





Current Status of Management of Adult Non-Hodgkin's Lymphoma in Egypt

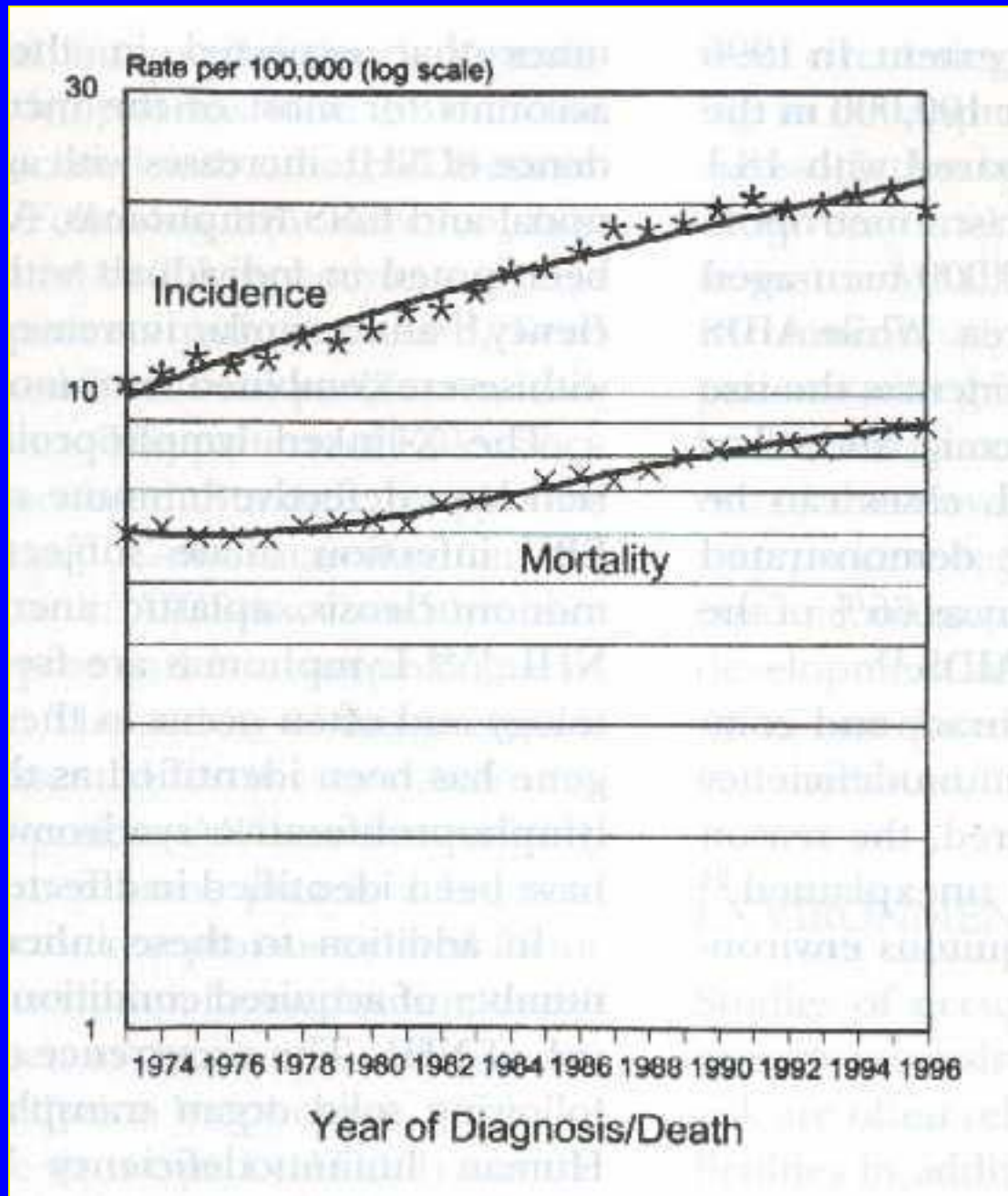
By

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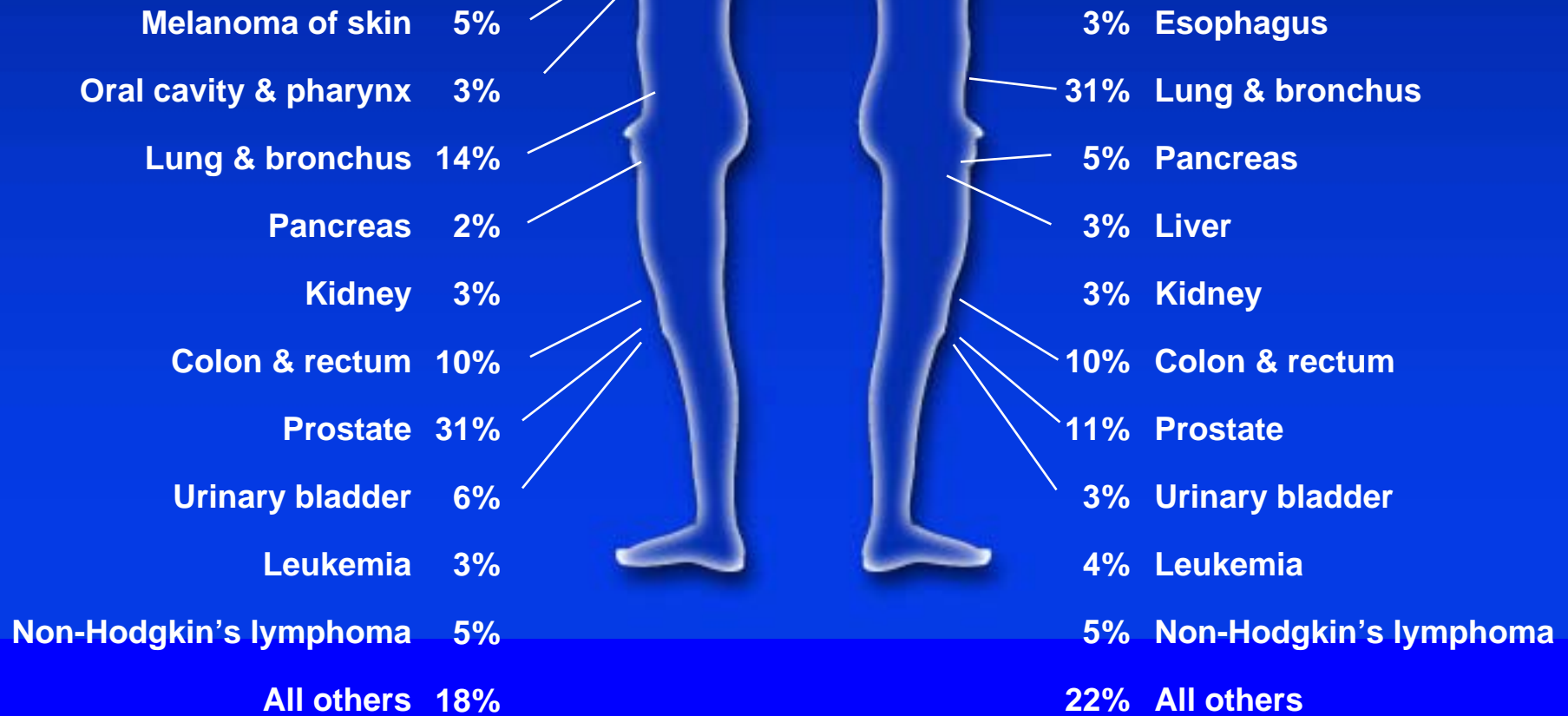
Dean , National Cancer Institute

Cairo University



Estimated incidence

Estimated deaths



Estimated incidence

Melanoma of skin	4%
Thyroid	2%
Breast	31%
Lung & bronchus	13%
Pancreas	2%
Colon & rectum	11%
Ovary	4%
Uterine corpus	6%
Urinary bladder	2%
Non-Hodgkin's lymphoma	4%
All others	21%

Estimated deaths

Brain	2%
Breast	15%
Lung & bronchus	25%
Pancreas	6%
Stomach	2%
Colon & rectum	11%
Ovary	5%
Uterine corpus	2%
Non-Hodgkin's lymphoma	5%
Leukemia	4%
All others	23%

