Approach To Lymphoma

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LYMPHOMA

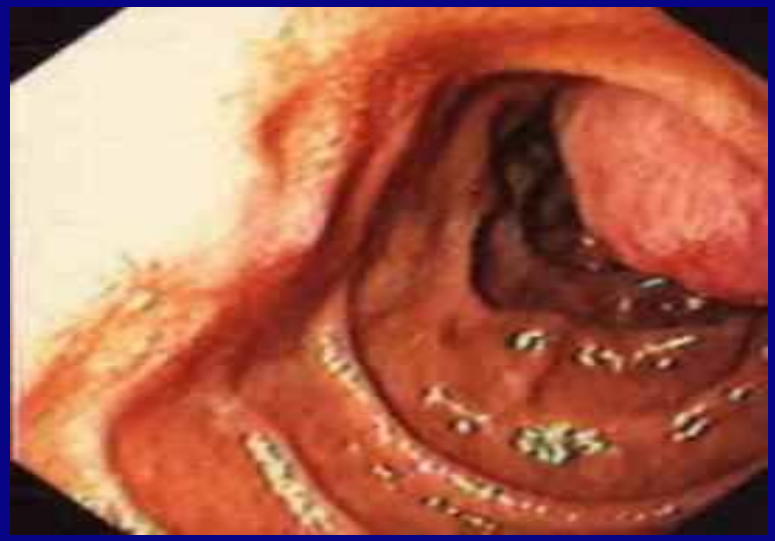
CLASSIFICATION

1. **HODGKIN'S**

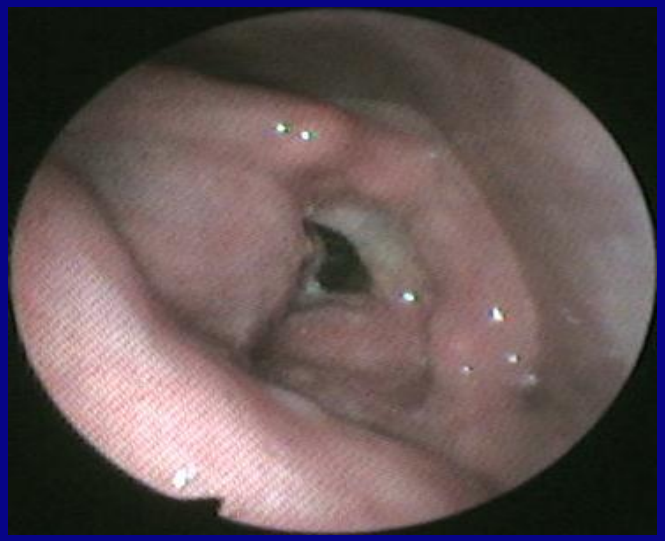
   Characterised by the presence of Reed Sternberg cells

2. **NON HODGKIN'S**

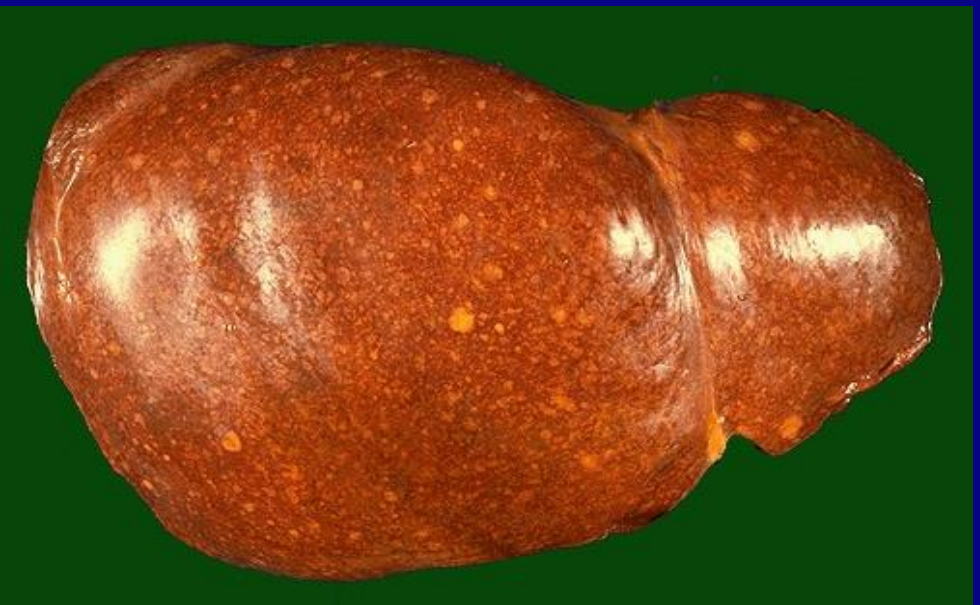
INTESTINE



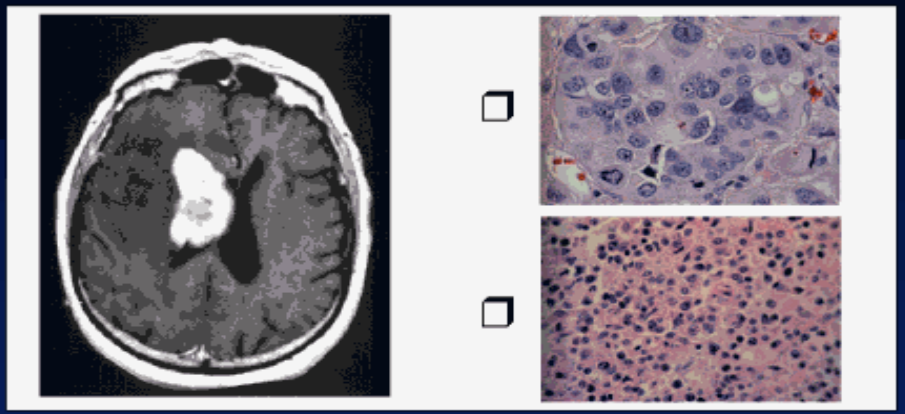
LARYNX

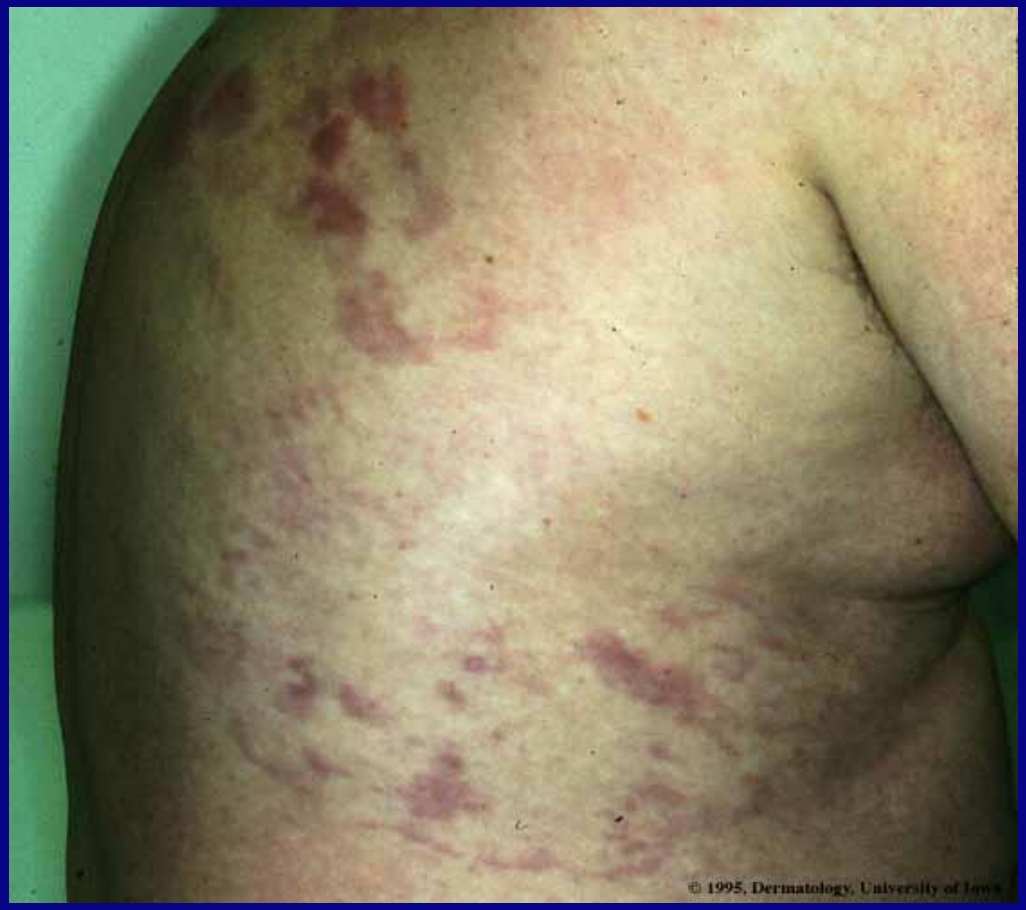


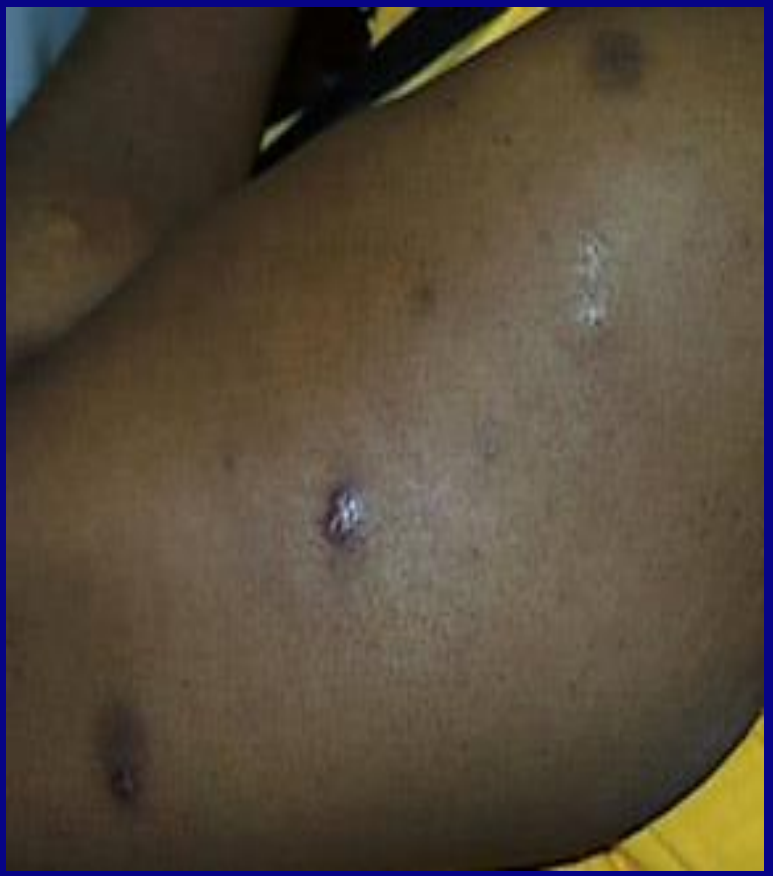
LIVER



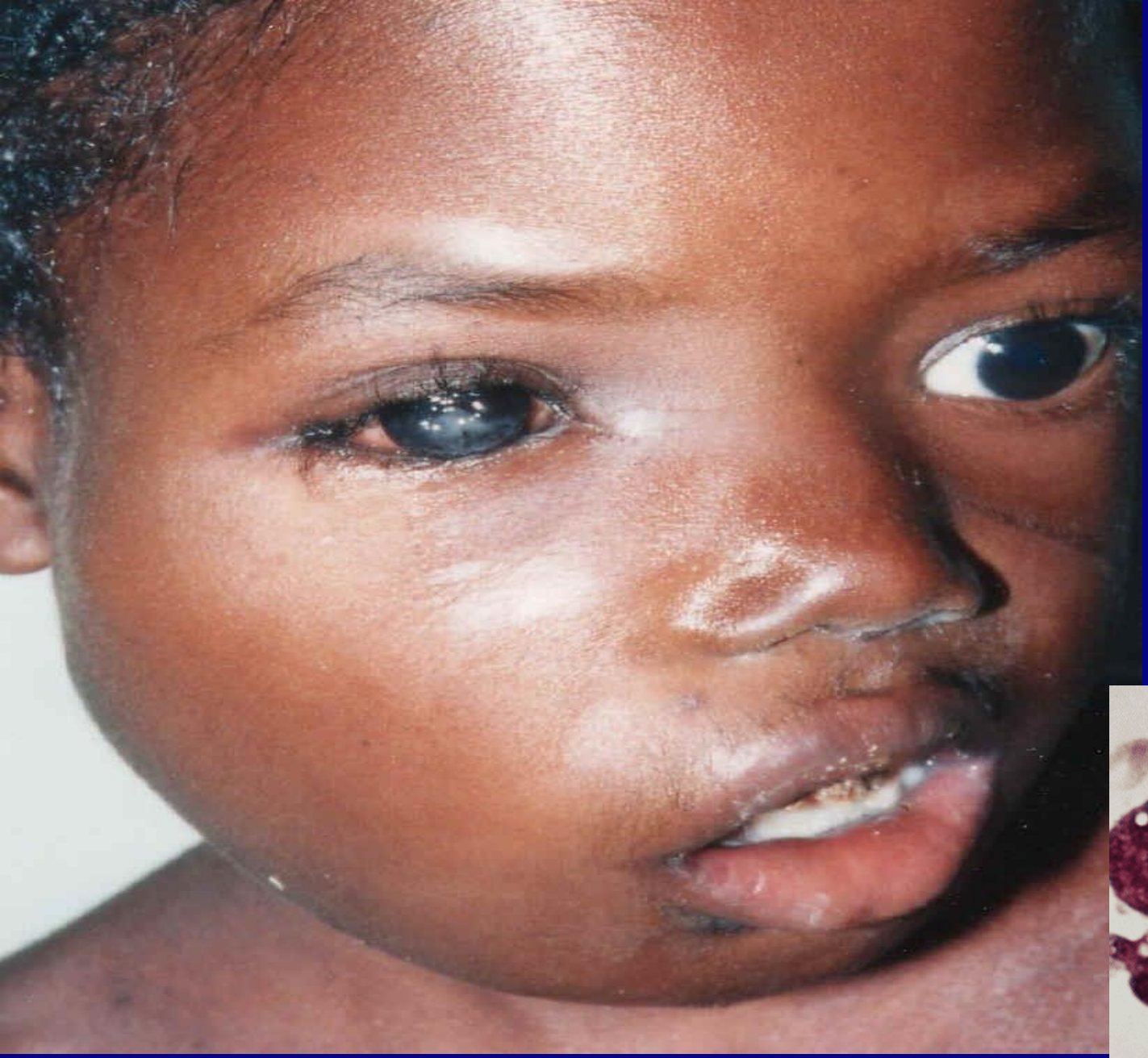
Case 1. Primary CNS Lymphoma
Neuropathology

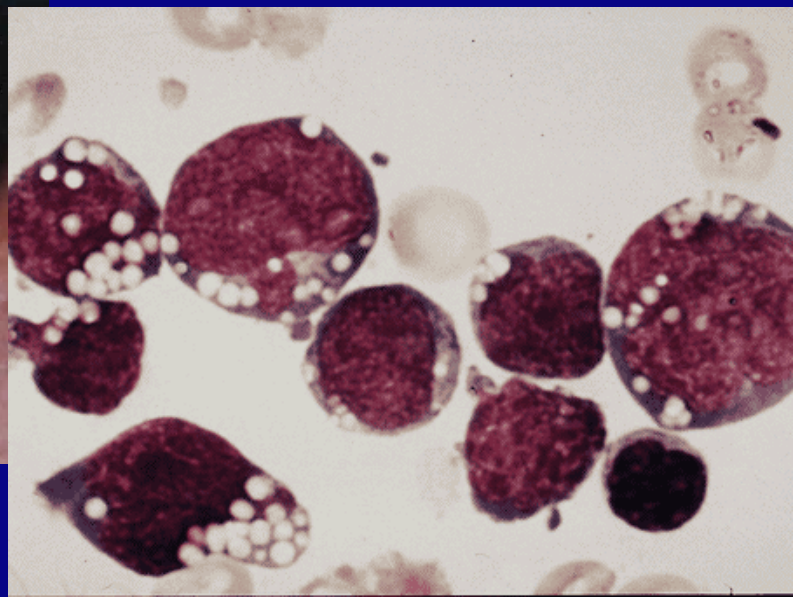






SKIN





WHO Classification

B-cell neoplasms

Precursor B-cell neoplasm

Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)

Mature (peripheral) B-cell neoplasms

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (with or w/o villous lymphocytes)
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa- associated lymphoid tissue type
Nodal marginal zone B-cell lymphoma (with or w/o monocytoid B cells)
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt's cell leukemia

T- and NK-cell neoplasms

Precursor T-cell neoplasm

Precursor T-lymphoblastic lymphoma/leukemia (precursor T- cell acute lymphoblastic leukemia)

Mature (peripheral) T-cell neoplasms

T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (human T-cell lymphotropic virus type I positive)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy type T-cell lymphoma
Hepatosplenic gammadelta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Anaplastic large cell lymphoma, T/null-cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, T/null-cell, primary systemic type

NON HODGKIN'S LYMPHOMA

Few Questions….And still a few answers to all….

1. Am I going to die soon?
2. Why me?
3. Has it spread too much?
4. Is there any effective treatment?
5. Am I going to be fine?

Types of Lymphoma

Indolent (low grade)

- Life expectancy in years, untreated
- 85-90% present in Stage III or IV
- Incurable

Intermediate

Aggressive (high grade)

- Life expectancy in weeks, untreated
- Potentially curable

Etiology of NHL

- Immune suppression
  - congenital (Wiskott-Aldrich)
  - organ transplant (cyclosporine)
  - AIDS
  - increasing age
- DNA repair defects
  - ataxia telangiectasia
  - xeroderma pigmentosum

Etiology of NHL

- Chronic inflammation and antigenic stimulation
  - *Helicobacter pylori* inflammation, stomach
  - *Chlamydia psittaci* inflammation, ocular adnexal tissues
  - Sjögren's syndrome
- Viral causes
  - EBV and Burkitt's lymphoma
  - HTLV-I and T cell leukemia-lymphoma
  - HTLV-V and cutaneous T cell lymphoma
  - Hepatitis C

Epidemiology

- Indolent lymphomas - **rare in young people**
- Large cell lymphoma (DHL) – commonest lymphoma
- Burkitt's and lymphoblastic lymphoma are **common in adolescents**.
- AIDS patients develop **aggressive, high grade lymphomas.**

Clinical Features

- Lymphadenopathy
- Cytopenias
- Systemic symptoms
- Hepatosplenomegaly
- Fever
- Night sweats

Diagnosis of NHL

- **Excisional biopsy** is a must
- **Immunohistochemistry** to confirm cells are lymphoid
  - LCA (leukocyte common antigen)
  - Monoclonal staining with Igκ or Igλ
- **Flow cytometry**:
  - CD 19, CD20 for B cell lymphomas
  - CD 3, CD 4, CD8 for T cell lymphomas

Diagnosis of NHL

- **Chromosome changes**
  - 14;18 translocation in follicular lymphoma
  - t(8;14), t(2;8), t(8;22) in Burkitt's lymphoma
  - t(11;14) in mantle cell lymphoma

Staging Workup

- Complete Blood Count (CBC)
- Biochemical investigations (UA, LDH, LFT, Creat, K+)
- CT scans of chest, abdomen and pelvis
- PET CT scan
- Bone marrow biopsy and aspirate
- (Lumbar puncture)
  - AIDS lymphoma
  - T cell lymphoblastic lymphoma
  - High grade lymphoma with positive marrow

Staging: Ann Arbor

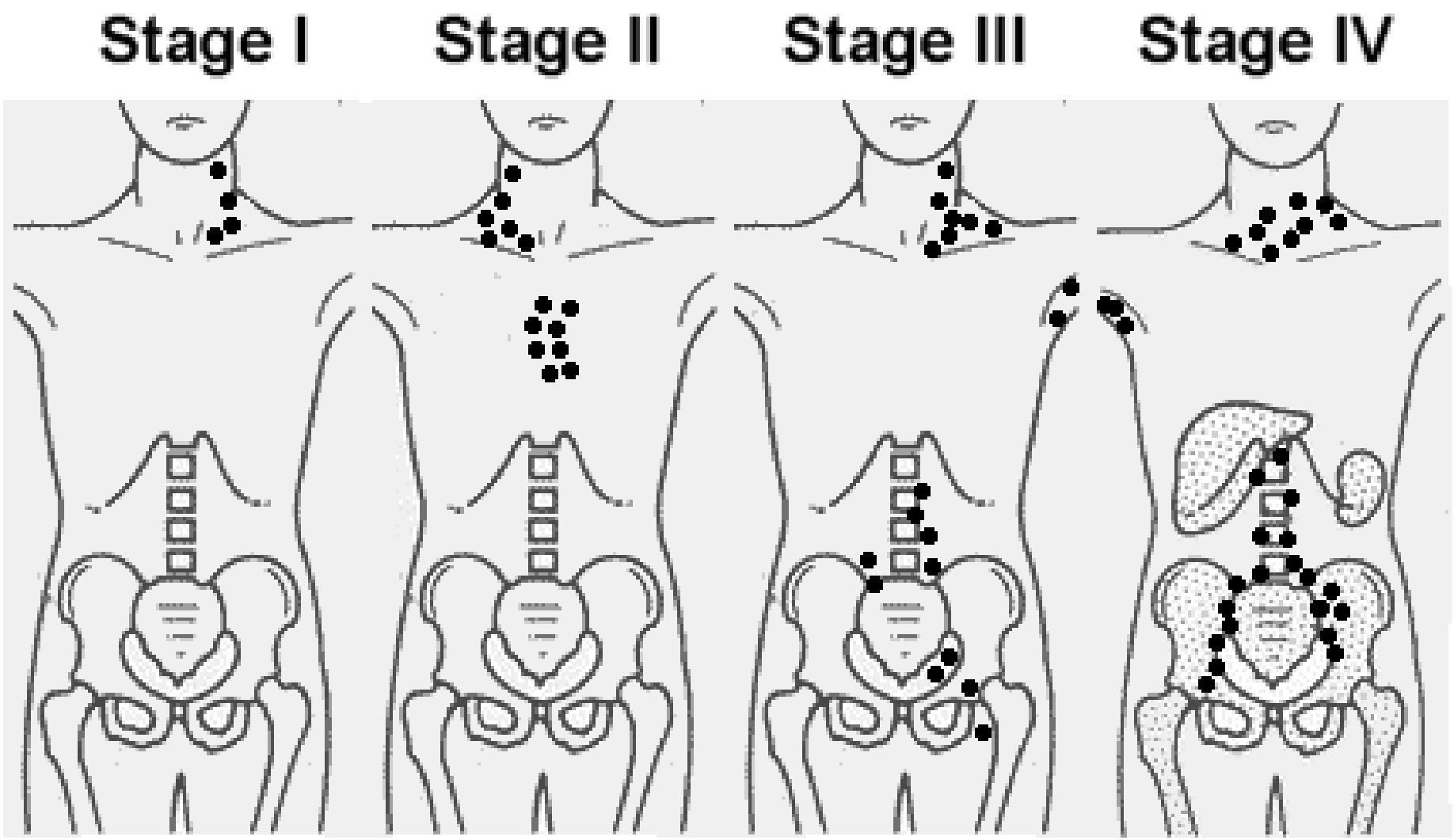
I. 1 lymph node region or structure

II. >1 lymph node region or structure, same side of diaphragm

III. Both sides of diaphragm

IV. Extranodal sites beyond “E” designation

subscripts: A, B, E, S


Stage I
Stage II
Stage III
Stage IV

INTERNATIONAL PROGNOSTIC INDEX (IPI)

- **A**ge - - -< /= 60 vs. > 60
- **P**erformance status ----<2 vs. > 2
- **L**DH ---→ < 1 x Normal vs. > 1 x Normal
- **E**xtranodal Disease ---< /=1 vs. > 1
- **S**tage of Disease ----I / II vs. III /IV

APLES

Age adjusted IPI (aaIPI) –No AE

International Prognostic Index

LOW	**0 or 1**
LOW –INTERMEDIATE	**2**
HIGH – INTERMEDIATE	**3**
HIGH	**4 or 5**

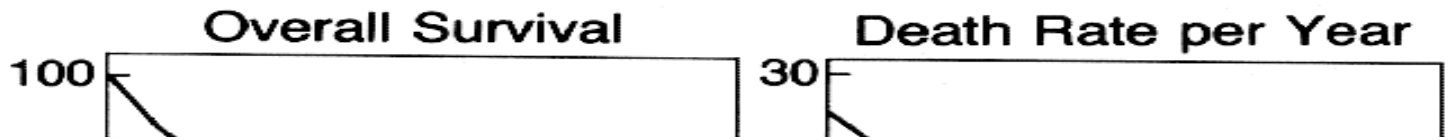
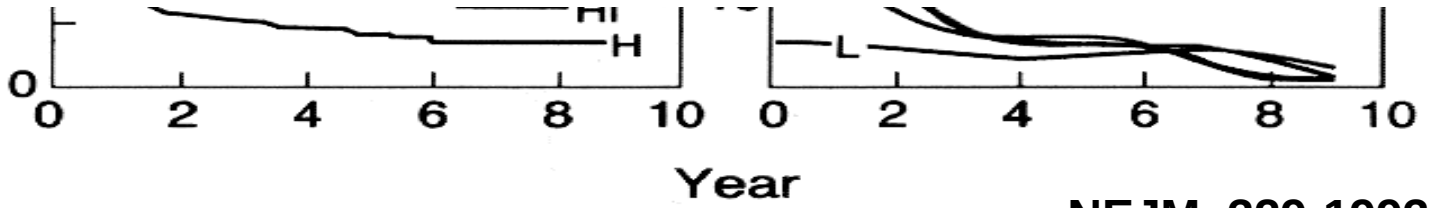


TABLE 6 International Prognostic Index

	Number of Risk Factors	Complete Response Rate (%)	Five-year Relapse-free Survival (%)	Five-year Overall Survival (%)
All patients*				
Low	0 or 1	87	70	73
Low intermediate	2	67	50	51
High intermediate	3	55	49	43
High	4 or 5	44	40	26
Age-adjusted index, patients ≤60 years†				
Low	0	92	86	83
Low intermediate	1	78	66	69
High intermediate	2	57	53	46
High	3	46	58	32

*Adverse factors: age > 60 years, increasing lactate dehydrogenase, performance status 2 to 4, more than one extranodal site, Ann Arbor Stage III or IV.

†Adverse factors: elevated lactate dehydrogenase, performance status 2 to 4, Ann Arbor Stage III or IV.



NEJM, 329;1993, 987 - 984

TUMOR LYSIS SYNDROME

- Hypekalaemia
- Hyperuricaemia
- Hyperphosphataemia
- Hypocalcaemia
- Renal failure

- Sodium bicarbonate – 600 mg 3 times a day

(10 mg/kg/day 3 times a day)

- Allopurinol – 300 mg once a day (5-6 mg/kg/day)
- Adequate hydration
- Rasburicase

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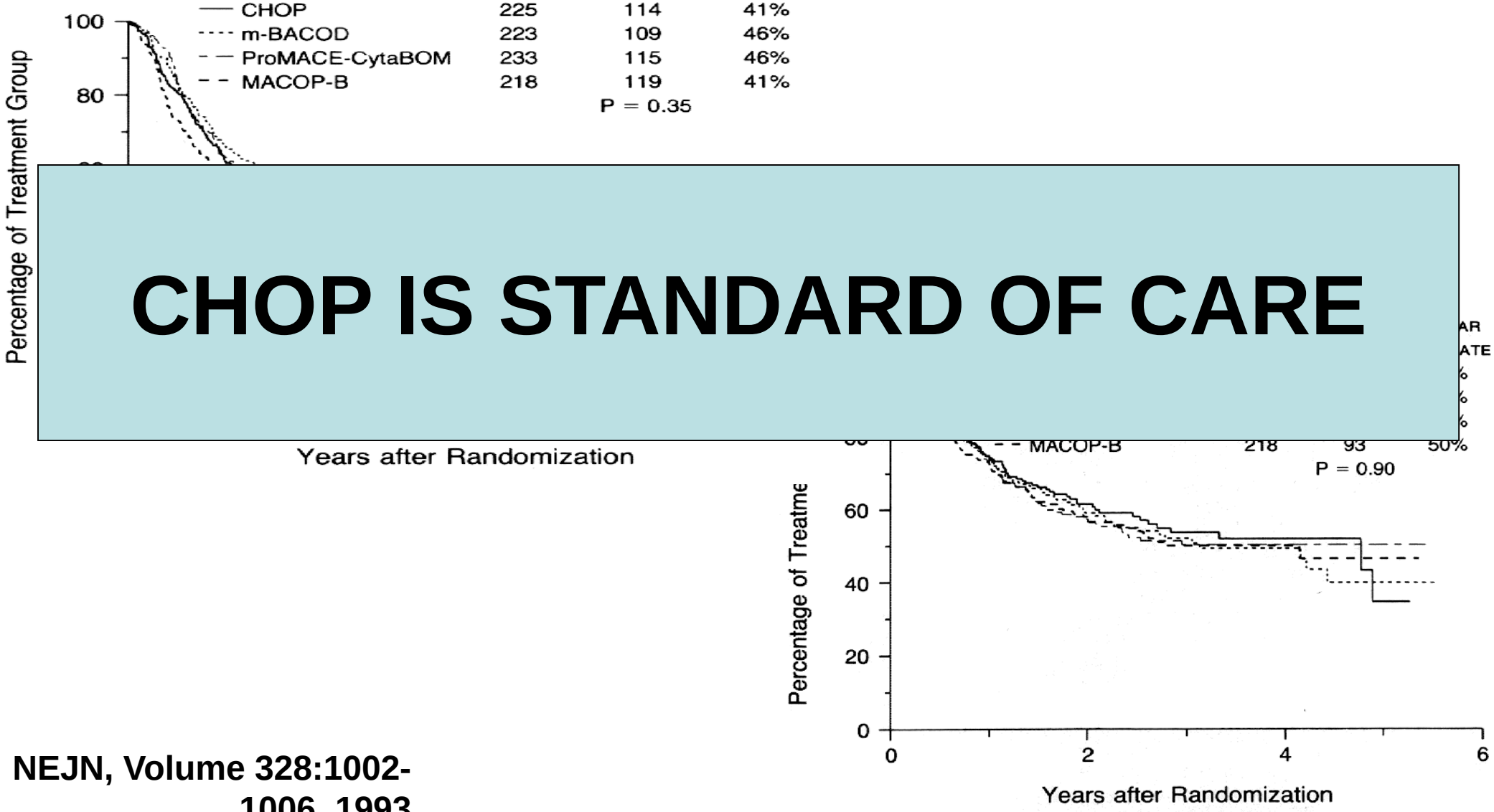
NON HODGKINS LYMPHOMA
CHOP

	Level A	Level B	Level C		
1. Adriamycin	50 mg/m2	35 mg/m2	25 mg/m2	iv	Day 1
2. Vincristine	1.4 mg/m2	1.4 mg/m2	1.4 mg/m2	iv	Day 1
3. Cyclophosphamide	800 mg/m2	400 mg/m2	200 mg/m2	iv	Day 1
4. Prednisolone	60 mg/m2	60 mg/m2	60 mg/m2	p/o	Days 1-5

Repeat at 21 Day intervals for 6 cycles and restage.

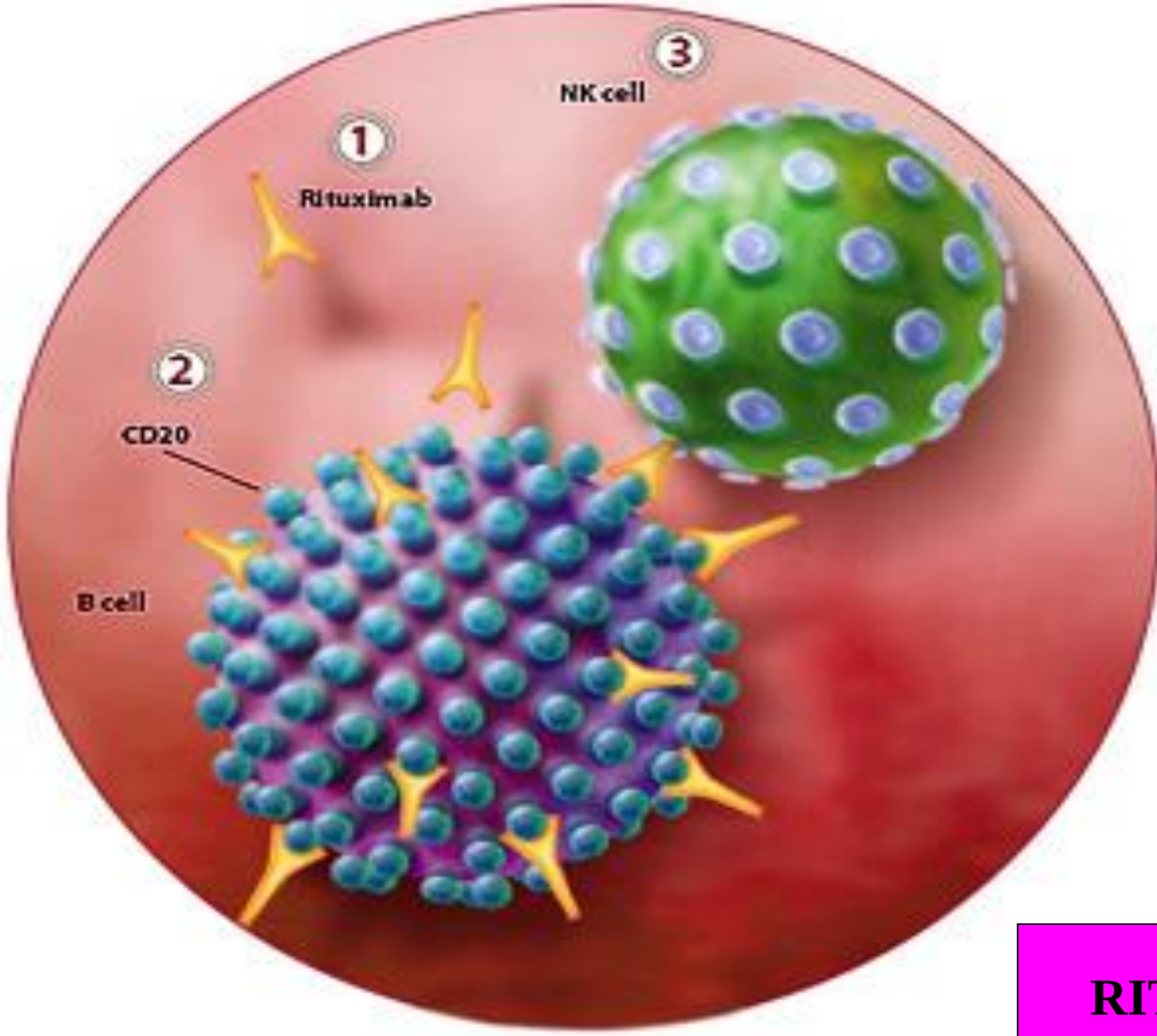
Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma

	Patients at Risk	Relapses or Deaths	3-Year Estimate
CHOP	225	114	41%
m-BACOD	223	109	46%
ProMACE-CytaBOM	233	115	46%
MACOP-B	218	119	41%
		P = 0.35	



CHOP IS STANDARD OF CARE

NEJN, Volume 328:1002-1006, 1993



RITUXIMAB

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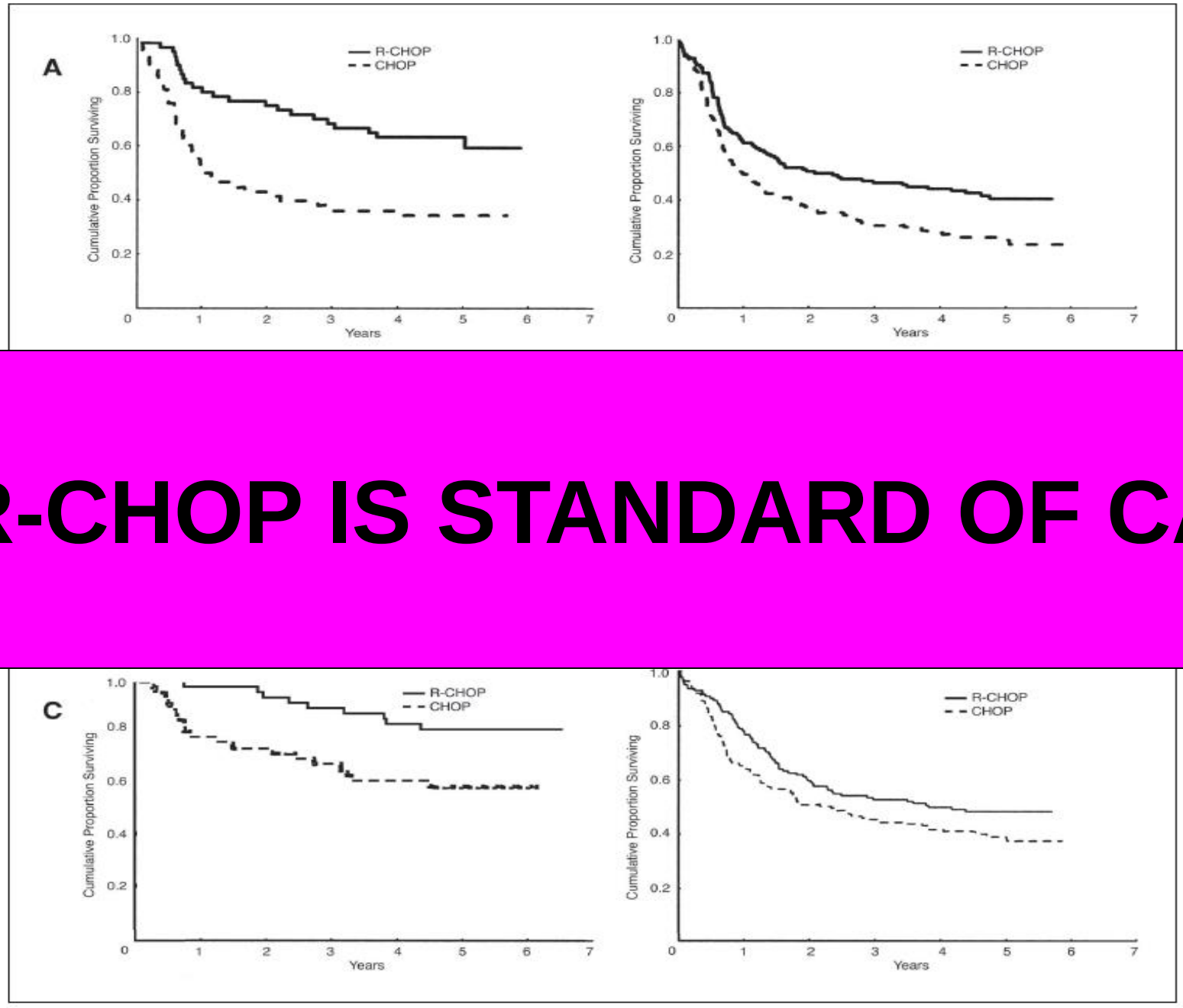

R-CHOP IS STANDARD OF CARE

Fig 2. Event-free survival (A), progression-free survival (B), and overall survival (C) with a median follow-up of 5 years of patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab plus CHOP (R-CHOP) according to the age-adjusted International Prognostic Index score at diagnosis: (1) low-risk patients (scores 0 and 1); (2) high-risk patients (scores 2 and 3). All differences are statistically significant except for overall survival in high-risk patients: *P* values are .00085, .0037, .00013, .00078, .023, and .062, respectively.

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6; 2005

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NON HODGKINS LYMPHOMA

R - CHOP

RITUXIMAB – 375 mg /m2 on DAY 1

	Level A	Level B	Level C		
1. Adriamycin	50 mg/m2	35 mg/m2	25 mg/m2	iv	Day 1
2. Vincristine	1.4 mg/m2	1.4 mg/m2	1.4 mg/m2	iv	Day 1
3. Cyclophosphamide	800 mg/m2	400 mg/m2	200 mg/m2	iv	Day 1
4. Prednisolone	60 mg/m2	60 mg/m2	60 mg/m2	p/o	Days 1-5

6 cycles at an interval of 21 days

CHOP PER CYCLE – Rs. 5000 / -
R-CHOP PER CYCLE – Rs. 45,000 / -

FOLLICULAR LYMPHOMA – NATURAL HISTORY OF DISEASE

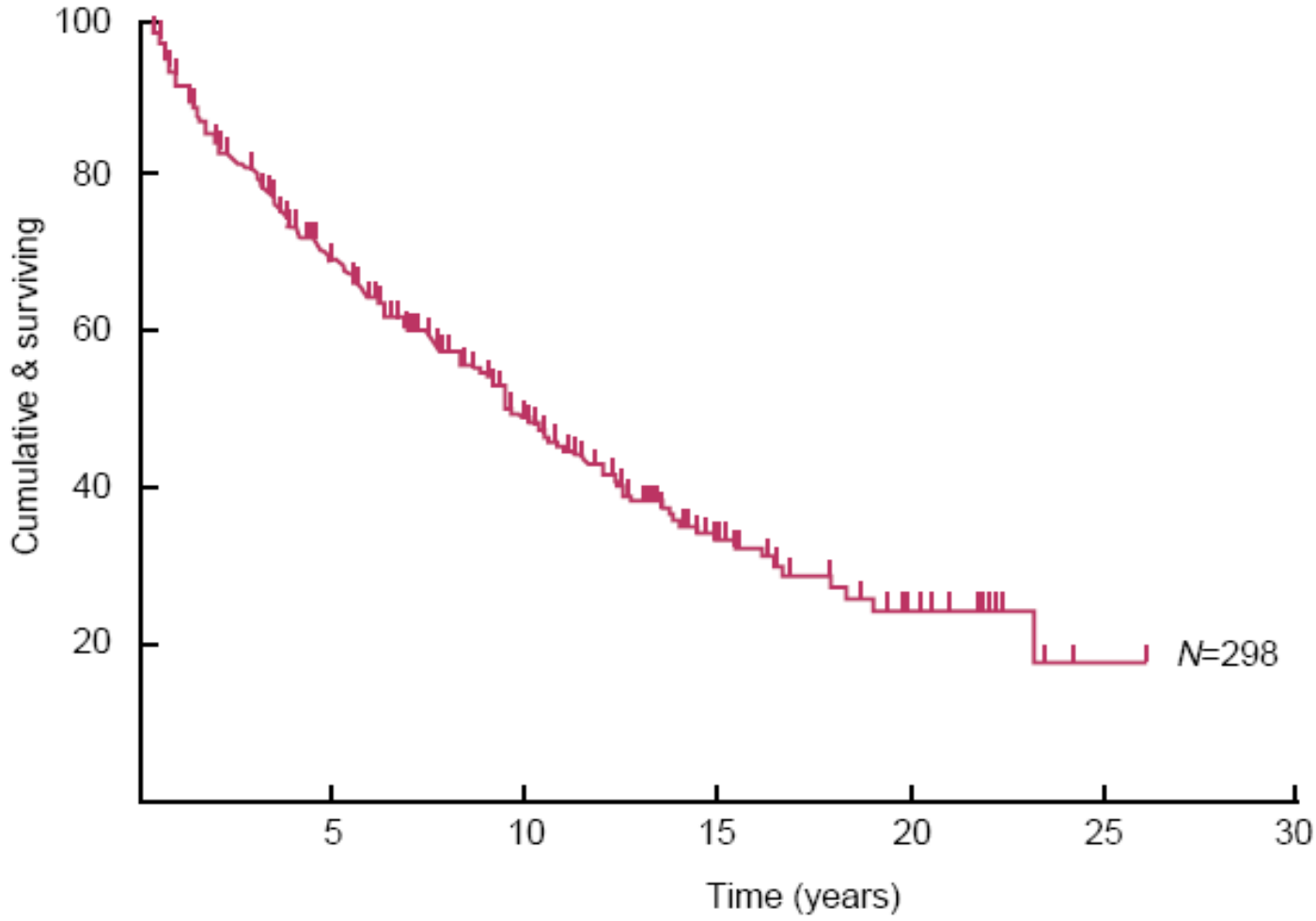
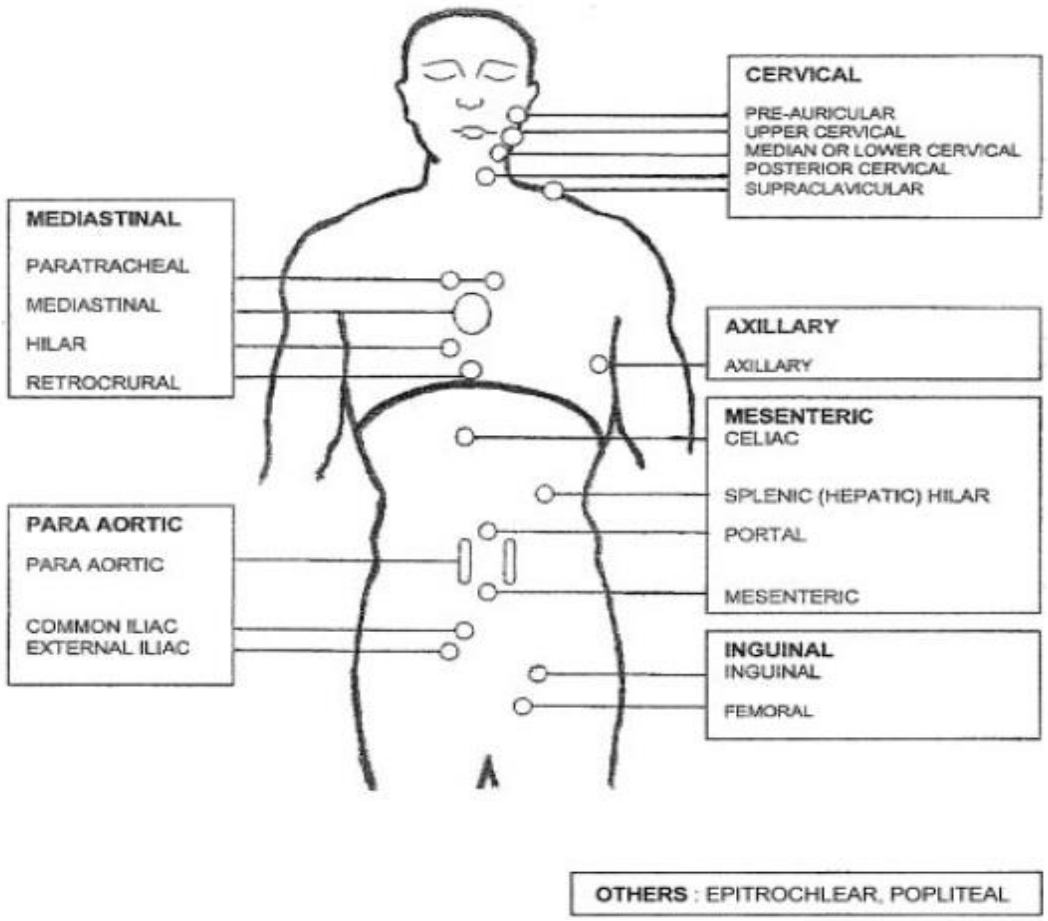


Figure 4. Overall survival of patients with follicular lymphoma treated at St Bartholomew's Hospital (SBH), London.

Follicular Lymphoma International Prognostic Index



1. AGE - <60 vs. > 60 years
2. Stage –I / II vs. III / IV disease
3. Hb% - > 12 gm% vs. < 12 gm%
4. Nodal site - < /= 4 vs. > 4 areas
5. LDH –Above normal vs. Normal

LOW – 0 -1
INTEMEDIATE – 2
HIGH – >=3

No. of risk factors*	FLIPI score	Proportion of patients, %	Overall survival at 5 y, %	Overall survival at 10 y, %
0 or 1	Low	36	91	71
2	Intermediate	37	78	51
3 to	High	27	53	36

Blood. 2004;104:1258-1265

Reasons to Treat in Advanced Indolent Lymphomas

- **Constitutional symptoms**
- **Anatomic obstruction**
- **Organ dysfunction**
- **Cosmetic considerations**
- **Painful lymph nodes**
- **Cytopenias**

STAGE I / II – ABOUT 40% CURABLE WITH RADIOTHERAPY

Treatment Options:

Indolent lymphomas

- 10-15% in Stage I or II

  Potentially curable

  Local radiotherapy

- 85-90% Stage III or IV

  Incurable

  Treatment does not prolong survival

Treatment Options in Advanced Indolent Lymphomas

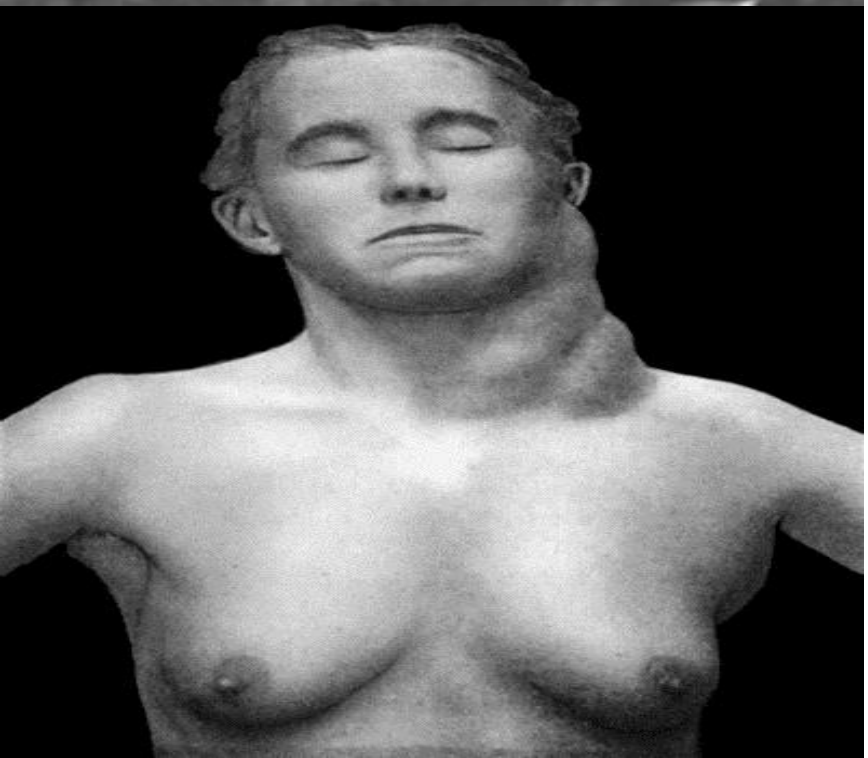
- Observation only.
- Radiotherapy to site of problem.
- Systemic chemotherapy
  - oral agents: chlorambucil and prednisone
  - IV agents: CHOP, COP, fludarabine, 2-CDA.
- Antibody against CD20: Rituxan, Bexxar, Zevalin.
- Stem cell or bone marrow transplant.

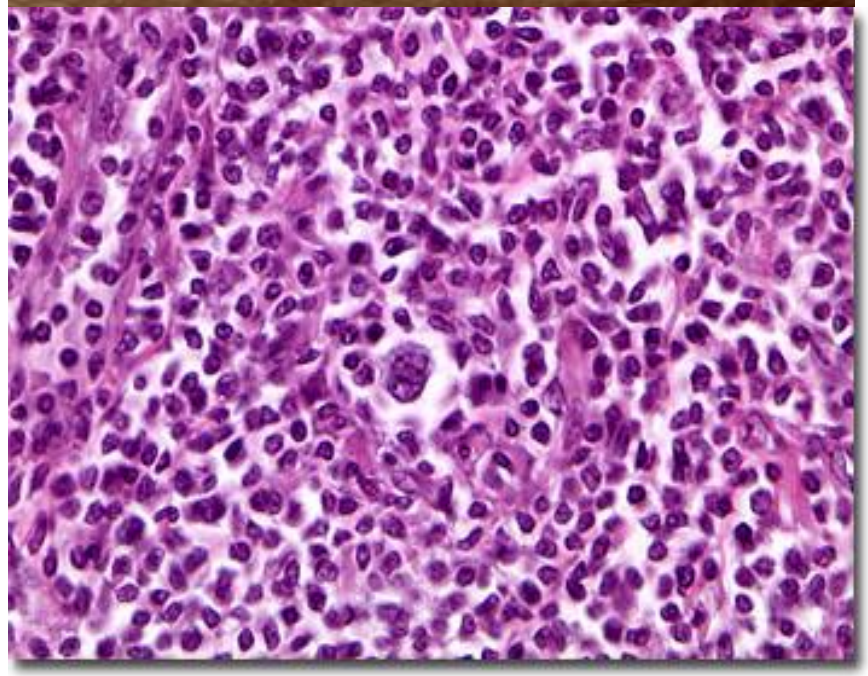
Follow Up - 3 scenario

- IN Remission – Follow up 1st 3 monthly and then 6 monthly for 5 years
- Progressive disease / Refractory disease – Palliation vs. Definitive treatment
- Relapse after achieving CR / PR – Palliation vs. Definitive therapy

DEFINITIVE THERAPY

- Salvage Chemotherapy followed by Autologous stem cell transplantation
- Salvage chemotherapy
  - RICE
  - DHAP
  - ICE
  - MINE
  - MIME
- 2-3 cycles of salvage chemotherapy
- 50% cure rate with chemo sensitive diseases





Thomas Hodgkin, in 1832,

… *when he described this disease for the first time, had a rather dull armentarium to treat this sickness:* ***surgery, herbs, arsenic acid and mainly tender loving care.***

Dorothee Reed, 70 yr later wrote:

…*the treatment for this disease is dismal. All patients die within 3–4 yr. Even if you resect the tumor totally, it will recur and grow even faster than before…and finally the patient dies of cachexia or due to tuberculosis or other fatal infections…*

- MOPP Chemotherapy -1960 – NCI –**Hypothesis** was cancer can be cured
- 1970 – Answer was **YES** – No more Hypothesis

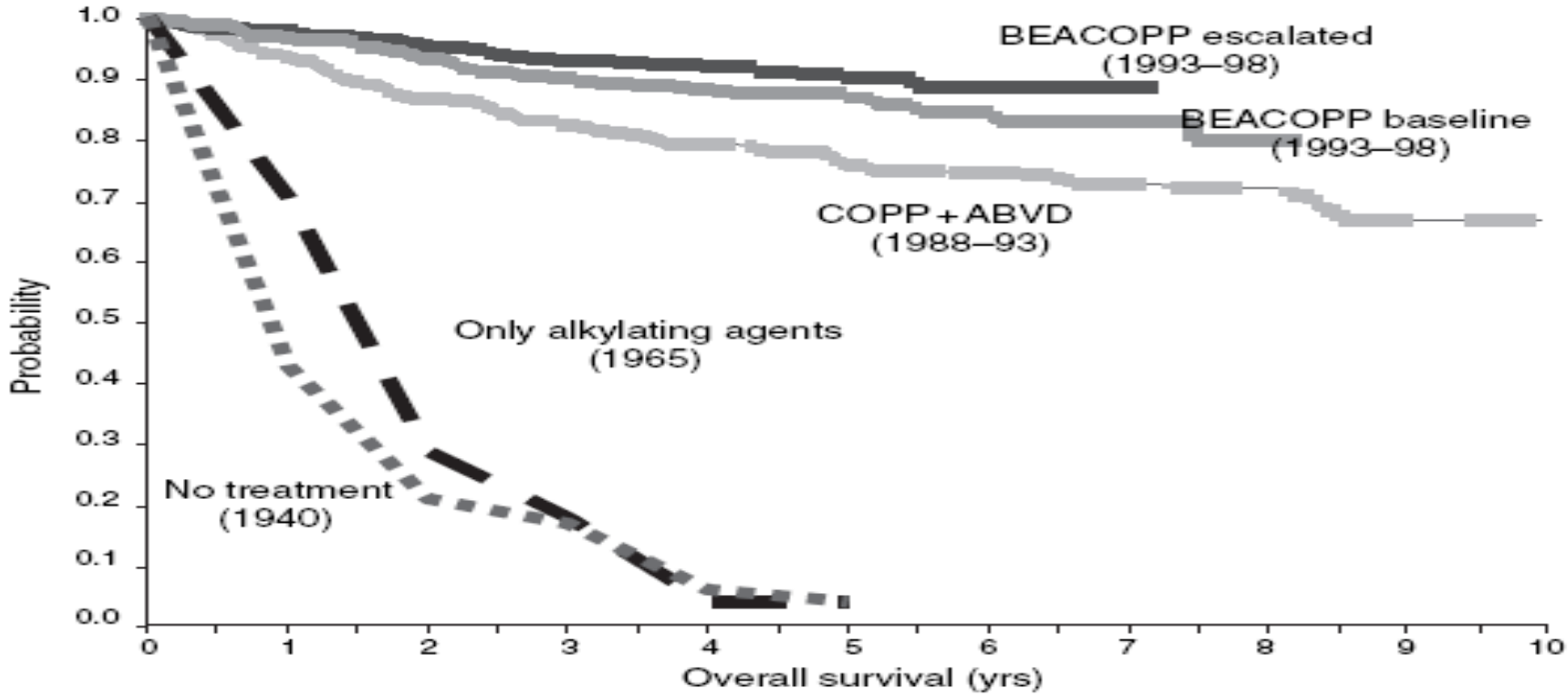


Fig. 1. Progress made in the treatment of advanced stage Hodgkin's lymphoma during the last century; data modified from de Vita including data from GHSG HD9 trial.

Eur J Haematol 2005: 75(Suppl. 66): 6–13

INTERNATIONAL PROGNOSTIC FACTORS

- Age >= 45 years
- Sex – Male
- Stage – IV
- Haemoglobin - < 10.5 gm%
- TWBC count - > 15 x 10^9 / L
- Lymphocyte count - < 0.6 x 10^9 / L or < 8% of white cell differential
- Serum Albumin < 4 g/dl

HASENCLEVER INDEX

Table 1
Definition of treatment groups according to the European Organization for Research and Treatment of Cancer/Groupe d'Etude des Lymphomes de l'Adulte, German Hodgkin's Lymphoma Study Group, and National Cancer Institute of Canada/Eastern Cooperative Oncology Group

Treatment group	EORTC/GELA	GHSG	NCIC/ECOG
Early stage favorable	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors	Standard risk group: favorable CS I–II (without risk factors)
Early stage unfavorable (intermediate)	CS I–II with ≥1 risk factor (supradiaphragmatic)	CS I, CSIIA ≥1 risk factors; CS IIB with C/D but without A/B	Standard risk group: unfavorable CS I–II (at least one risk factor)
Advanced stage	CS III–IV	CS IIB with A/B; CS III–IV	High risk group: CS I or II with bulky disease; intraabdominal disease; CS III, IV
Risk factors (RF)	A. Large mediastinal mass B. Age ≥50 years C. Elevated ESR[a] D. ≥4 involved regions	A. Large mediastinal mass B. Extranodal disease C. Elevated ESR[a] D. ≥3 involved areas	A. ≥40 years B. Not NLPHL or NS histology C. ESR ≥50 mm/h D. ≥4 involved nodal regions

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; NCIC, National Cancer Institute of Canada; NLPHL, nodular lymphocyte predominance; NS, nodular sclerosis.

[a]Erythrocyte sedimentation rate (≥50 mm/h without or ≥30 mm/h with B symptoms).

Hematol Oncol Clin N Am 21 (2007) 897–914

Table 6. Brief ABVD Chemotherapy Followed by Radiation for Limited-Stage Hodgkin's Lymphoma

	Milan[10]	Vancouver[11]	GHSG*[12]
Eligible stages	IA, IB, IIA	IA, IIA	IA, IIA
No. of patients	140	268	204
Median follow-up, months	87	67	22
ABVD treatment, months	4	2	2
Radiotherapy field	Involved or extended	Extended, 1989-1997; involved, 1997-2004	Extended
Disease-free survival, %	95	98	96
Overall survival, %	93	97	98

Abbreviations: GHSG, German Hodgkin Study Group; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

*Only patients with absence of unfavorable prognostic factors were included in the GHSG study.

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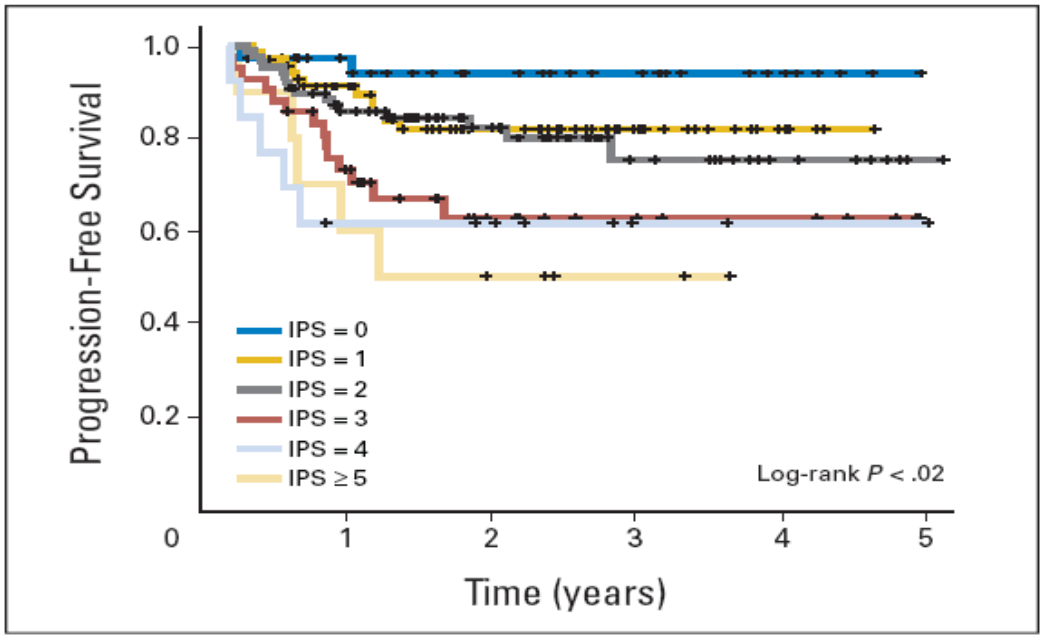
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Interim 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: A Report From a Joint Italian-Danish Study



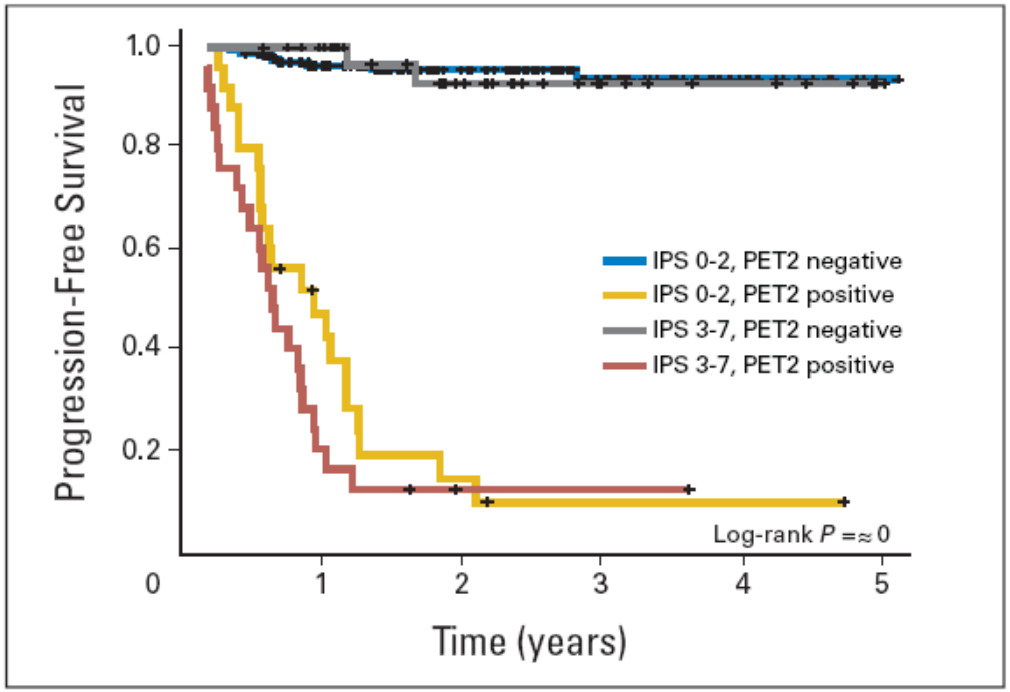


Fig 2. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.

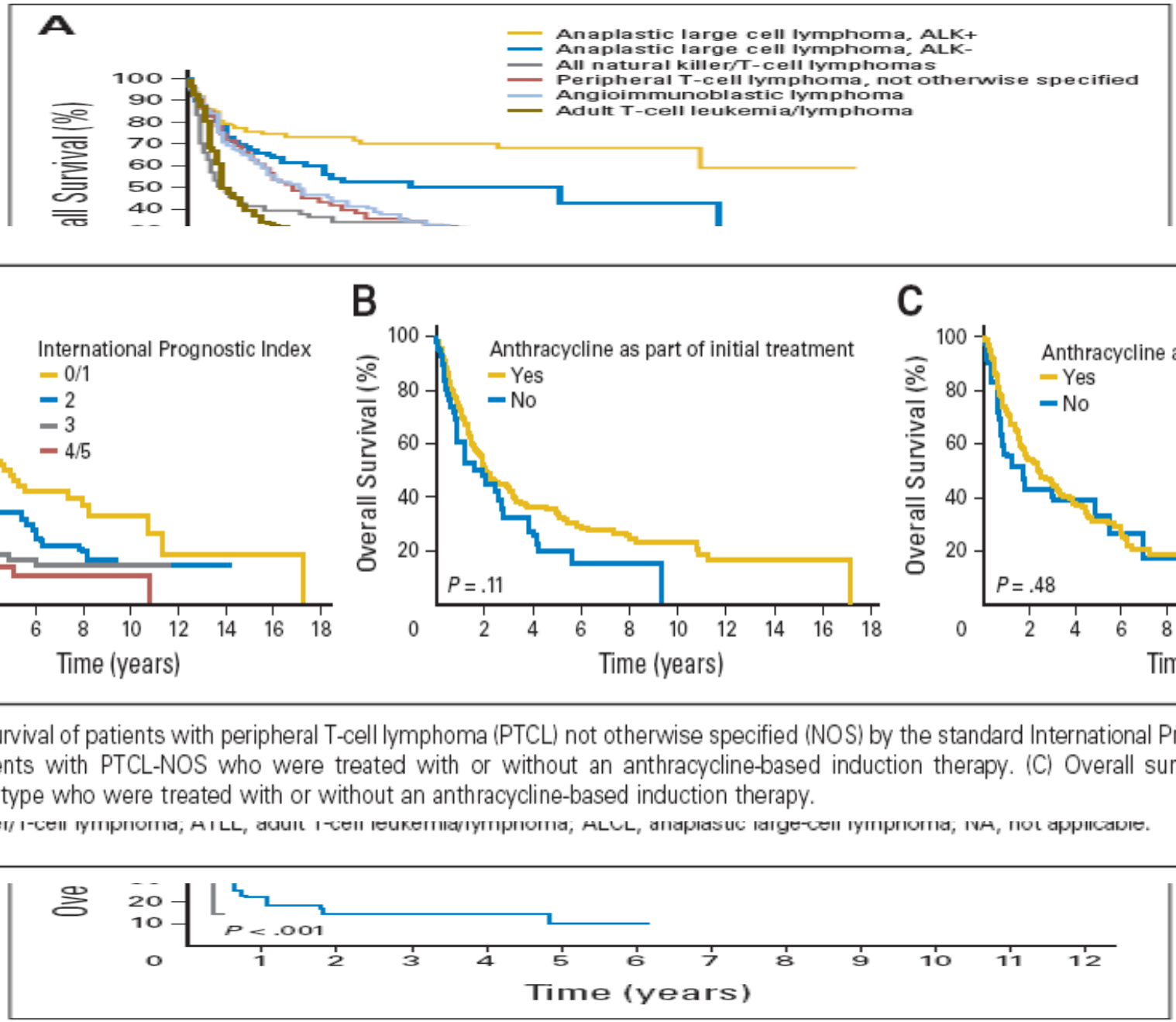


Fig 3. (A) Overall survival of patients with peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) by the standard International Prognostic Index. (B) Overall survival of the patients with PTCL-NOS who were treated with or without an anthracycline-based induction therapy. (C) Overall survival of the patients with angioimmunoblastic type who were treated with or without an anthracycline-based induction therapy.

NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma; NA, not applicable.

Fig 2. (A) Overall survival of patients with the common subtypes of peripheral T-cell lymphoma (PTCL) common subtypes of PTCL. T-cell lymphoma.

International T cell Lymphoma Project, JCO, 2008

Table 1. Clinical subdivision of noncutaneous, mature T/NK neoplasms, unique features, and expected 5-year survival.

	Unique Features	Survival (%)
Nodal		
Anaplastic large cell, ALK-positive	t(2;5)(p23;q35) and variants; extranodal involvement (50-80%), skin (21-35%)	60-90
Anaplastic large cell, ALK-negative	Distinguish from primary cutaneous anaplastic large cell lymphoma (ALCL)	10-45
Angioimmunoblastic	Autoimmunity	10-30
Peripheral T-cell lymphoma, unspecified	Most common, survival dependent on IPI	15-35
Extranodal		
Nasal	Epstein-Barr virus association, central nervous system risk	
Localized		50-70
Disseminated (nasal type)	Sites: skin, gastrointestinal tract, testis, orbit	5-10
Enteropathy associated	Celiac disease; small bowel obstruction	5-20
Hepatosplenic, $\gamma\delta$	Isochromosome 7, trisomy 8; can occur in organ transplants	5-15
Subcutaneous panniculitis-like	Aggressive with hemophagocytosis; may be indolent	10-30
Leukemia		
T-Prolymphocytic leukemia	Chromosome 14 abnormalities	10-20
Adult T-cell lymphoma/leukemia	HTLV-1 association, hypercalcemia. Four types: acute (55-65%) chronic, smoldering leukemia and lymphoma (20-25%)	0-15*
Large granular lymphocytic leukemia	Rheumatoid arthritis, neutropenia	50-75
Aggressive NK leukemia	May represent leukemic phase of extranodal NK neoplasms (nasal type)	0-10

*Survival pertains to the acute leukemia and lymphoma presentations of ATLL

THANK YOU