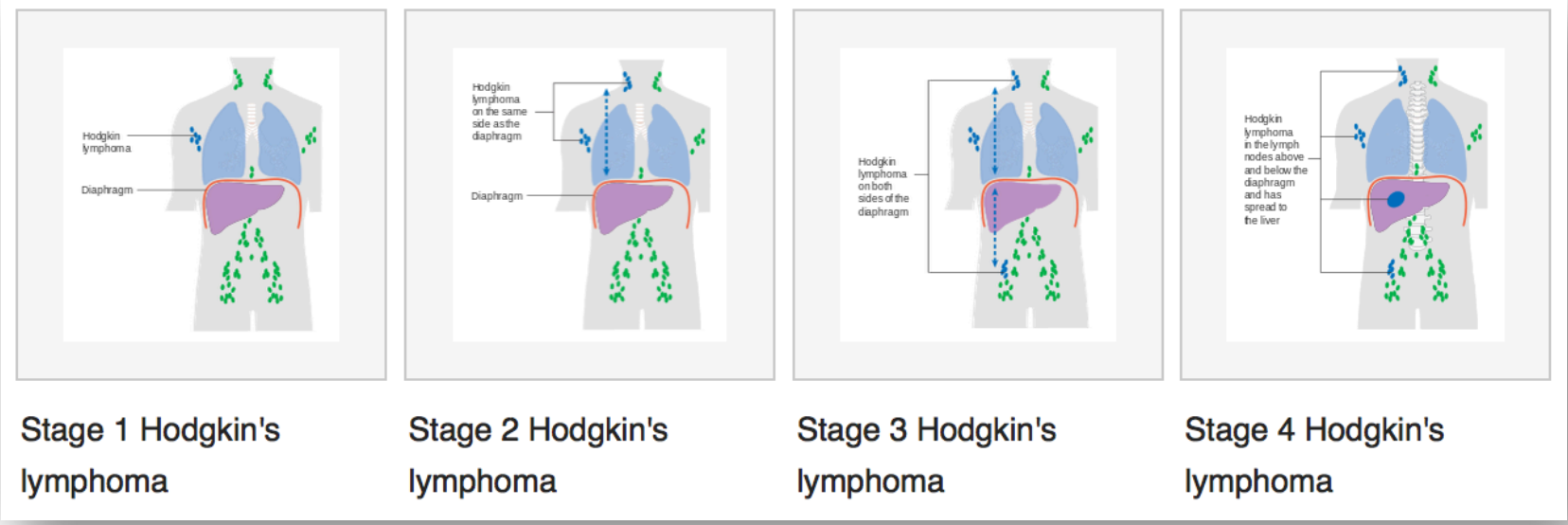
Subtypes of Classical Hodgkin Lymphoma (cHL)*



- Nodular sclerosing HL
  - Most common subtype
  - Composed of large tumor nodules
  - Nodules show scattered lacunar classical Reed Sternberg (RS) cells that are reactive
- Mixed-cellularity subtype
  - Common subtype
  - Composed of numerous classic RS cells with inflammatory cells
  - Frequently associated with EBV infection
  - Can be confused with “cellular” phase of nodular sclerosing CHL.
- Lymphocyte-rich
  - Rare subtype
  - Has most favorable prognosis
- Lymphocyte-depleted
  - Rare subtype
  - Composed of large numbers of pleomorphic RS cells with intermixed with reactive lymphocytes, which can be confused with DLBCL
- *~5% of patients have “nodular lymphocyte predominant Hodgkin lymphoma”

Staging of Hodgkin Lymphoma (HL)

- Stage I
  - Involvement of single lymph node region
  - Typically, cervical nodes or single extralymphatic site (stage IE)
- Stage II
  - Involvement of two or more lymph node regions on **same** side of diaphragm
  - One lymph node region and a contiguous extralymphatic site (IIE)
- Stage III
  - Involvement of two or more lymph node regions on both sides of the diaphragm
  - Can include spleen (IIIS) and/or limited contiguous extralymphatic organ sites (IIIE, IIIES)
- Stage IV
  - Disseminated involvement of one or more extralymphatic organs



Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

- Uncommon entity in contrast to classical Hodgkin lymphoma (cHL)
  - Considered indolent
- Represent ~5% of Hodgkin lymphoma
- Universally expresses CD20 which is a hallmark of the disease
  - Does not express CD15 or CD30
- *BCL6* gene rearrangements have been frequently observed
- Majority present with early-stage disease
- Unlike cHL, late relapses may occur, as well as propensity to transform to an aggressive B-cell NHL
- Deaths caused by NLPHL are rare
  - Morbidity is caused by secondary malignancies

(NLPHL) – Pathology

- The term “Popcorn cells” has been used due to the number of increased nucleoli and and microscopic appearance
- One mixture of LP cells and small B cells is required for a diagnosis of NLPHL
- LP cells are usually seen in the background of B-cell-rich lymphoid follicles associated with follicular dendritic cell meshworks
- Unlike Reed-Sternberg cells in classical HL (cHL), LP cells lack expression of CD15, CD30, and EBV
- Typical B-cell phenotype is seen – cells express CD20, CD45, CD75 and often J-chain
- Epithelial membrane antigen is present in ~50% of cases
- Progressive transformation of germinal centers (PTGCs) can be mistaken for NLPHL

https://doi.org/10.1182/blood-2013-07-453241.

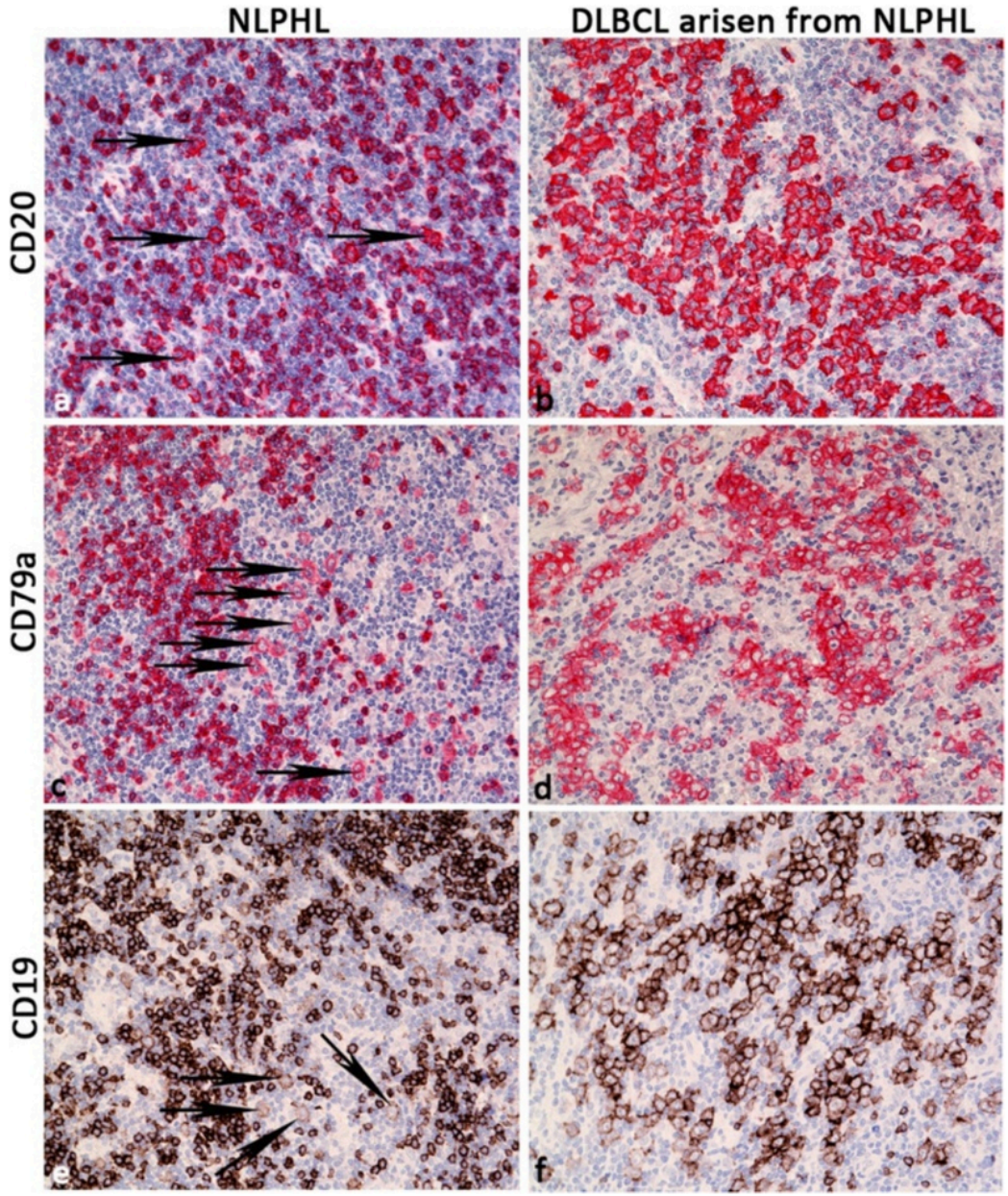
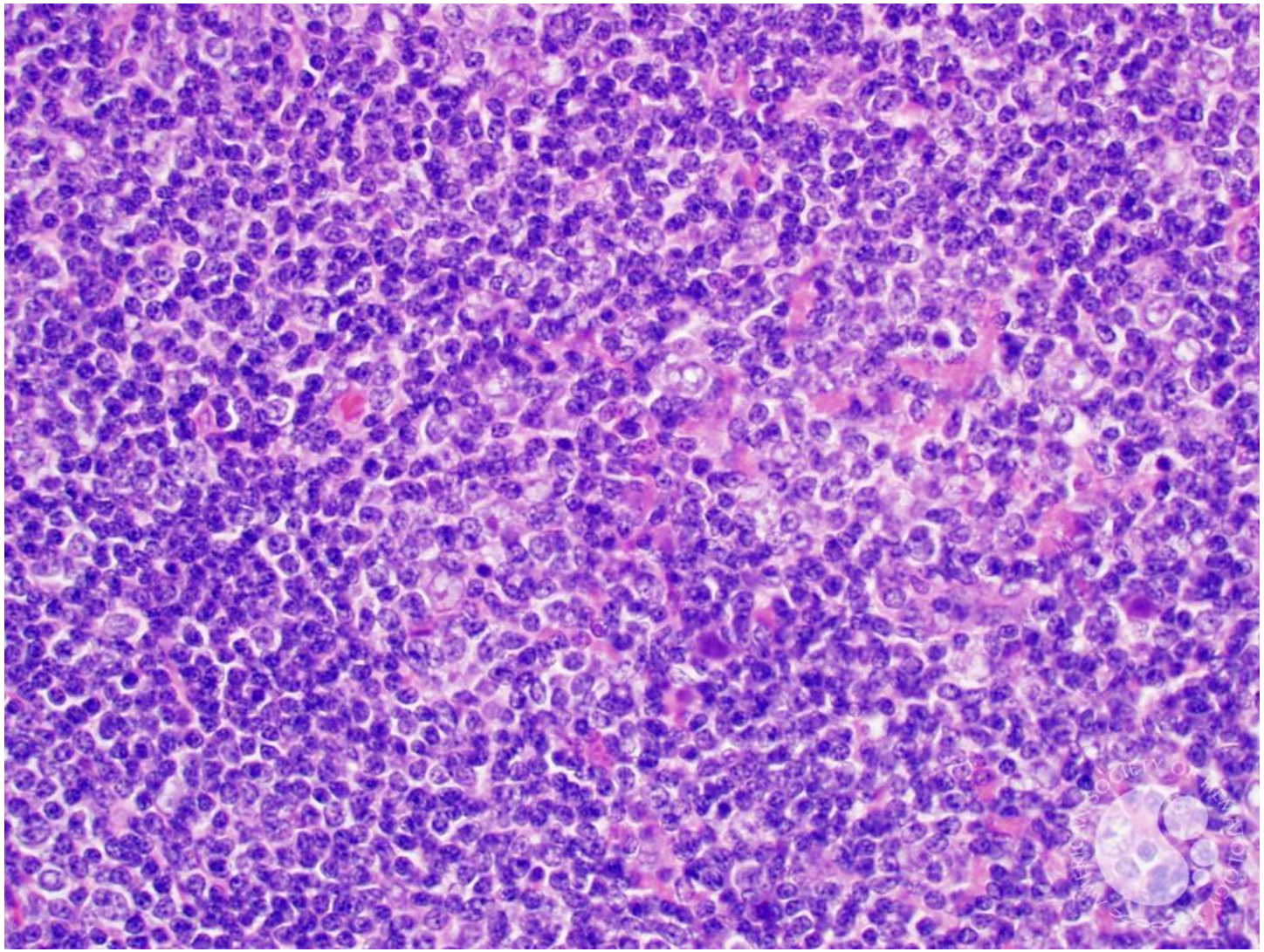
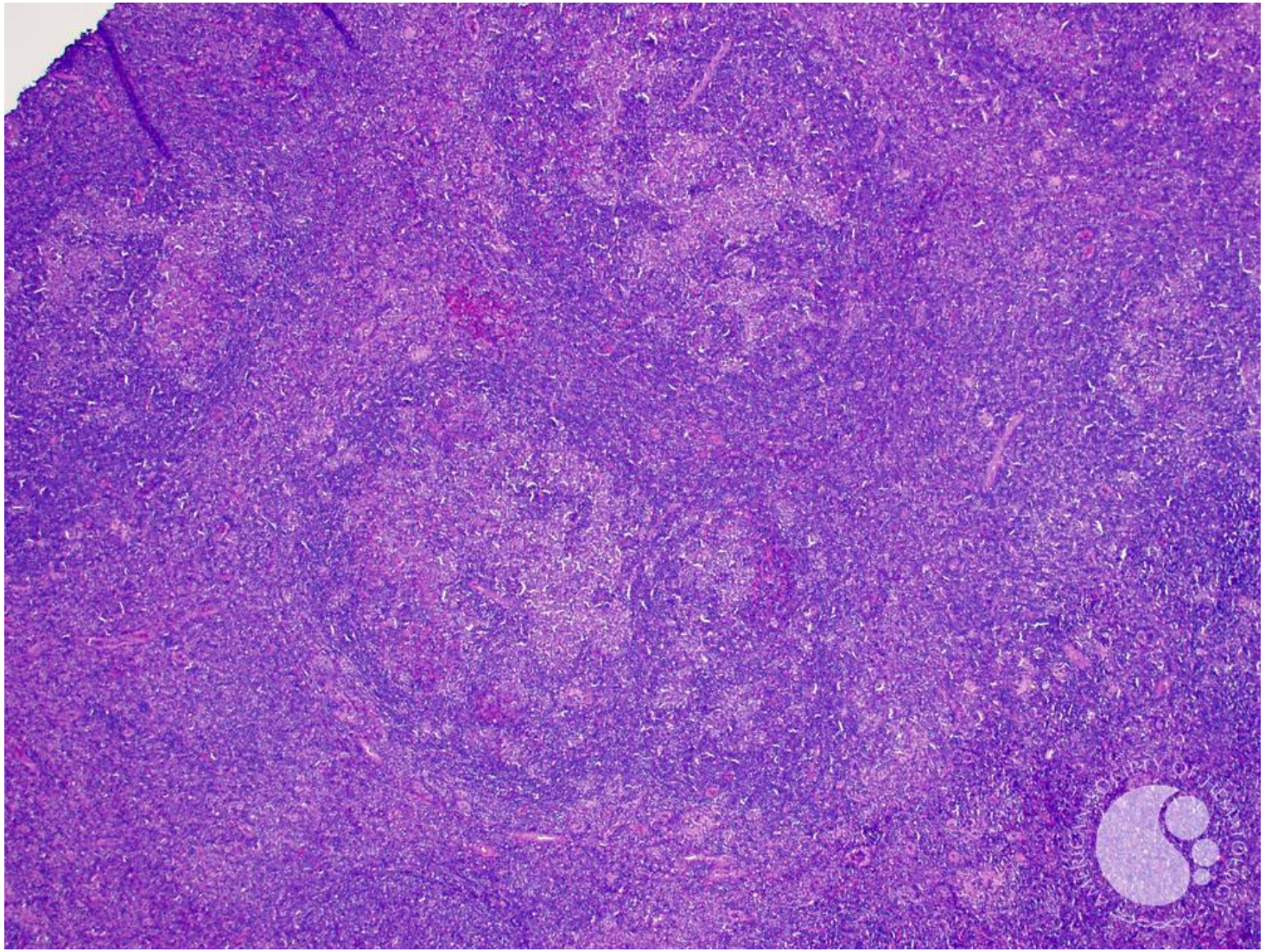


Figure 3 B cell phenotype in composite lymphomas of NLPHL and "LP type" DLBCL. a. Moderate CD20 expression in LP cells of NLPHL (arrows: CD20, 200×). **b**. More enhanced CD20 expression in "LP type" DLBCL (same lymph node and same section, CD20, 200×). **c**. Weak CD79a expression in LP cells of NLPHL (arrows: CD79a, 200×). **d**. More enhanced CD79a expression in "LP type" DLBCL (same lymph node, CD79a, 200×). **e**. Weak CD19 expression in LP cells of NLPHL (arrows: CD19, 200×). **f**. More enhanced CD19 expression in "LP type" DLBCL (same lymph node, CD19, 200×).

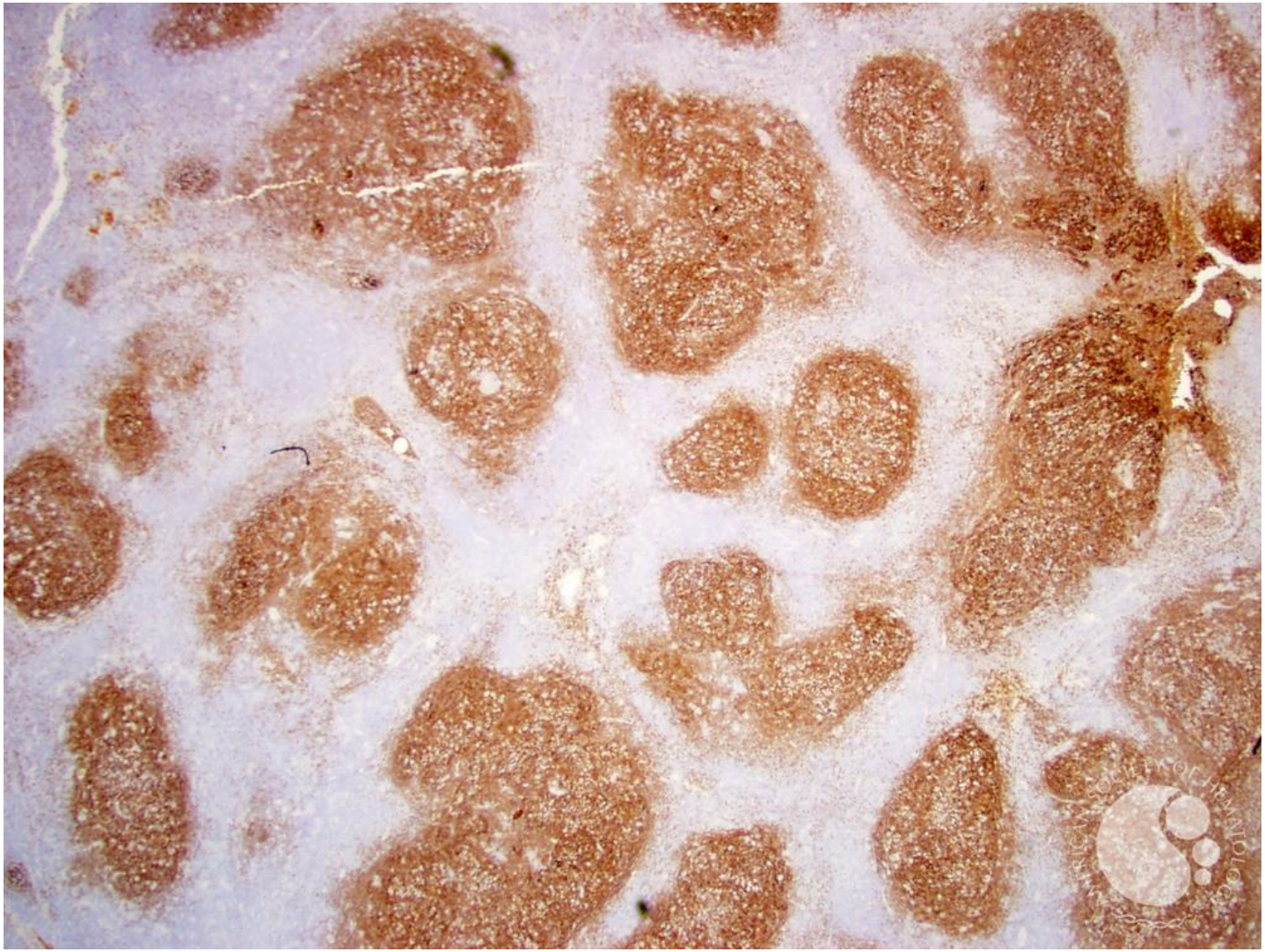
Nodular lymphocyte Predominant Hodgkin lymphoma 4



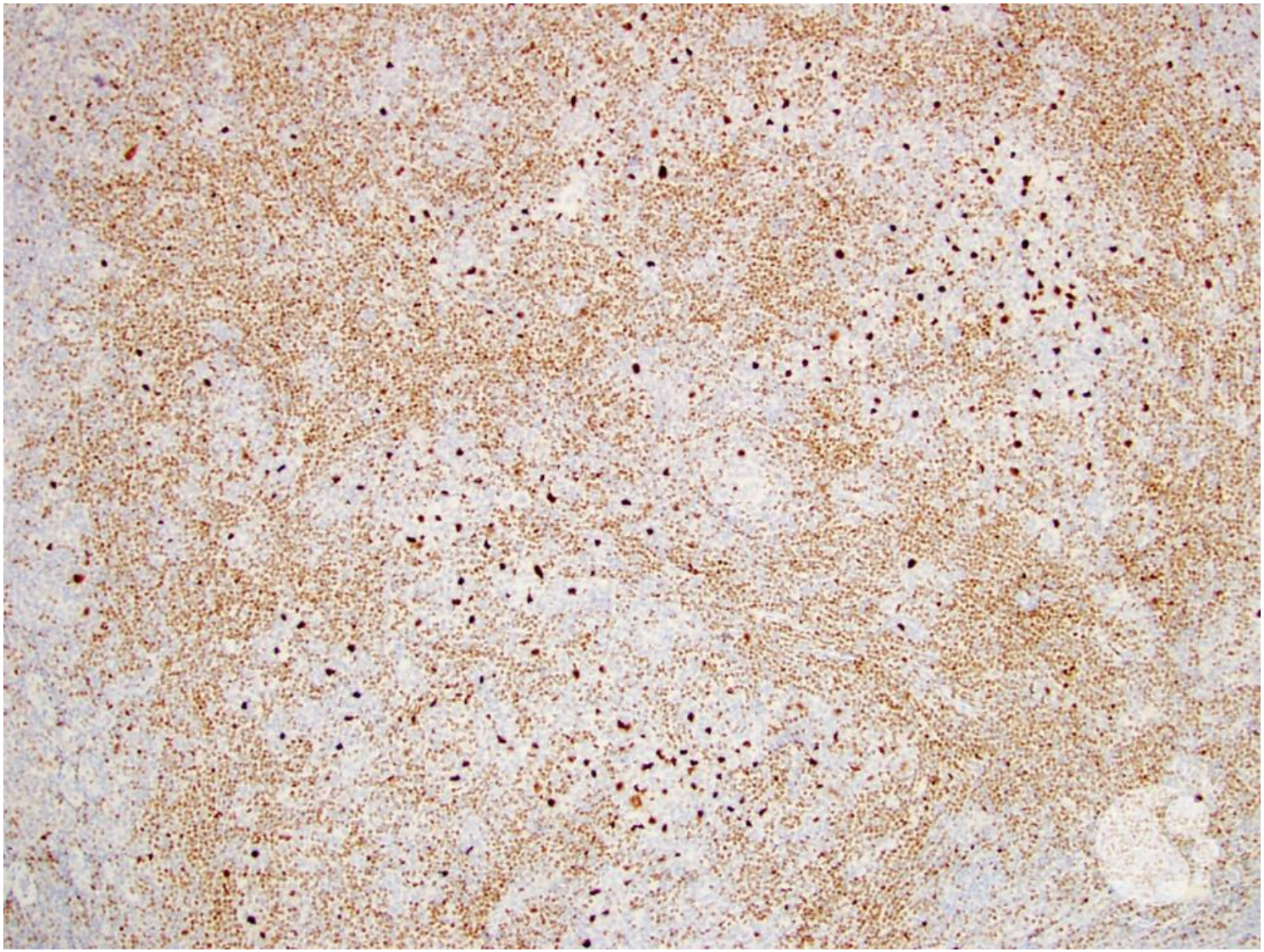
Nodular lymphocyte Predominant Hodgkin lymphoma 3



Nodular lymphocyte Predominant Hodgkin lymphoma 2



Nodular lymphocyte Predominant Hodgkin lymphoma 1



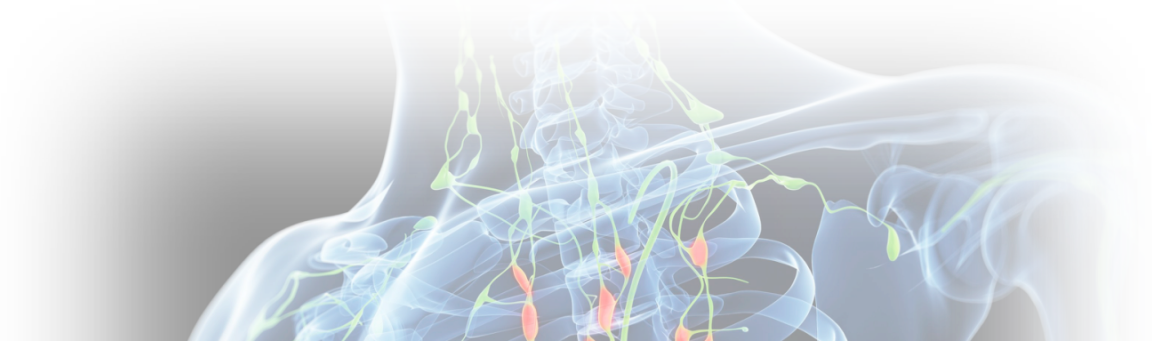


Table 3. NCCN and ESMO guidelines for NLPHL

	Stage					
Guideline	**IA, no risk factors[40]**	**IB**	**IIA**	**IIB**	**III/IV A**	**III/IV B**
NCCN guidelines, version 2.2013[39] (all category 2A unless otherwise indicated)	Observe* or ISRT	CHT ± rituximab ± ISRT	Observe or ISRT	CHT ± rituximab ± ISRT	CHT ± rituximab ± RT or observation† or local RT‡	CHT ± rituximab ± RT
ESMO[40]	IFRT	CHT ± IFRT	CHT ± IFRT	CHT ± IFRT	CHT	CHT

CHT, chemotherapy (for details see reference).
*Option for completely excised solitary lymph node
†Category 2B
‡Palliation only

Risk factors for transformation and recurrent NLPHL in advanced-stage NLPHL

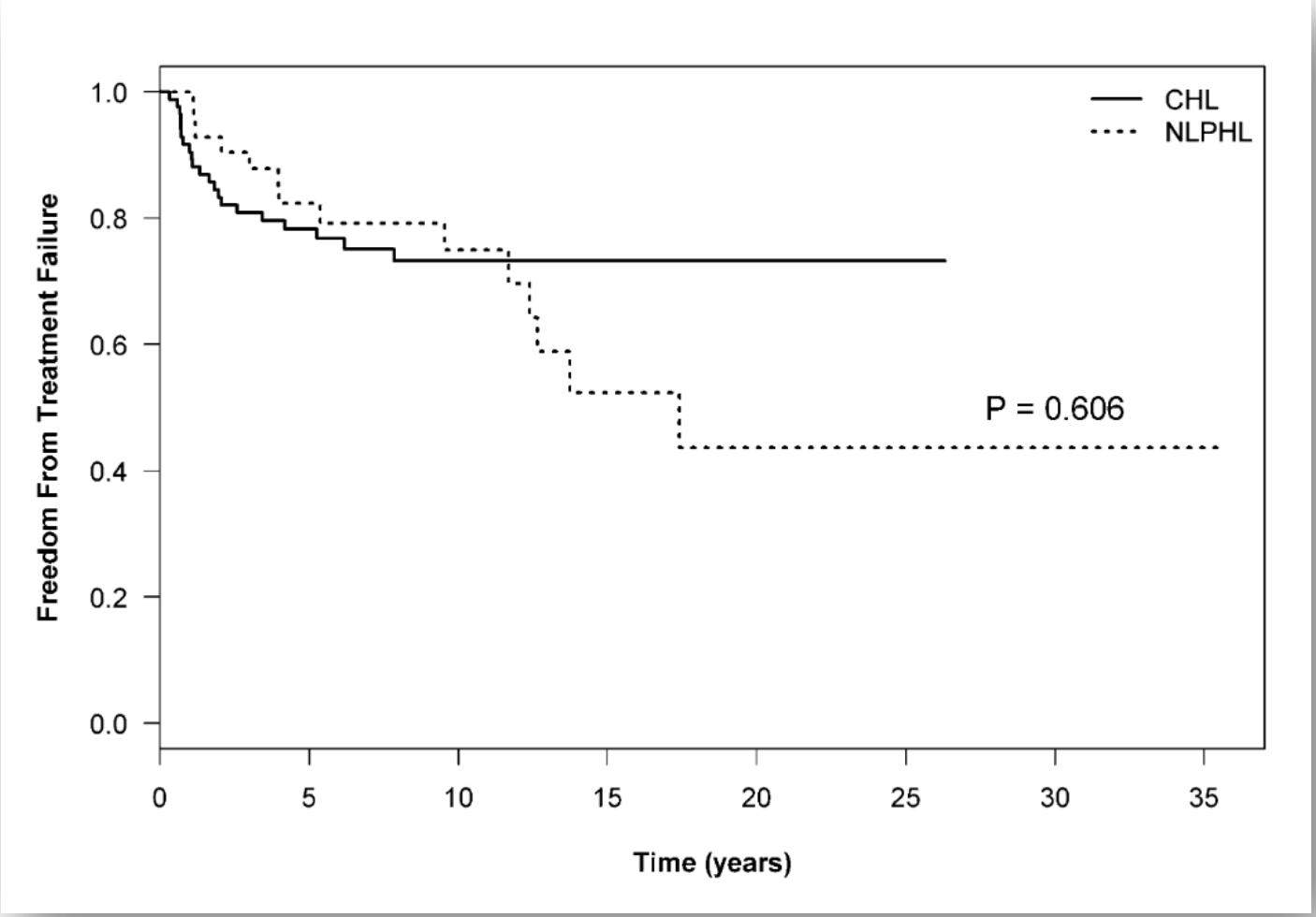
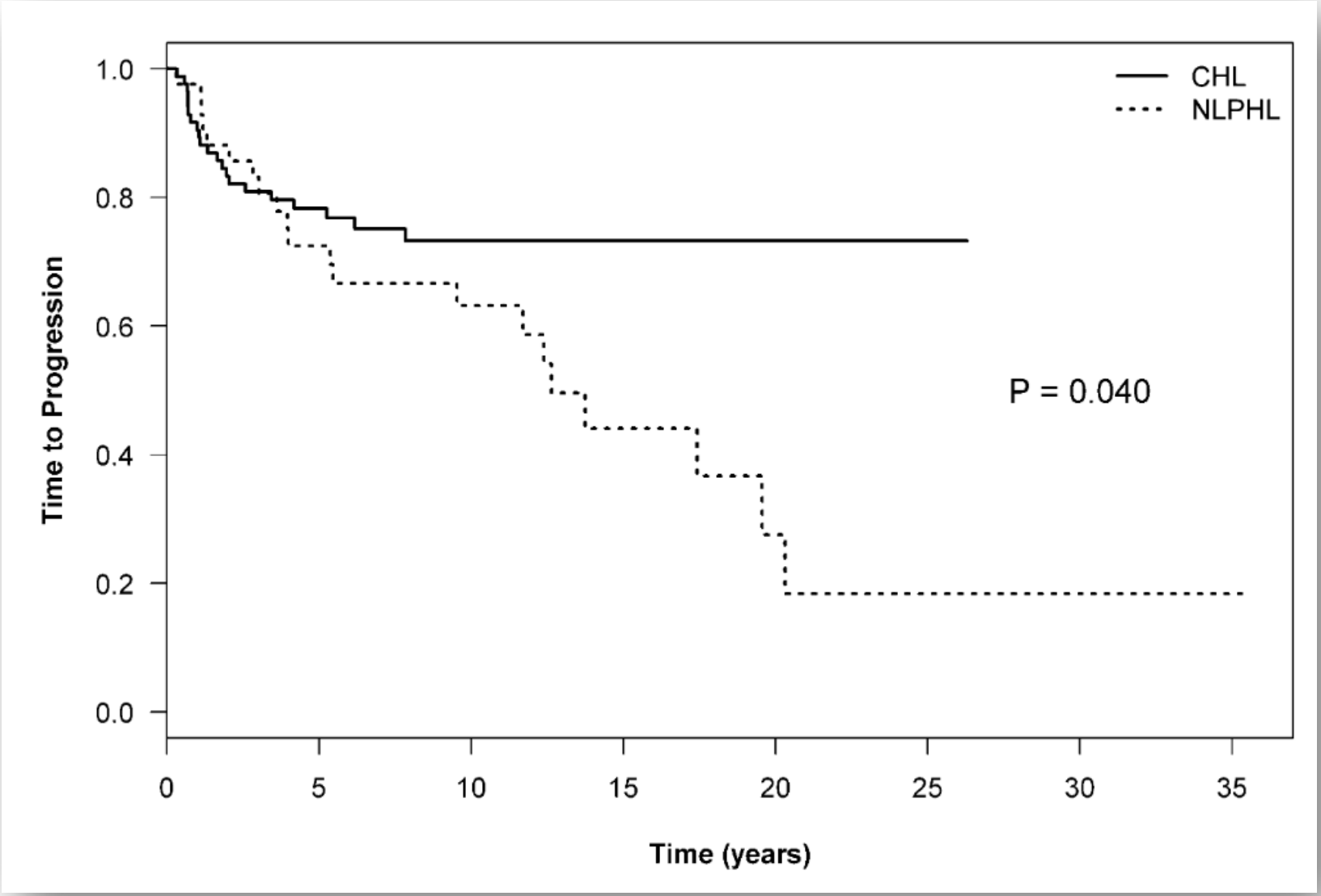


Table 2. Outcome of patients with advanced-stage NLPHL compared with matched controls with advanced-stage CHL

		Survival (%)			
	HL subtype	5-Year	10-Year	15-Year	*P*
HL-FFTF	NLPHL	82	75	52	.610
	CHL	78	73	73	
TTP	NLPHL	72	63	44	.040
	CHL	78	73	73	
OS	NLPHL	89	83.5	74	.826
	CHL	91	81	68	
TTT	NLPHL	12	15	24	.00018
	CHL	0	0	0	

TTT, time to transformation.

TTP in NLPHL vs CHL



Overall Survival in NLPHL vs CHL

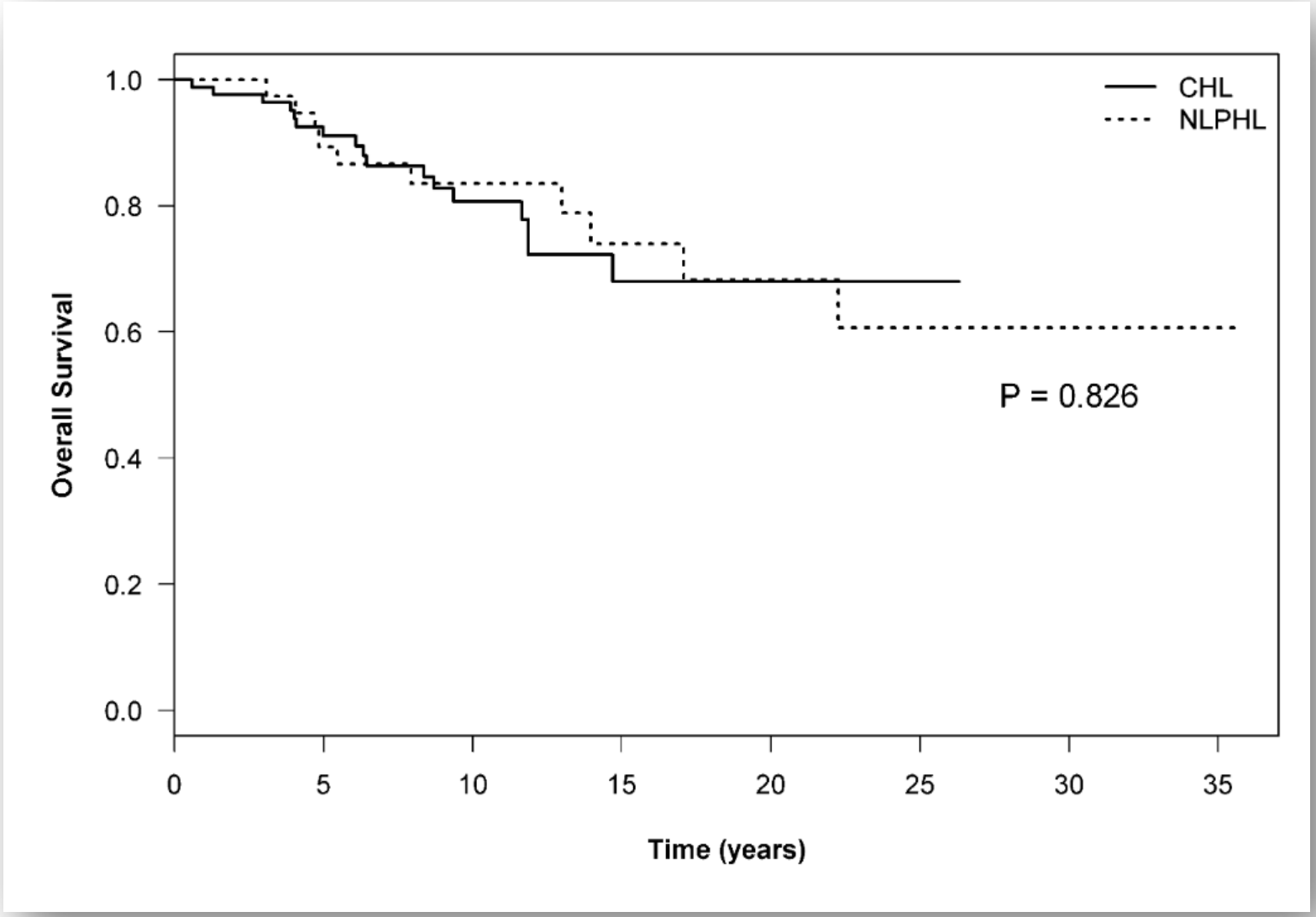
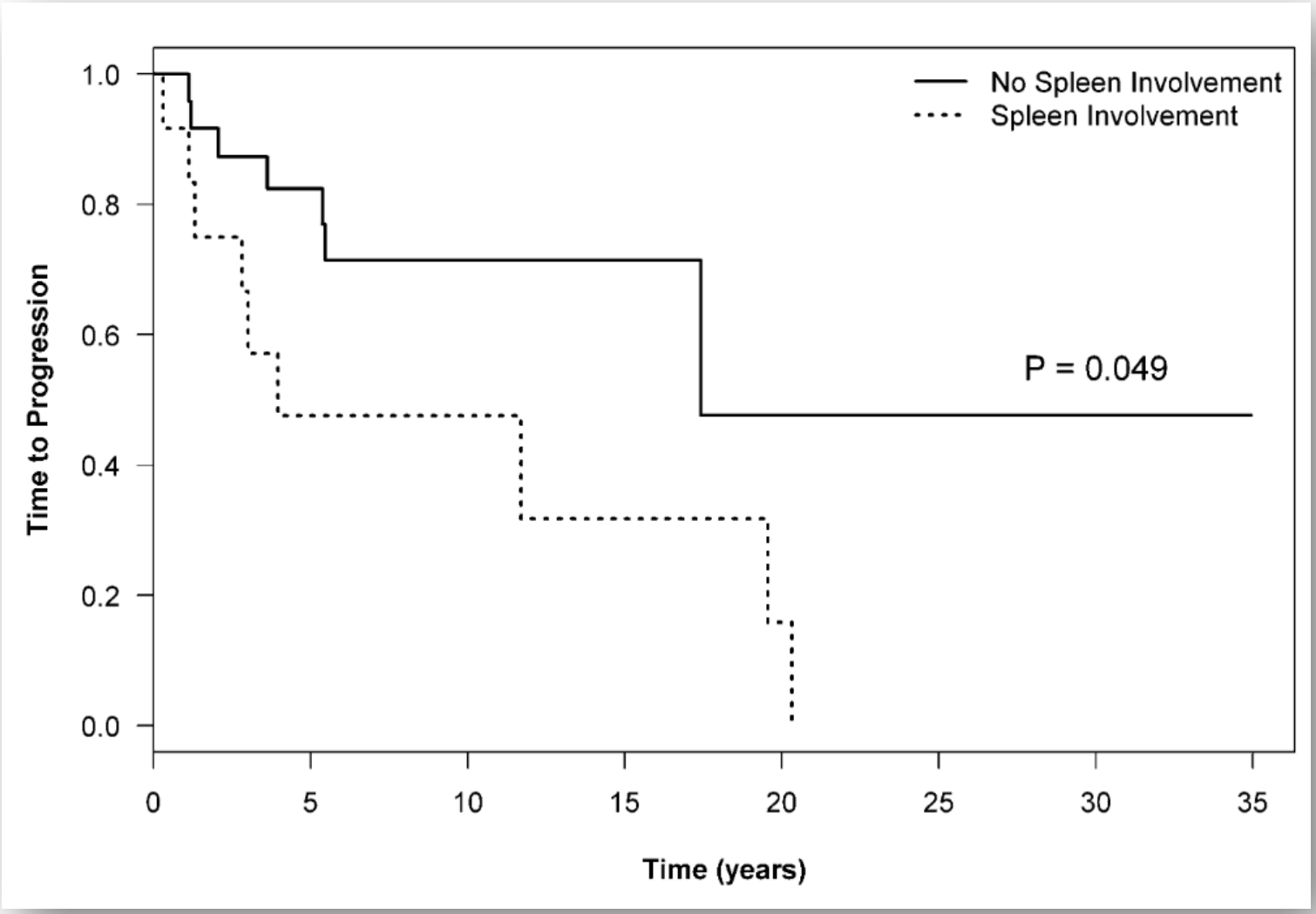


Table 3. Cause of death in NLPHL and CHL patients

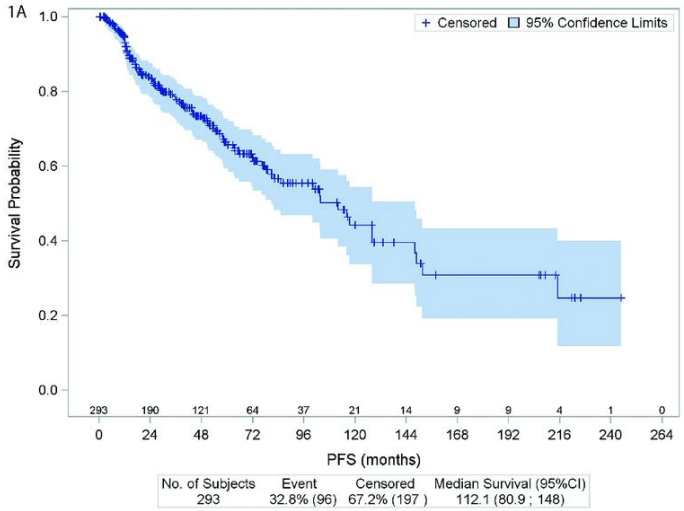
	NLPHL (n = 10)		CHL (n = 17)	
Cause of death	**No.**	**%**	**No.**	**%**
HL	1	10	8	47
Aggressive NHL	4	40	0	
Secondary cancers	1	10	3	18
Cardiac	4	40	6	35

TTP in patients treated with ABVD by splenic involvement at diagnosis of NLPHL



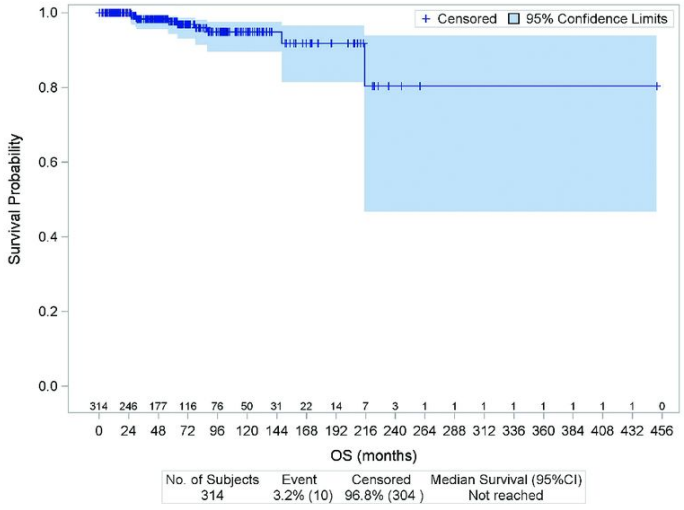
Kaplan-Meier estimates for progression-free survival

1A



No. of Subjects	Event	Censored	Median Survival (95%CI)
293	32.8% (96)	67.2% (197)	112.1 (80.9 ; 148)

1B



No. of Subjects	Event	Censored	Median Survival (95%CI)
314	3.2% (10)	96.8% (304)	Not reached

Julien Lazarovici et al. Haematologica 2015;100:1579-1586

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Journal of the European Hematology Association
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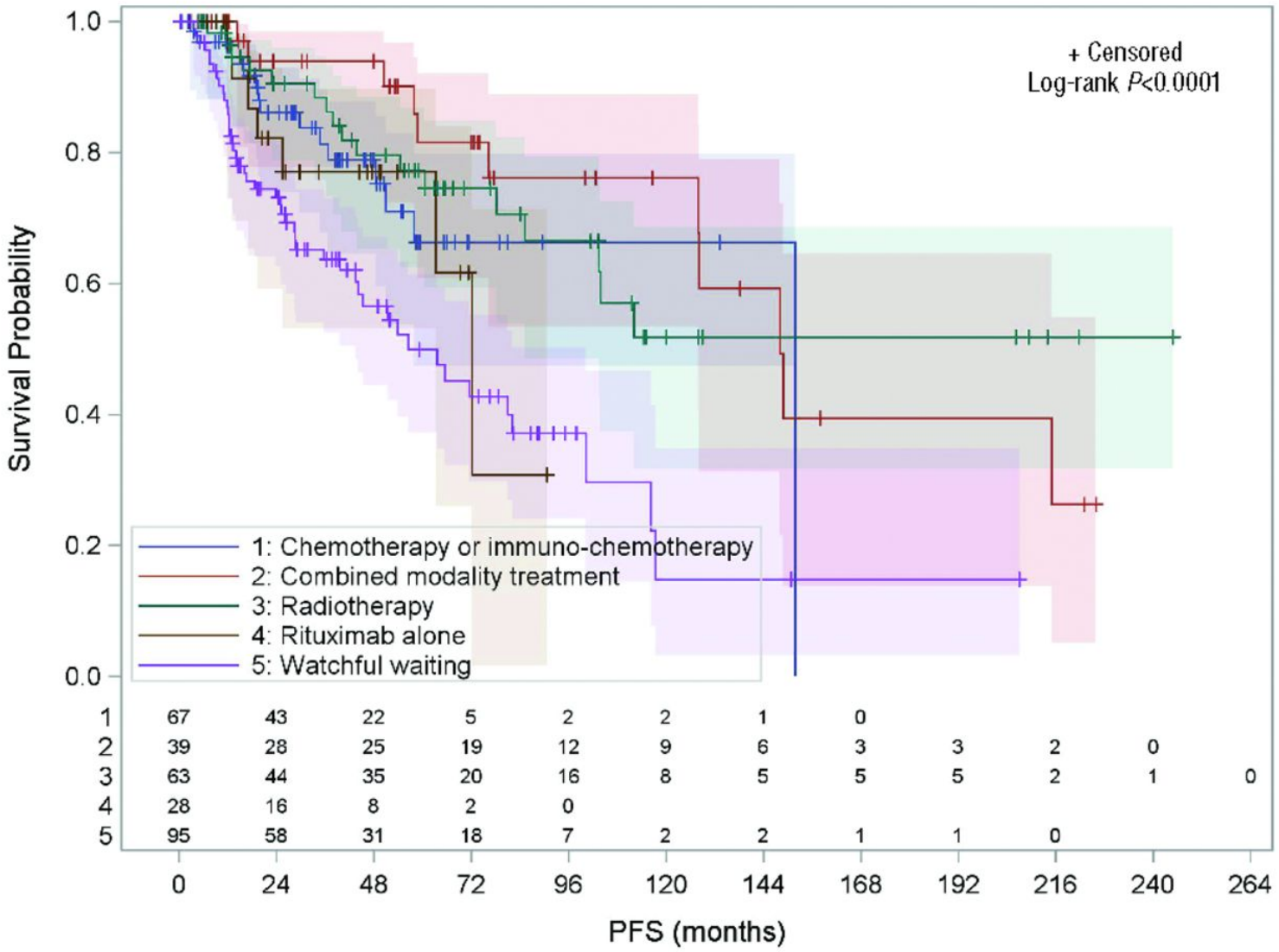
Progression-free survival by management at diagnosis



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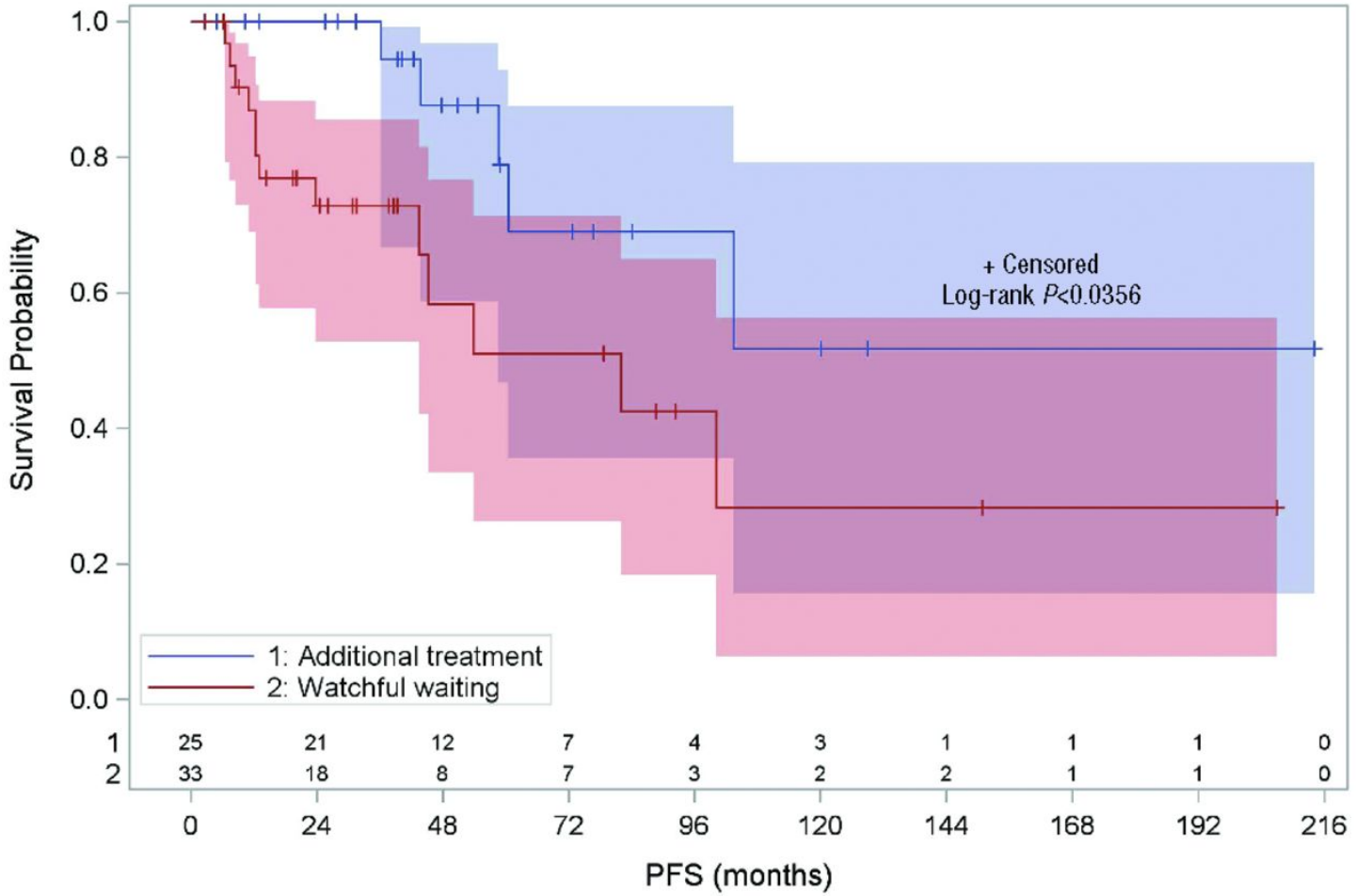
Progression-free survival of 58 patients after complete surgical resection



	No. of Subjects	Event	Censored	Median Survival (95%CI)
Additional treatment	25	20% (5)	80% (20)	Not reached
Watchful waiting	33	39.4% (13)	60.6% (20)	82 (43.5 ; NA)

Julien Lazarovici et al. Haematologica 2015;100:1579-1586

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Management of patients at diagnosis

Table 2.

Management of patients at diagnosis and first relapse/progression.

Management of patients at diagnosis	Stage I-II	Stage III-IV		Total
Watchful waiting	104	10		114 (36.3%)
Radiotherapy[1]	62	1		63 (20.1%)
Rituximab alone	24	4		28 (8.9%)
Chemotherapy or immuno-chemotherapy[2]	36	32		68 (21.7%)
Combined modality treatment[3]	33	7		40 (12.7%)
Radiotherapy plus rituximab	0	1		1 (0.3%)
Management at first relapse/progression	**Stage I-II**	**Stage III-IV**	**Stage unknown**	**Total**
Watchful waiting	13	4	2	19 (17.0%)
Radiotherapy	19	0	8	27 (24.1%)
Rituximab alone	13	3	3	19 (17.0%)
Chemotherapy or immuno-chemotherapy[4]	11	19	7	37 (33.0%)
Combined modality treatment[5]	4	1	2	7 (6.2%)
Radiotherapy plus rituximab	1	0	1	2 (1.8%)
Management unspecified	1	0	0	1 (0.9%)

[1]Radiotherapy doses: 43 patients (68.2%) received 30 to 36 Gy, 7 patients (11.1%) 38 to 40 Gy, 2 patients (3.2%) 20 Gy, 3 patients (4.8%) 4 Gy. The dose of radiotherapy was unknown for 8 patients (12.7%). [2]Chemotherapy (47), immuno-chemotherapy (61), including ABVD or ABVD-like regimens (76), BEACOPP (1), CHOP or CHOP-like regimens (18, all treated without radiotherapy), CVP (7), other regimens (2), unspecified (4). [4]Chemotherapy alone (13), chemotherapy + rituximab (31). Chemotherapy included: ABVD or ABVD-like (14), BEACOPP (1), CHOP (15), ACVBP (5), MINE (2), DHAP or DHA-carboplatin (2), ICE (1), CVP (1), other regimens (2), unspecified (1). ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; MOPP: mechlorethamine, vincristine, procarbazine, prednisone; DHAP: dexamethasone, cytarabine, cisplatin; ICE: ifosfamide, carboplatin, etoposide.

Table 3.

Response to initial and second-line treatments.

Response to initial treatment (evaluable patients, n=200)	CR/CRu	PR	SD	Progression	Unknown
All	166	10	2	5	17
Radiotherapy	54	1	1	1	6
Rituximab alone	24	3	0	0	1
Chemotherapy or immuno-chemotherapy	55	5	1	2	5
Combined modality treatment	32	1	0	2	5
Radiotherapy plus rituximab	1	0	0	0	0
Response to second-line treatment (evaluable patients, n=92)	**CR/CRu**	**PR**	**SD**	**Progression**	**Unknown**
All	66	10	2	2	12
Radiotherapy	19	3	1	0	4
Rituximab alone	12	5	0	0	2
Chemotherapy or immuno-chemotherapy	27	2	1	2	5
Combined modality treatment	6	0	0	0	1
Radiotherapy plus rituximab	2	0	0	0	0

Risk of progression in NLPHL patients

Table 4.

Risk of progression after initial treatment.

	Hazard ratio	95% CI	P
Radiotherapy	0.345	0.196-0.610	0.0002
Rituximab alone	0.629	0.283-1.399	0.256
Chemotherapy or immuno-chemotherapy	0.476	0.266-0.855	0.0129
Combined modality treatment	0.292	0.148-0.577	0.0004

Hazard ratios are calculated with watchful waiting taken as a reference.

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