Epidemiology non-Hodgkin's Lymphomas

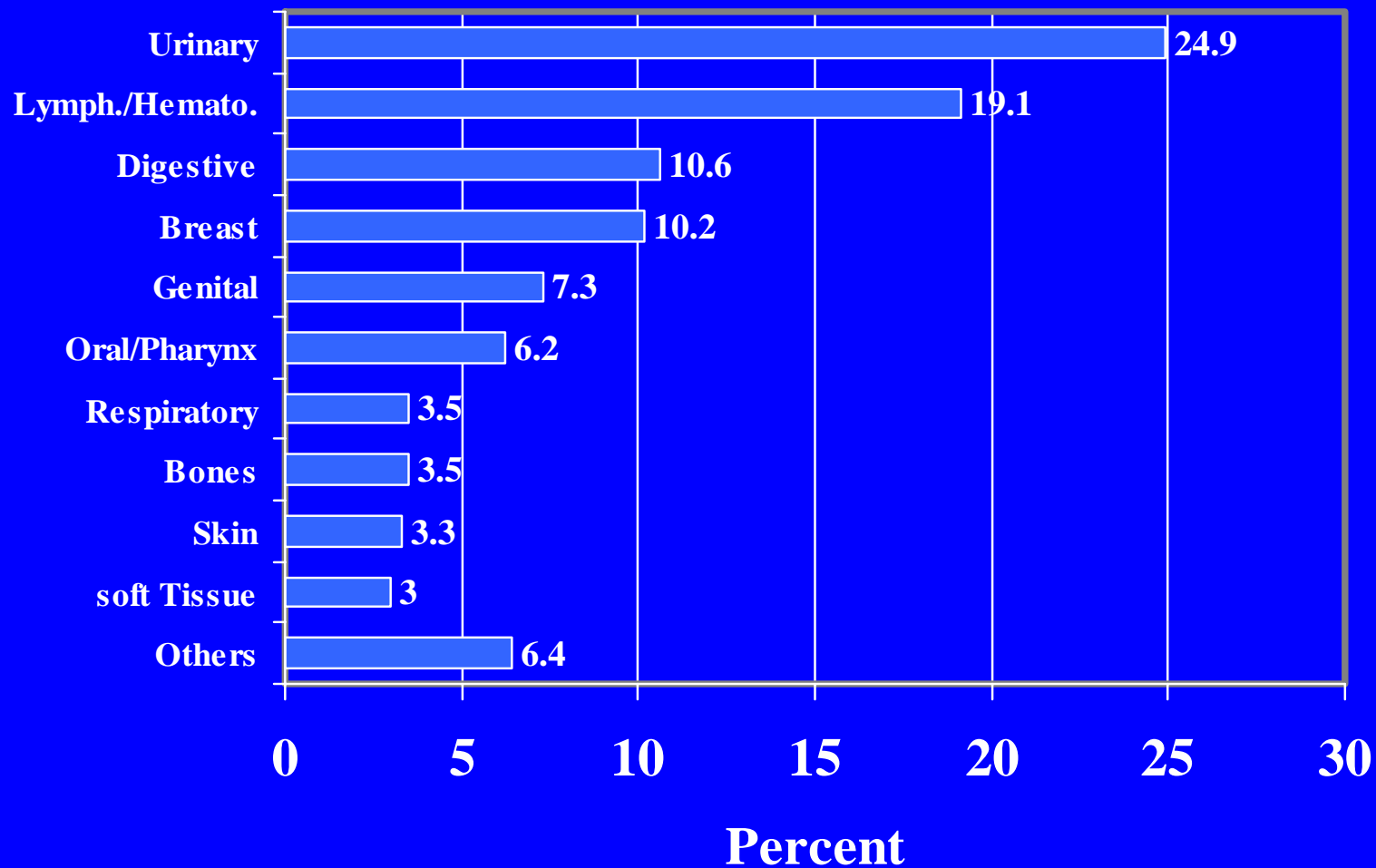
- Lebanon : 7% M , 5% F
- Iraq : 7.1% M , 5.1% F
- Sudan : 10% M , 3.2 % F
- Morocco : 10.1% M , 3.9% F
- KSA : 7.3 %
- Jordan : 5.9 %

NATIONAL CANCER INSTITUTE CAIRO UNIVERSITY





Site distribution
15975 Malignant cases
NCI - Cairo , 1986 - 1993



Cancer Registry of 13 607 new cases 8 cancer centers – (1999-2000)

Breast Cancer	27 %
Bladder Cancer	10 %
Lymphomas	10 %
Liver cancer	8 %
Leukemias	3 %
Lung Cancer	3 %
Colon Cancer	2 %

Current Status Of Management of Adult Non-Hodgkin's Lymphoma

Recent Developments:

- Classification
- