EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Self-assessment Case 2 – Session 7

Speaker: Dr Santosh Kumar C

Hyderabad, India
March 1-3, 2024

Introduction

- A 21 year old male
- Medical student
- Complaints
  - Dry cough
  - Breathlessness on bending forward/supine position
  - Progressively increasing swelling over his face
  - for 2 months

- No significant past history.

Before

After

Clinical Examination

- No palpable lymphadenopathy, no organomegaly
- Engorged neck veins
- Congested conjunctiva

Laboratory Investigations

- Blood count showed
  - WBC 9.7 x 10^9/l, Neutrophils – 68% , Lymphocytes – 32%
  - RBC 3.97 x 10^{12}/l
  - Hb 121 g/L
  - Hct 0.39
  - MCV 85 fl
  - MCH 30 pg
  - MCHC 33 g/l
  - Platelet count 351 x 10^9/l

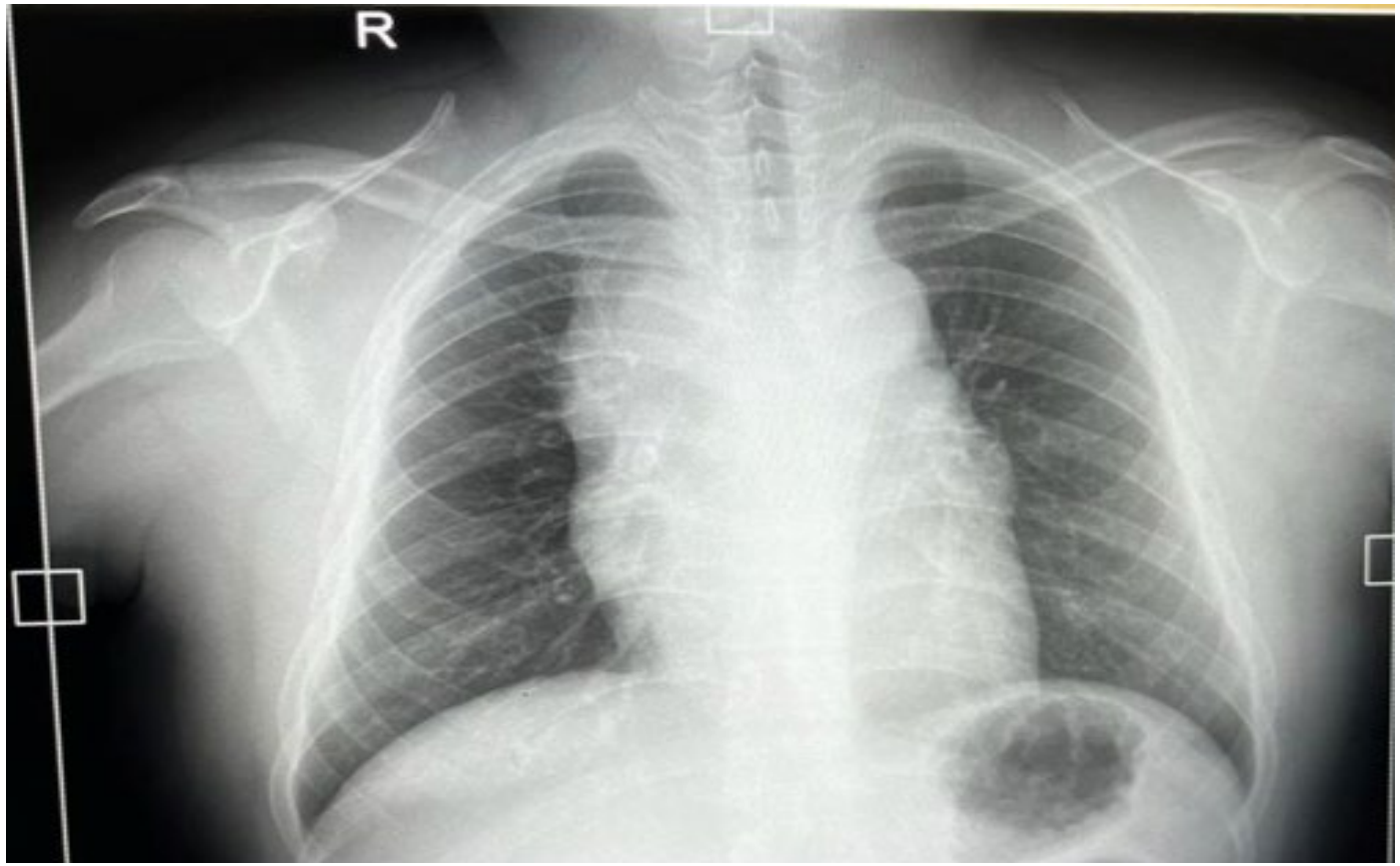
❖ Peripheral blood film examination showed no abnormal findings.

❖ Tumour markers

❖ LFT, RFT : NORMAL

❖ LDH – 761 U/L (<248)

Chest X RAY PA VIEW



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For each question you have 15 seconds.

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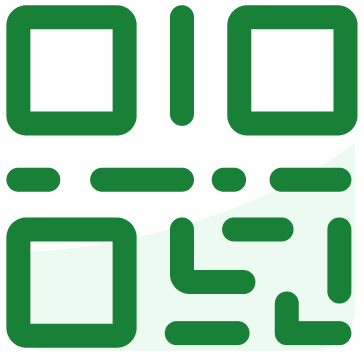

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Q1) Which of these diagnoses is least likely?

1. Acute Leukaemia
2. Lymphoma
3. Angioedema
4. Thymoma
5. Germ cell tumour

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7.41 Which of these diagnoses is least likely?

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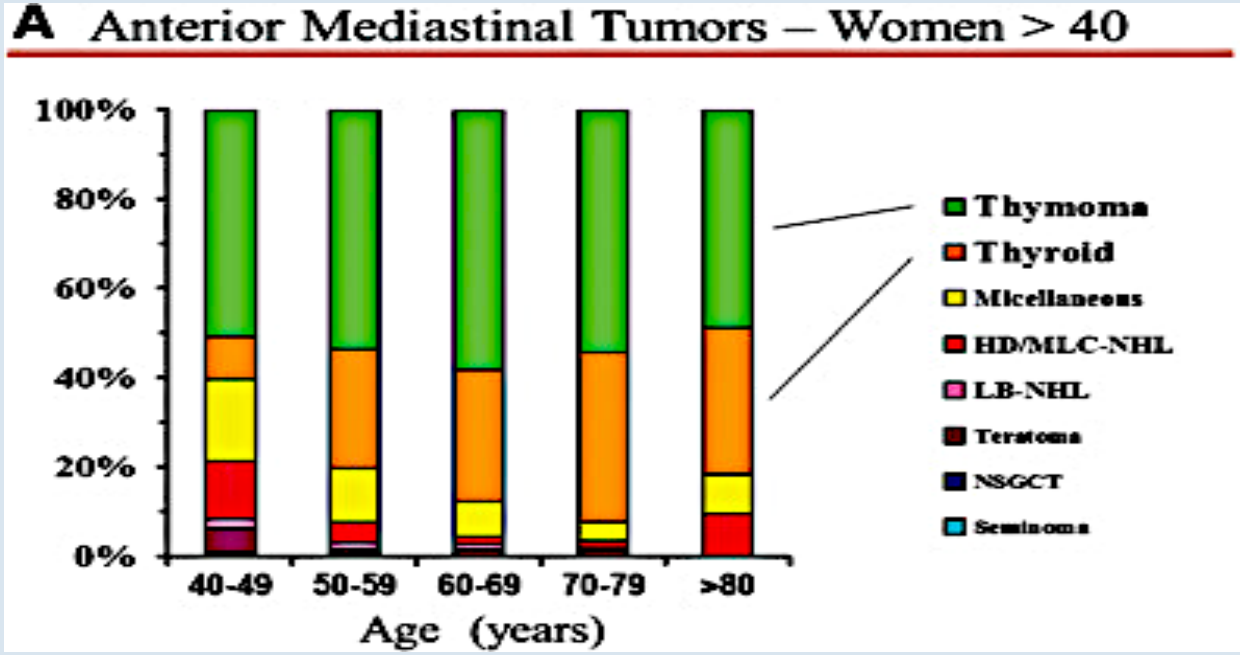
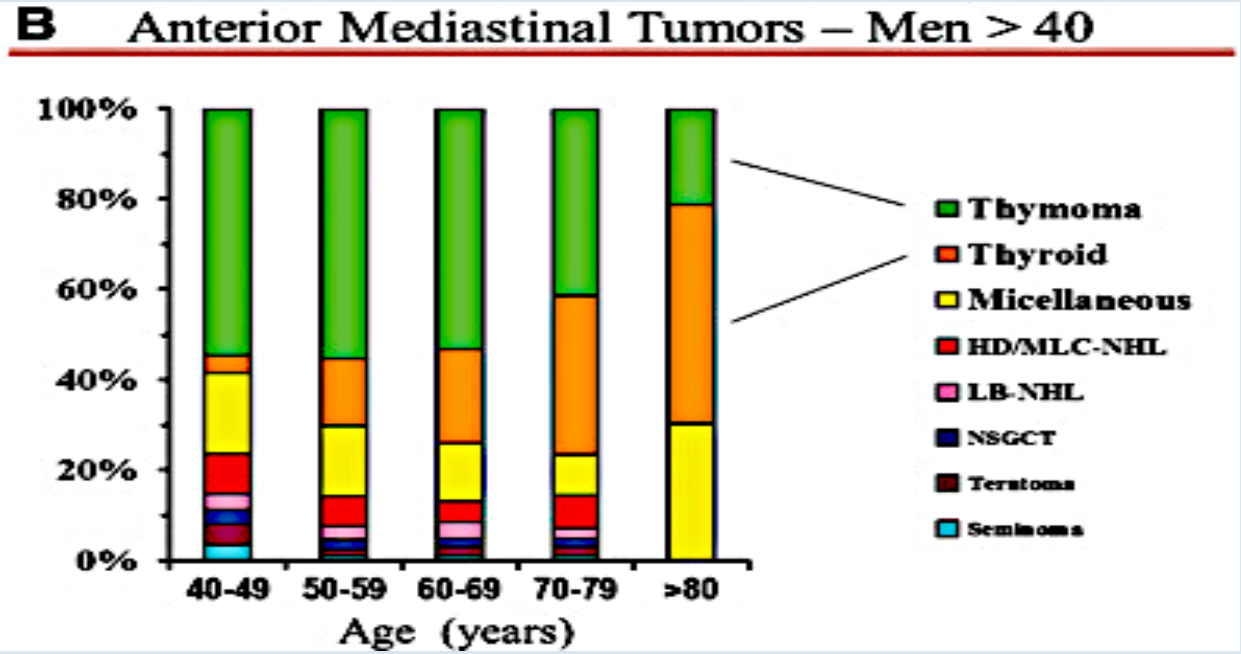
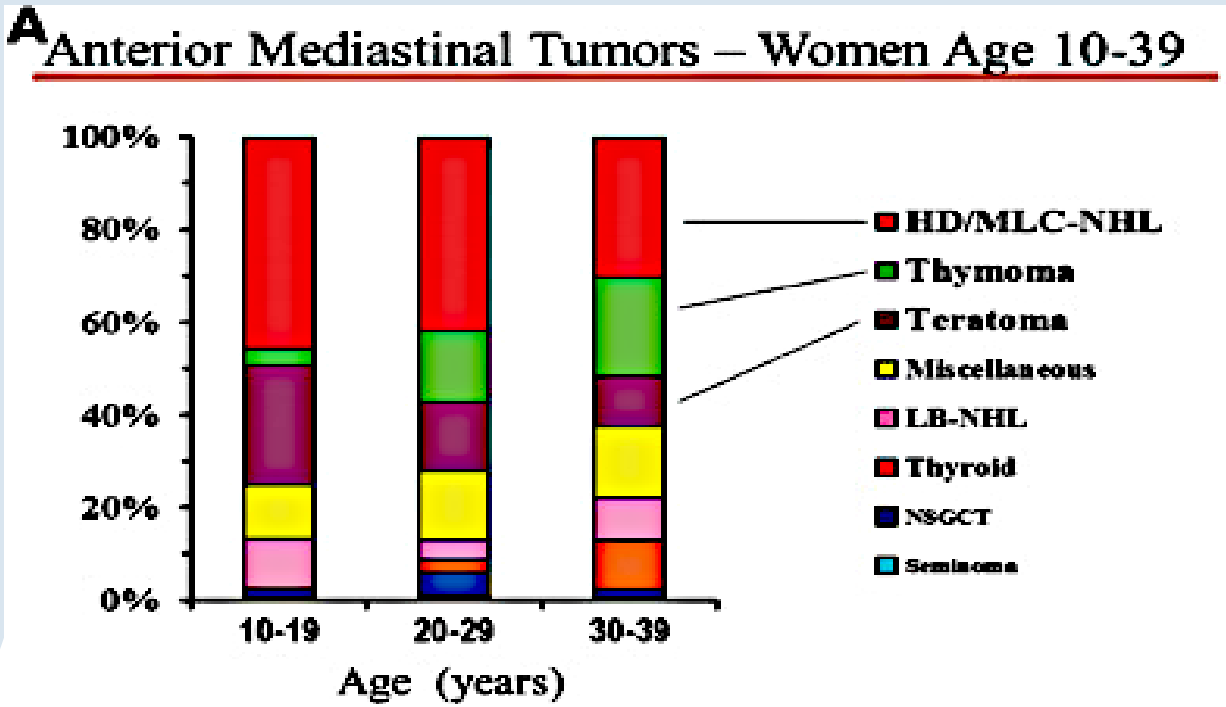
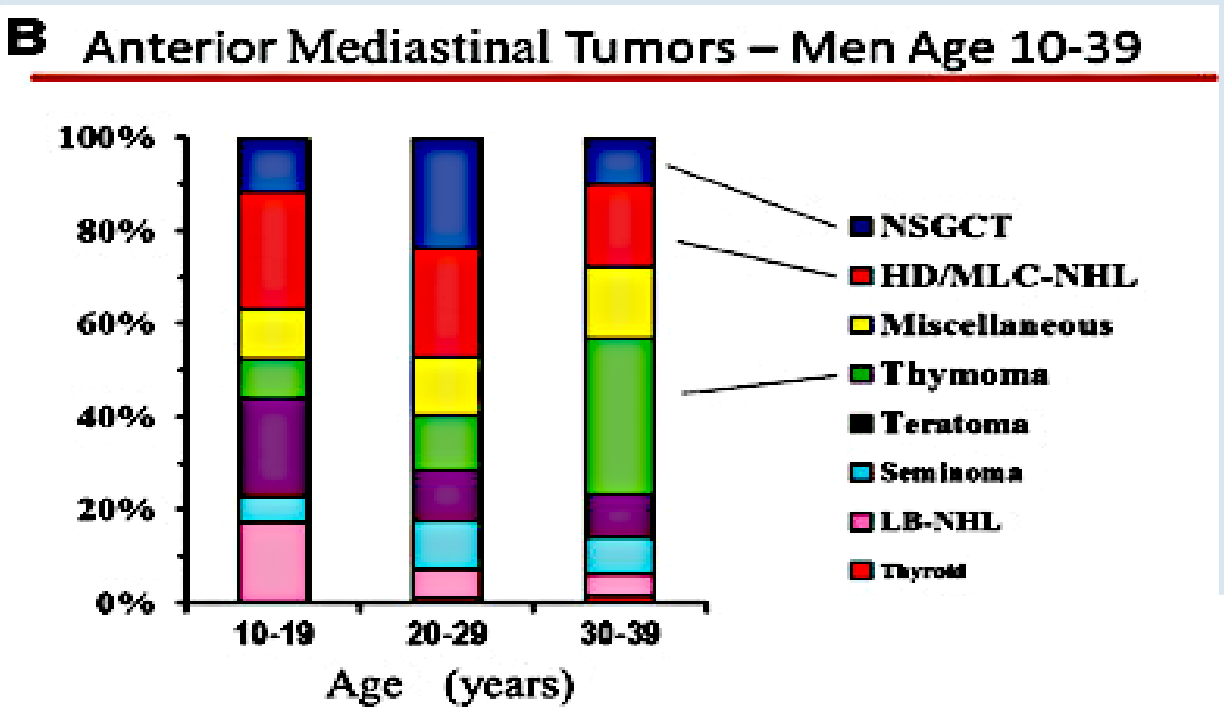

A Anterior Mediastinal Tumors – Women > 40
100%
80%
60%
40%
20%
0%
40-49
50-59
60-69
70-79
>80
Age (years)
Thymoma
Thyroid
Micellaneous
HD/MLC-NHL
LB-NHL
Teratoma
NSGCT
Seminoma


B Anterior Mediastinal Tumors – Men > 40
100%
80%
60%
40%
20%
0%
40-49
50-59
60-69
70-79
>80
Age (years)
Thymoma
Thyroid
Micellaneous
HD/MLC-NHL
LB-NHL
NSGCT
Teratoma
Seminoma


A Anterior Mediastinal Tumors – Women Age 10-39
100%
80%
60%
40%
20%
0%
10-19
20-29
30-39
Age (years)
HD/MLC-NHL
Thymoma
Teratoma
Miscellaneous
LB-NHL
Thyroid
NSGCT
Seminoma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100%
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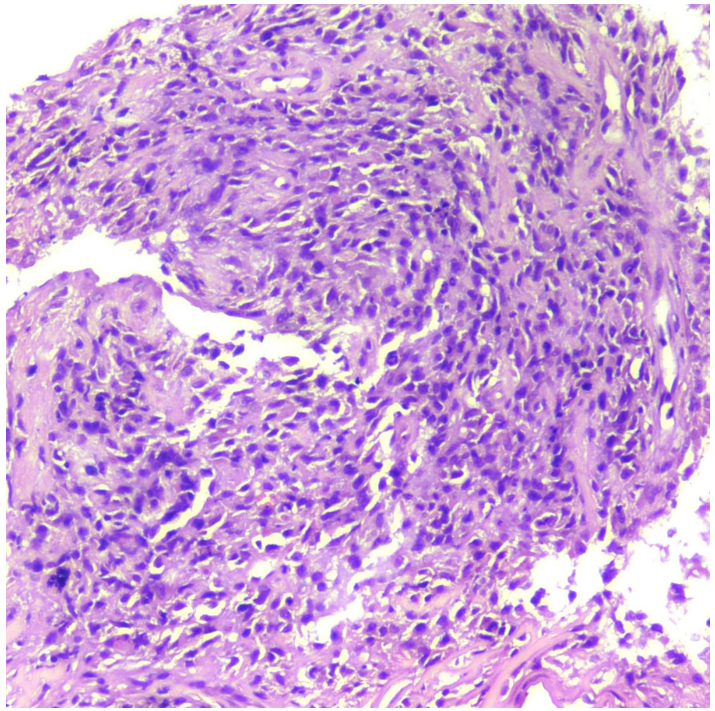
40%
20%
0%
10-19
20-29
30-39
Age (years)
NSGCT
HD/MLC-NHL
Miscellaneous
Thymoma
Teratoma
Seminoma
LB-NHL
Thyroid

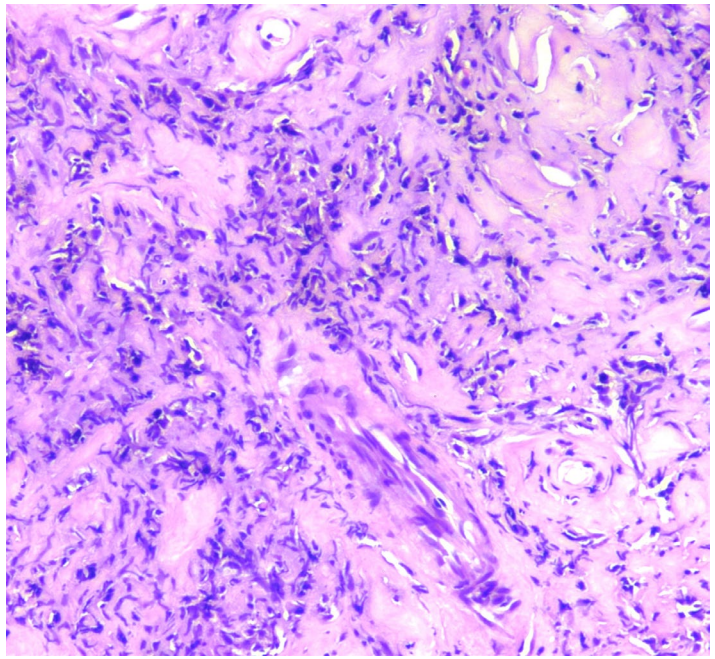
- CT scan guided biopsy from mediastinal mass was done for histopathology and immunohistochemistry evaluation.

Histopathology

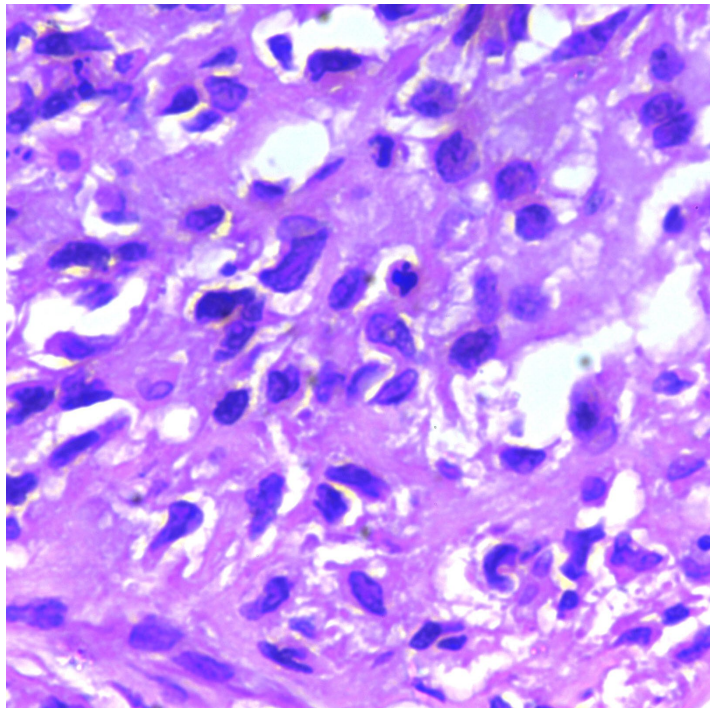
Intermediate to large atypical cells



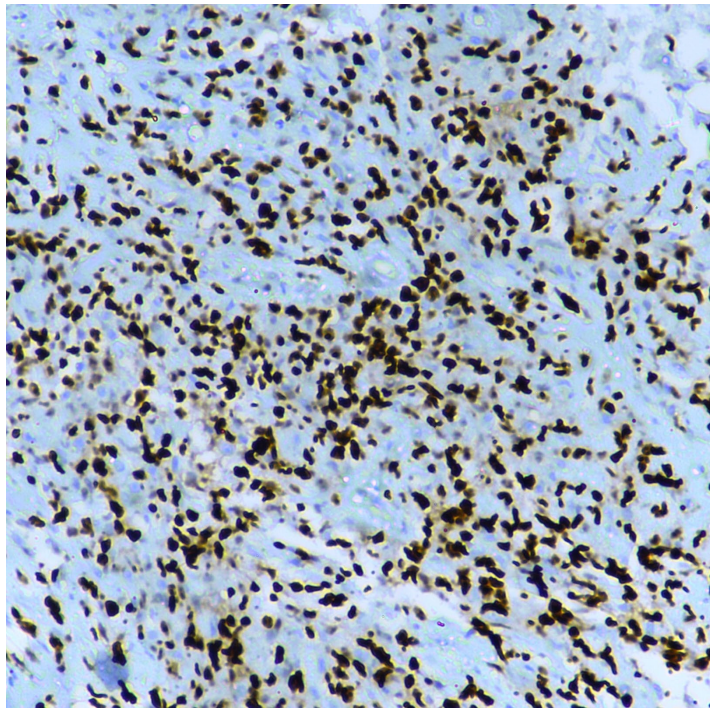
Large atypical cells amidst dense fibrosis



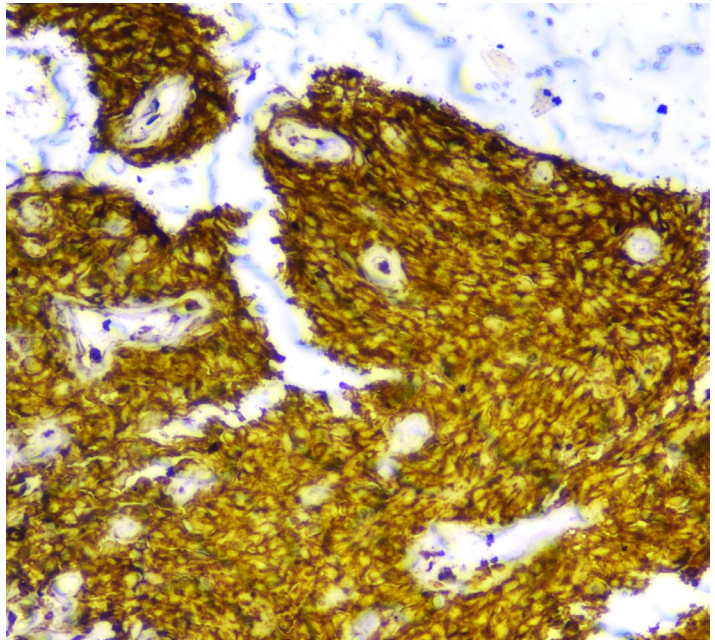
Mitotic activity



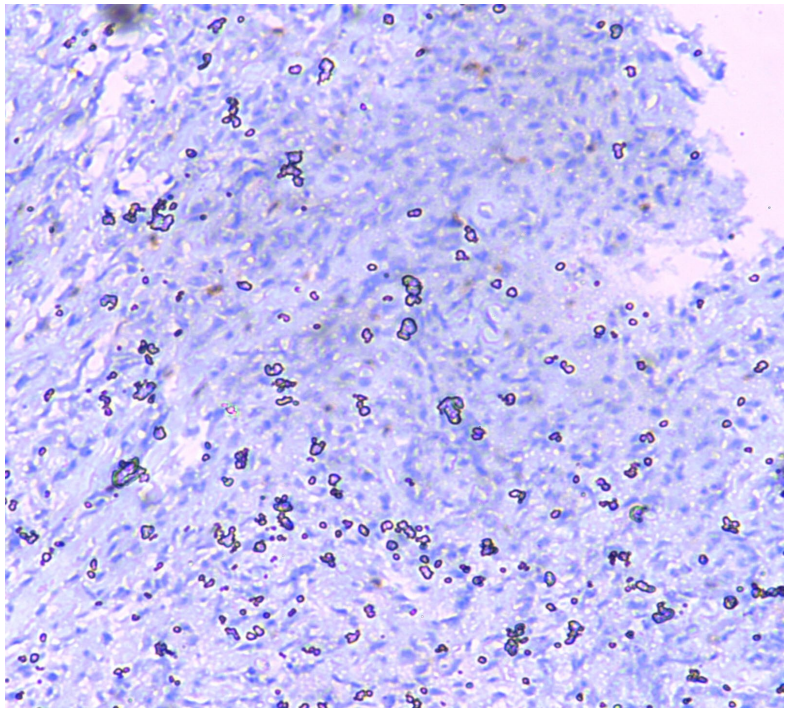
Ki 67 -70 %



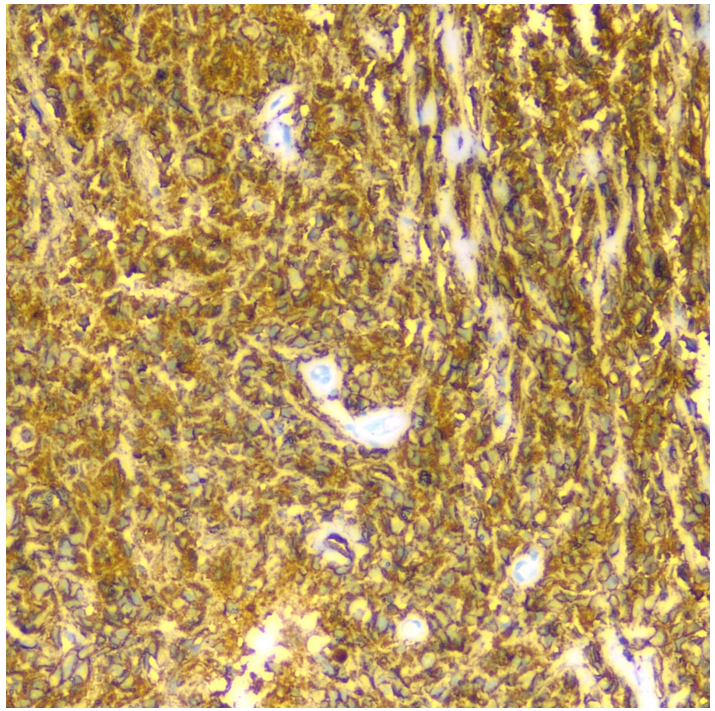
LCA +ve



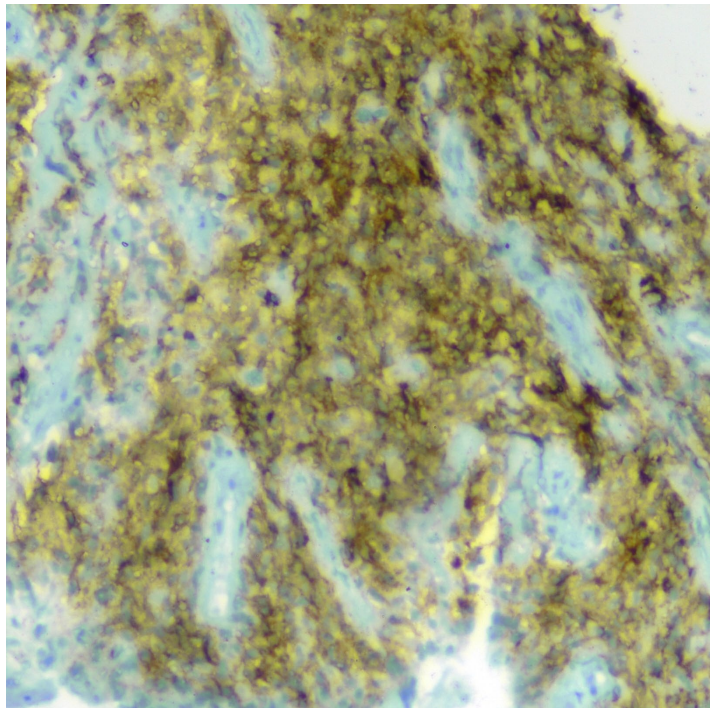
CD 3 -ve



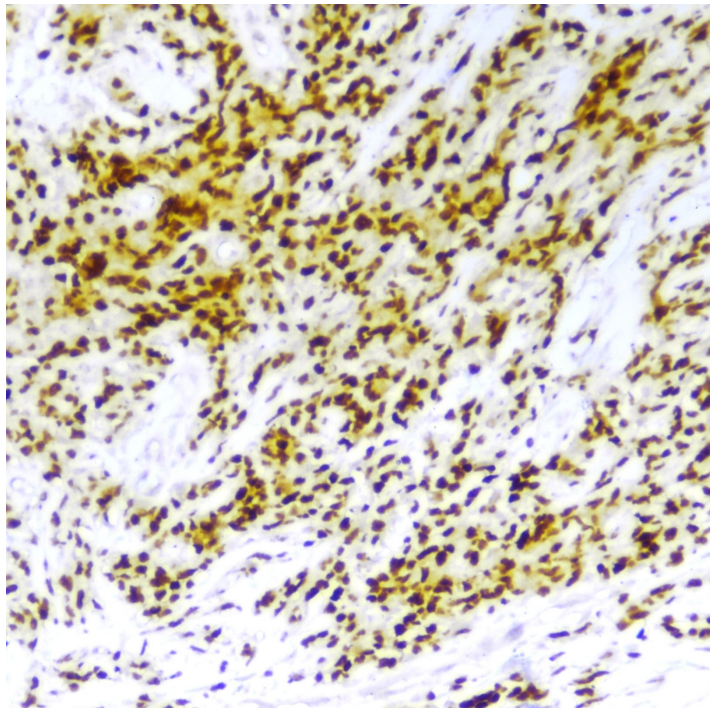
CD 20 positive



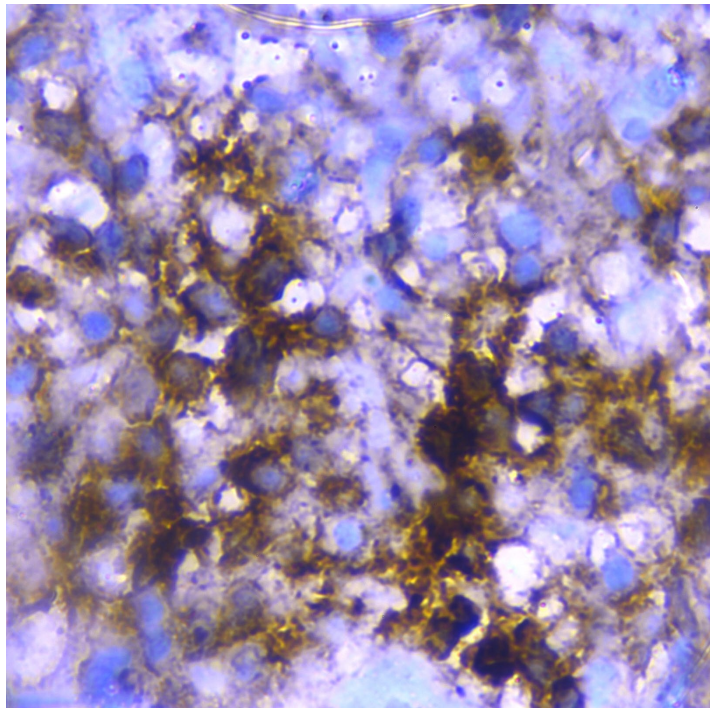
CD 23 positive



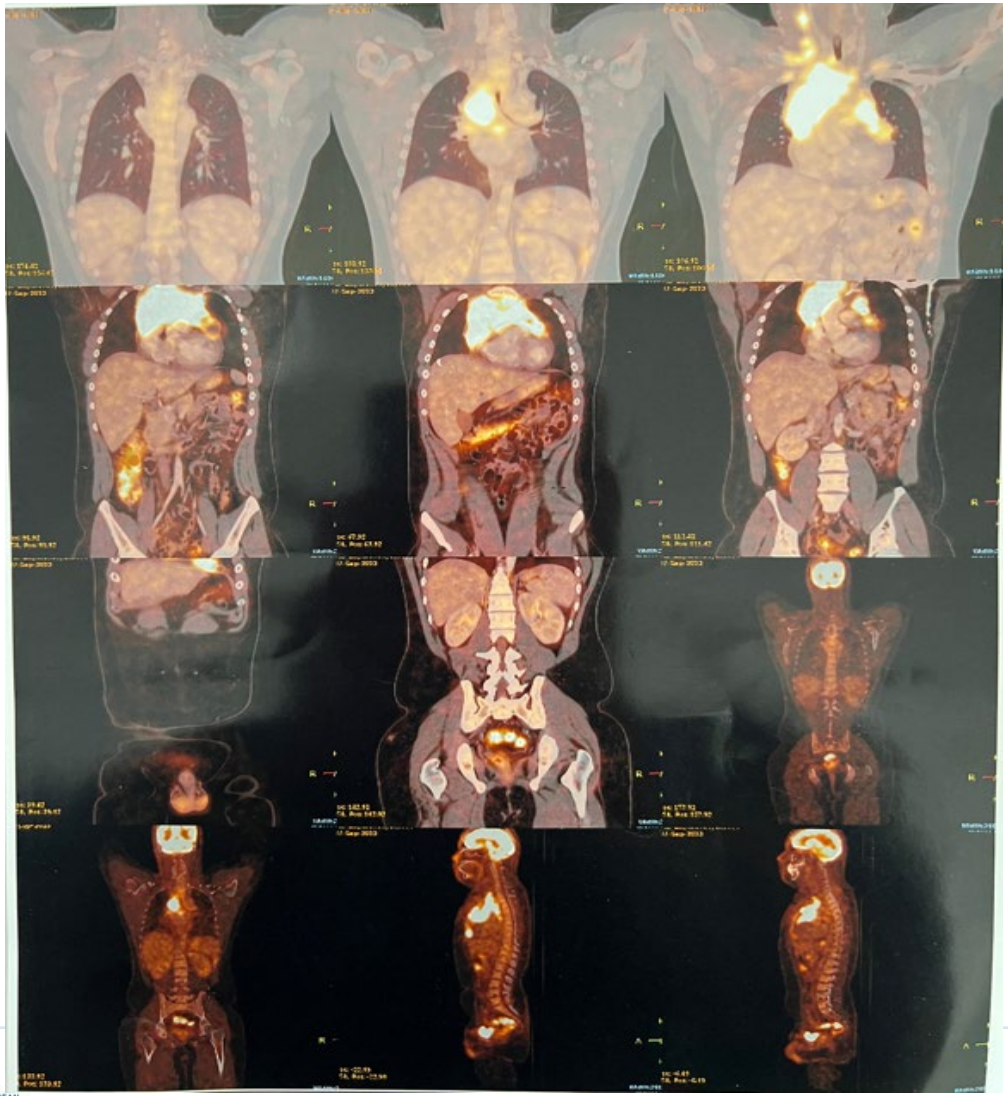
PAX 5 positive

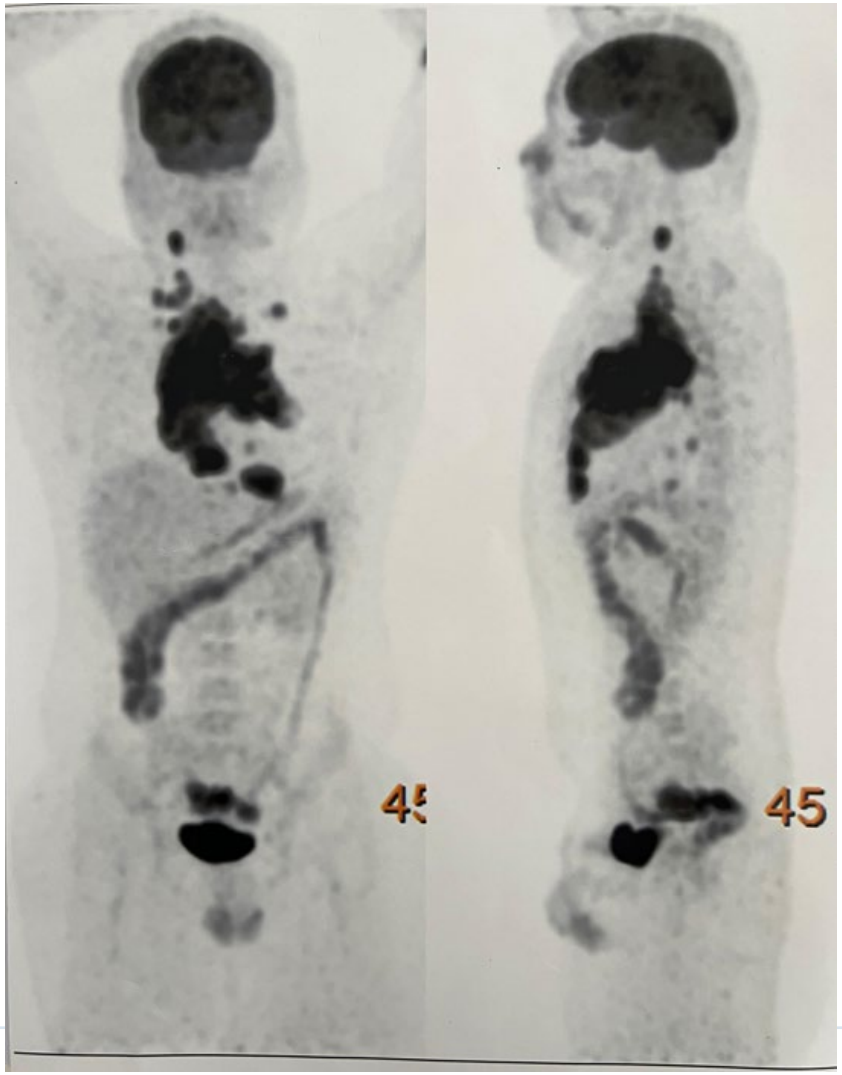


PDL1 positive



PET CT Scan whole body





Q2) What is the diagnosis?

1. Hodgkin Lymphoma
2. Diffuse large B Cell Lymphoma
3. Primary Mediastinal B Cell Lymphoma
4. Burkitt Lymphoma
5. Anaplastic large cell lymphoma

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7.42 What is the diagnosis?

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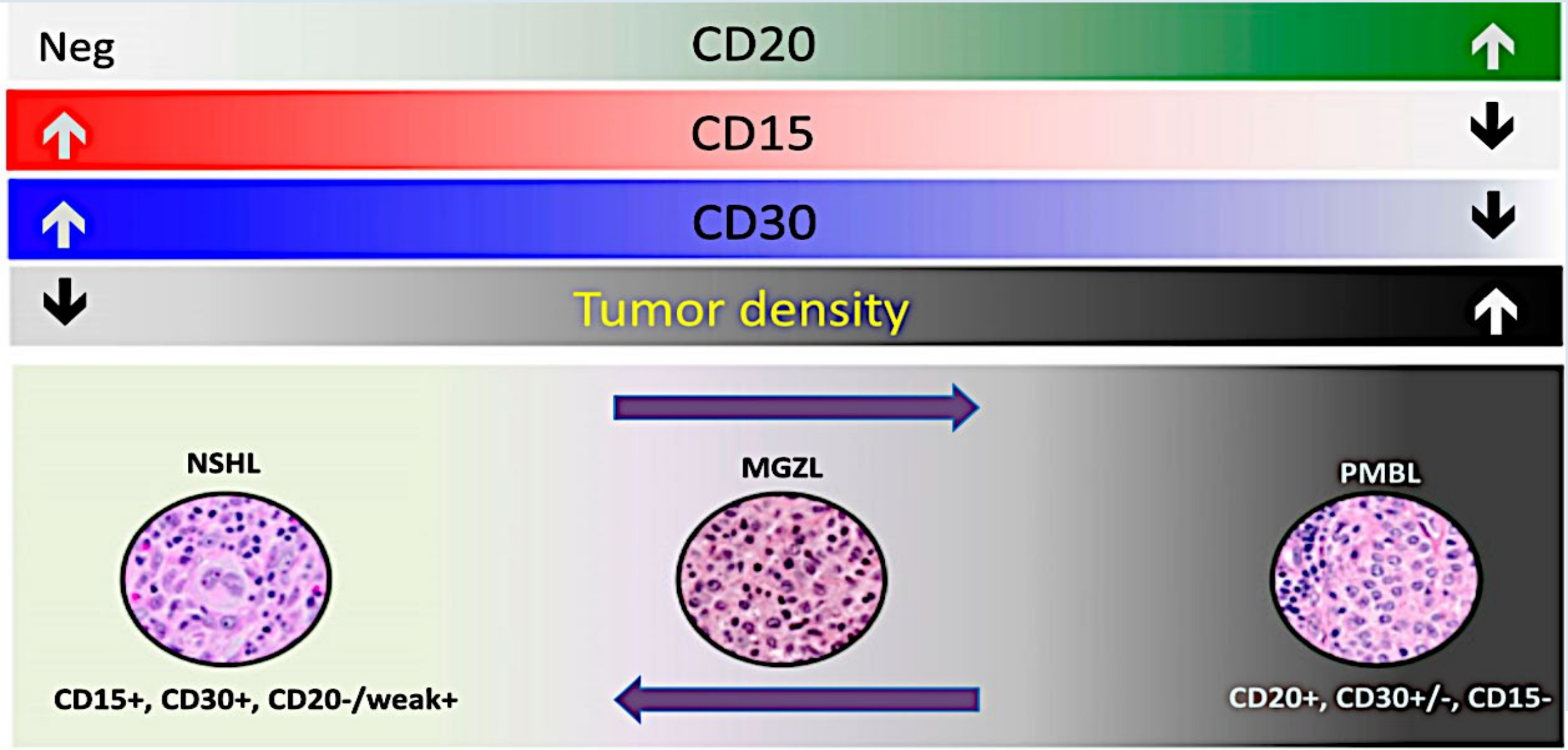
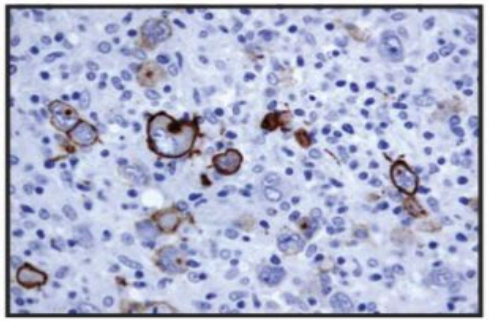
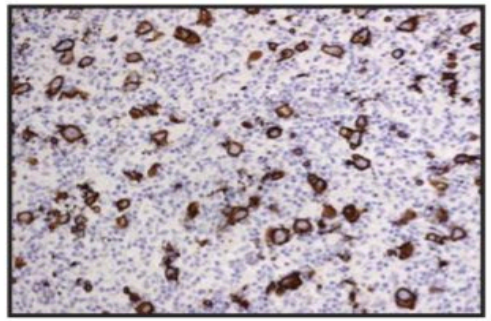
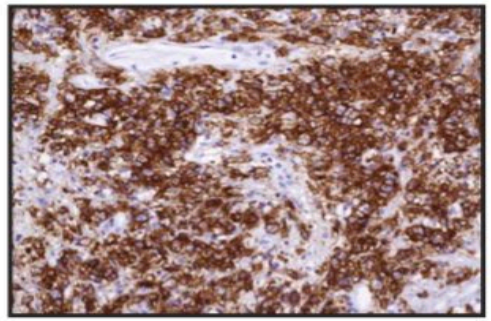
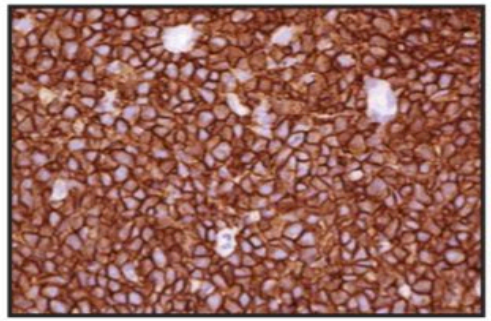
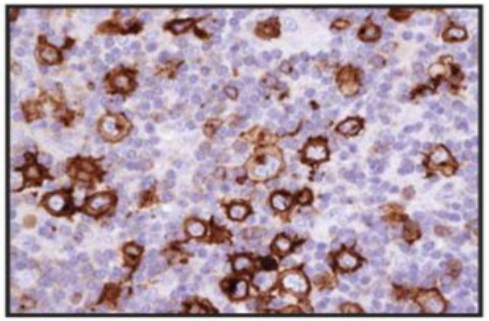
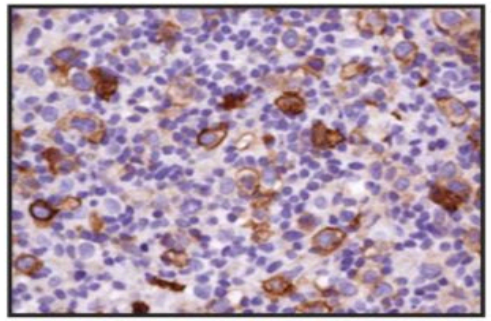
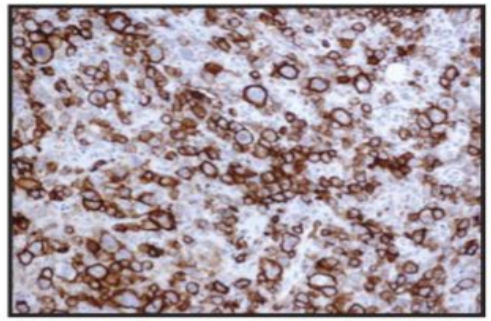
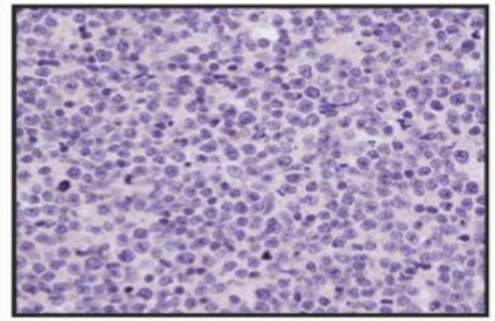
PMBCL Clinical presentation

- Third or fourth decade
- Female predominance 1.7-2 :1
- Anterior mediastinal mass with SVCS : 50 %
- With Pleural / pericardial effusion : 30 - 50 %
- 80% with stage I/II , 75% of cases are bulky
- Effusions are poor prognostic factor
- IPI Score : not representive
- Extra nodal disease : at the time of relapse

Features	PMBCL	cHL	DLBCL	MGZL
Female/male	3:1	1:1	1:1	1:3
Median age	35	28	55	35
Stage I-II	70-80%	55%	30%	70-80%
Mediastinal invol.	100%	80%	20%	80%
Extranodal sites	uncommon	uncommon	common	uncommn
Bone marrow	2%	3%	10-15%	3%
Elevated LDH	70-80%	rare	50%	70-80%
B symptoms	< 20%	40%	50%	40%
Bulky disease	70-80%	50%	10-15%	60-70%

Pathology


Neg
CD20
CD15
CD30
Tumor density
NSHL
MGZL
PMBL
CD15+, CD30+, CD20-/weak+
CD20+, CD30+/-, CD15-

	Nodular sclerosis Hodgkin's Lymphoma	Mediastinal grey zone lymphoma	PMBCL	DLBCL
Median age	30	30	35	65
Sex	Female	Male > Female	Female	Male ≥ Female
Typical manifestation	Supraclavicular LN / Mediastinal	Mediastinal	Mediastinum	Nodal
Bone marrow involvement	Uncommon	Rare	Rare	16 %
CD 20				
CD 30				

Q 3) Stage of PMBCL in this case?

1. Ann Arbor stage II
2. Lugano classification stage II
3. Locally advanced disease
4. All of the above
5. None of the above

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7.43 Stage of PMBCL in this case?

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Q 4)- Which is best possible treatment modality?

1. Chemotherapy
2. Chemoimmunotherapy
3. Chemoimmunotherapy ± Radiation
4. Radiation
5. None of the above

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7.44 Which is best possible treatment modality?

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Special considerations in management

- Young age
- Thrombosis
- Fertility
- Psychiatric
- Long term effects of Chemotherapy/Radiotherapy

Q 5)- Which is preferred chemoimmunotherapy regimen?

1. DA- EPOCH R
2. R CHOP
3. Hyper CVAD + R
4. R-V/MACOPB
5. R DHAP

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7.45 Which is preferred chemoimmunotherapy regimen?

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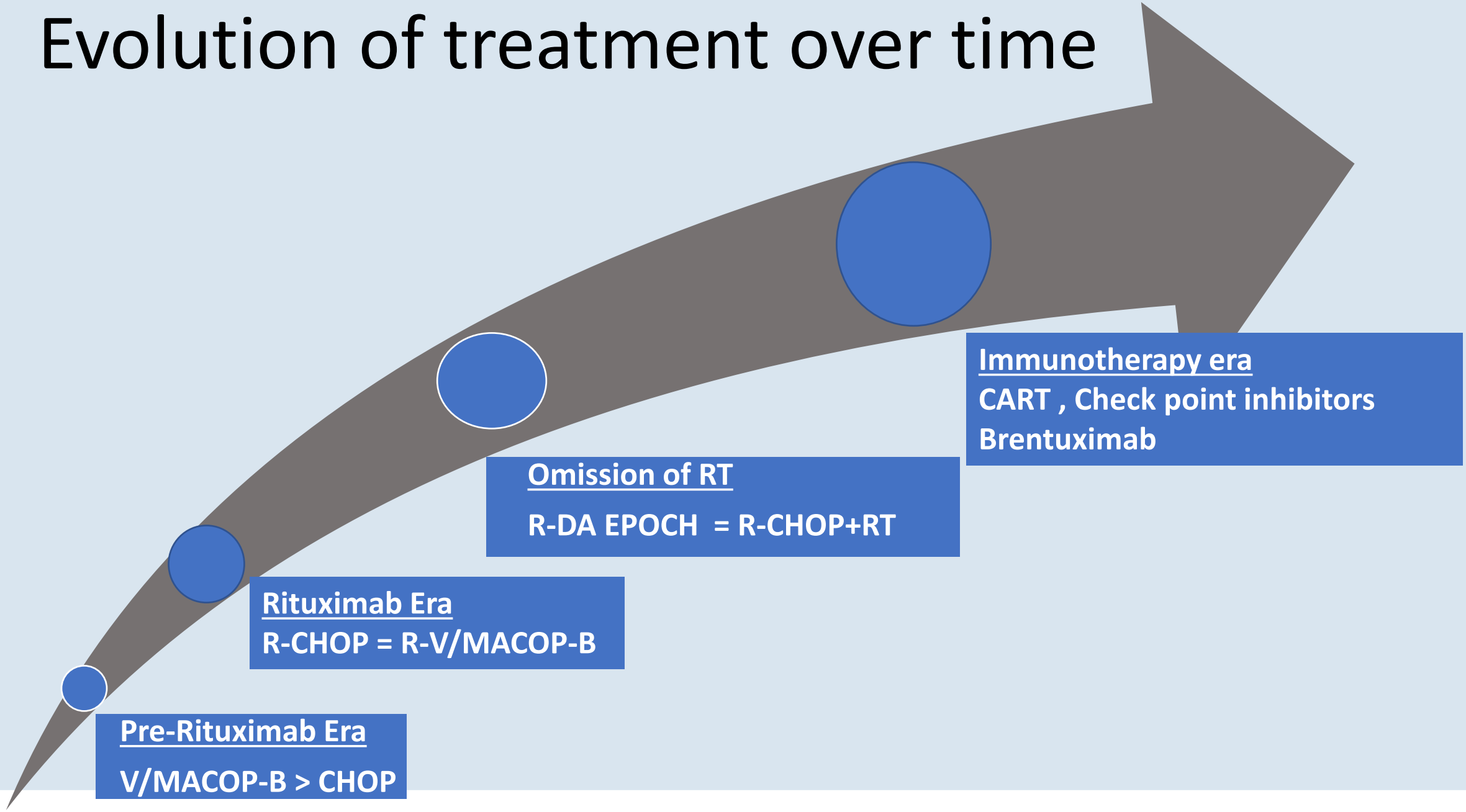
Evolution of treatment over time



	Study type	Treatment	RT %	N	PFS, %
Savage et al 2006	Retrospective	CHOP M/VACOP-B R-CHOP	Variable	153	75 (5 y)
Zinzani et al 2009	Retrospective	R-V/MACOP-B	71	45	84 (5 y)
Mint. Trail 2011	Prospective	R-CHOP-like (n=44) CHOP-like (n=43)	70	87	78 (3-y EFS) 52 (3-y EFS)
Pngalis 2012	Retrospective	R-CHOP CHOP	76	76 48	81 (5 y) 47 (5 y)
Soumerai 2014	Retrospective	R-CHOP	77	63	68 (5 y)
Avigdor 2014	Retrospective	R-VACOP-B (n = 30) R-CHOP (n = 13) VACAOP-B (n = 47) CHOP (n = 5)	0	95	83 (5 y) 69 (5 y) 62 (5 y) 20 (5 y)
Zinzani 2015	Retrospective	R-MACOP-B	69	74	88 (10 y)
Gleeson 2015	Prospective	R-CHOP 14 (n = 22) R-CHOP 21 (n = 28)	58	50	84 (5 y) 80 (5 y)
Moskowitz 2013	Prospective	R-CHOP14-ICE	0	54	78 (3 y)
Dunleavy 2013	Prospective	DA-EPOCH-R	4	51	93 (3 y)
Giuliano roth 2017	Retrospective	DA-EPOCH-R	16	118	87 (3-y EFS)

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., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

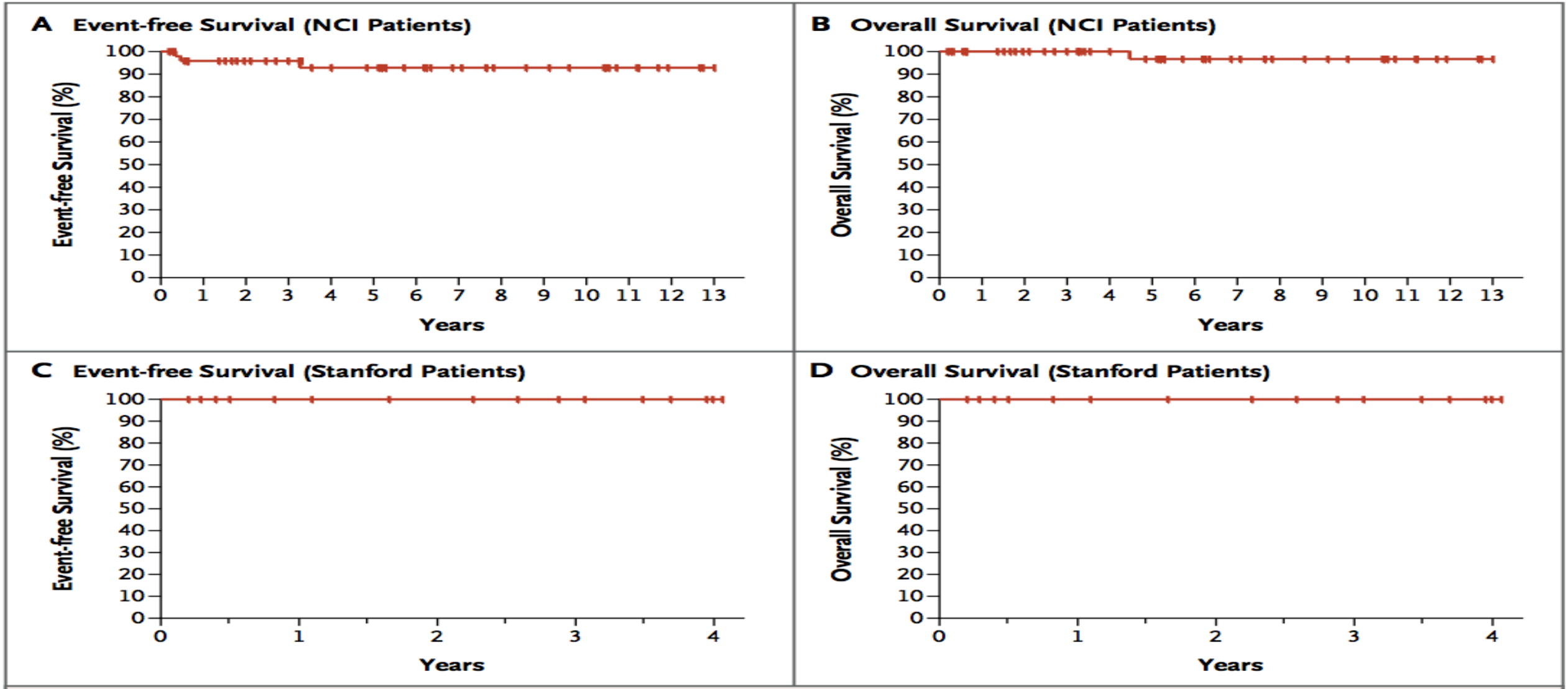


Figure 1. Kaplan–Meier Estimates of Event-free and Overall Survival of Patients with Primary Mediastinal B-Cell Lymphoma Receiving DA-EPOCH-R, According to Study Group.

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.

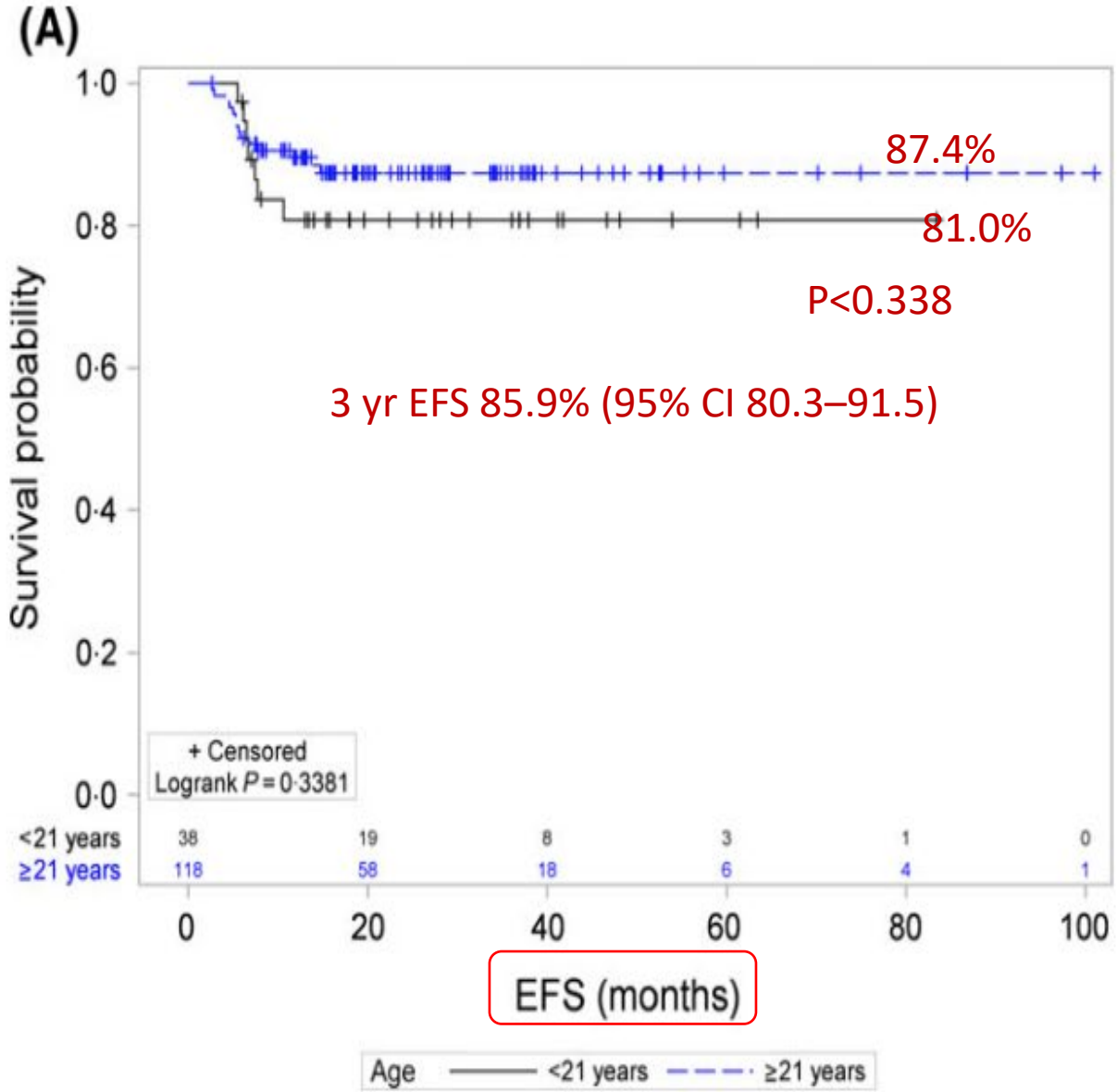
Real world Data

Table II. Treatment characteristics.

	Total cohort n = 156	Paediatrics (age <21 years) n = 38	Adults (age ≥21 years) n = 118	P value Paediatric *versus* adult
Total number of cycles of DA-EPOCH-R: median (range)	6 (1–8)	6 (6–8)	6 (1–8)	0·148
Patients escalated to at least dose level 4: n (%)	57/150 (38·0)	20/37 (54·1)	37/113 (32·7)	**0·031**
Patients not escalated beyond dose level 1: n (%)	15/150 (10·0)	2/37 (5·4)	13/113 (11·5)	0·360
Patients receiving RT: n (%)	23/154 (14·9)	4/36 (11·1)	19/118 (16·1)	0·598
Radiation dose, Gy: median (range)	36·4 (28·0–50·4)	30·6 (30·0–50·4)	36·4 (28·0–50·4)	0·887
Patients receiving growth factor support: n (%)	148/150 (98·7)	33/34 (97·1)	115/116 (99·1)	0·403
Type of growth factor: n (%)				
GCSF alone	55/148 (37·2)	19/32 (59·4)	36/116 (31·0)	**0·005**
PEG-GCSF alone	87/148 (58·8)	11/32 (34·4)	76/116 (65·5)	
Both	6/148 (4·1)	2/32 (6·3)	4/116 (3·4)	

DA-EPOCH-R, dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab; GCSF, granulocyte colony-stimulating factor; n, number; PEG-GCSF, pegylated granulocyte colony-stimulating factor; RT, radiotherapy.

Bold: P<0·5.



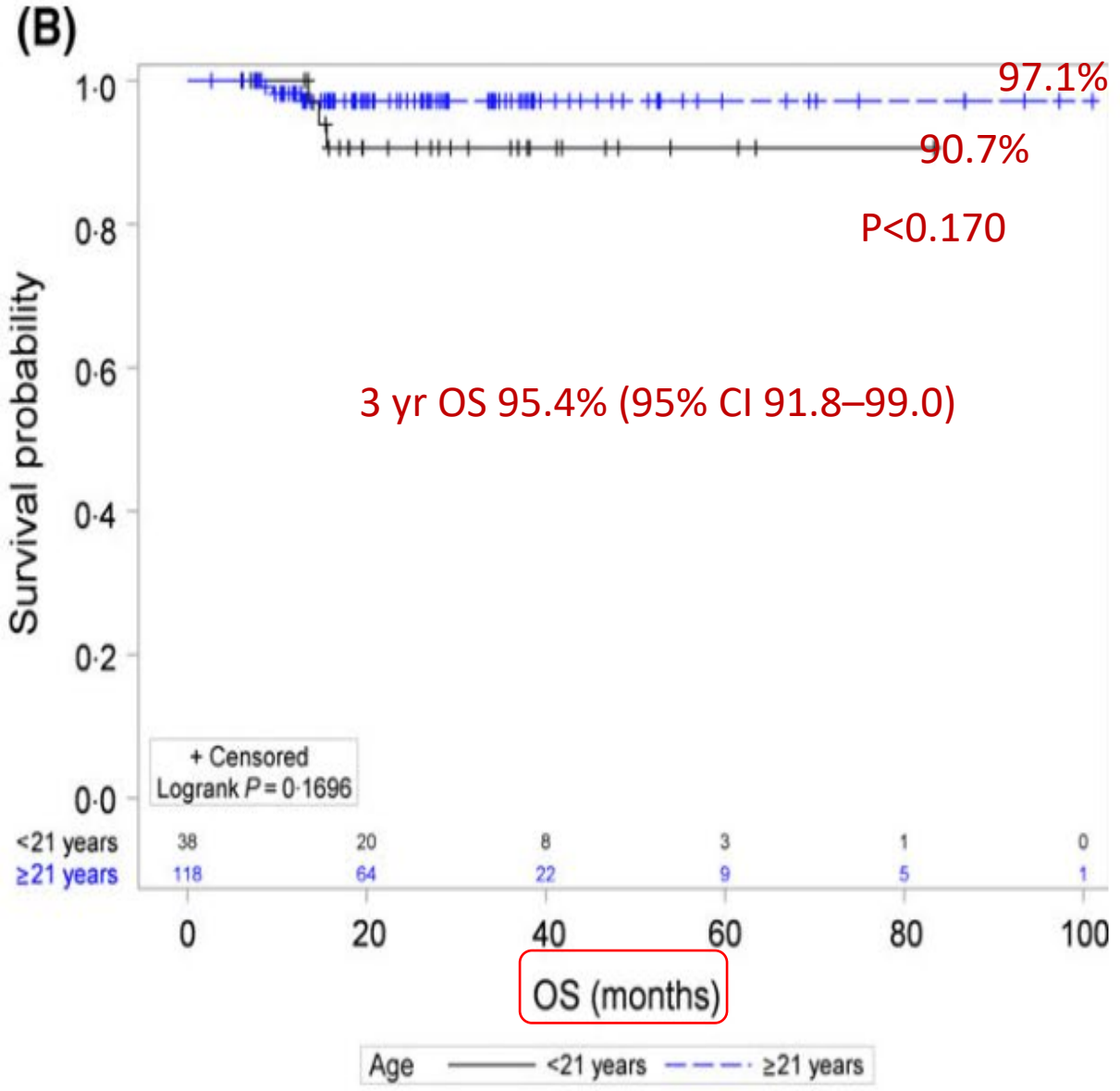


Fig 1. Kaplan–Meier estimate of (A) event-free survival (EFS); (B) overall survival (OS) for paediatric and adult patients.

Real world Indian Data

Parameter	N	EFS 2-yr %	*P* value	OS 2-yr %	*P* value
Age					
≤ 40 years	22	71	0.20	68	0.7
> 40 years	19	90		76	
Sex					
Male	22	71	0.1	72	0.29
Female	19	90		83	
HIV status					
Positive	12	67	0.1	67	0.21
Negative	29	85		74	
Stage					
1,2	18	89	0.2	82	0.29
3,4	23	78		73	
Subtype of NHL					
BL	32	80	0.138	77	0.124
PMBCL	5	100		100	
DLBCL	4	50		50	
Risk group					
aaIPI code 0,1	17	85	0.2	72	0.32
aaIPI score 2,3	24	75		70	

EFS event-free survival, *BL* Burkitt's lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *DLBCL* diffuse large B cell lymphoma, *aaIPI* age adjusted International prognostic index

- The maximum dose intensity of R-DAEPOCH was level two in 2/3rd
- High incidence (75%) : Poor prognostic features
- Relapsed three patients (baseline stage I in 2 and stage IV in one patient) : bulky disease upfront with mediastinal mass > 10 cm, high LDH, pleuropericardial effusion, and SVCS in 2 patients

References	
Zinzani et al. [8]	s)
Gleeson et al. [9]	))
Dunleavy et al. [3]	)
Giulino-Roth et al. [4	EFS)
Present study	EFS)

EFS event-free sur

- Patient is treated with 6 cycles of DA EPOCH R.

Q 6)- Which of the following is incorrect?

1.Chemotherapy should be given for 6-8 cycles.

2.PET CT scan should be done after 2-4 cycles to assess initial disease response.

3.Initial disease response should be assessed by history , clinical examination and by serum LDH.

4.End of treatment PET CT Scan should be done in all patients.

5.Follow up PET CT scan is not recommended for patients having complete metabolic response.

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7.46 Which of the following is incorrect?

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Response assessment

- Documented by history, physical examination, and laboratory studies (complete blood count, lactate dehydrogenase, and biochemical profile).
- PET/CT - six to eight weeks after completion of chemotherapy and 12 weeks after the completion of radiation therapy.

Two months after completion of therapy

- Previously noted FDG avid discrete and conglomerated mediastinal lymph nodes have shown complete metabolic and significant morphological regression, largest mass lesion now measuring 1.8 x 3.8 cm Vs 9.9 x 12 cm(Deauville score 1).

- Patient is presently on routine follow up every 3 months with CBC/kidney function test/liver function test/LDH.

Few Issues

- Inflammation in tumour
- Some FDG avidity in follow up PET Scan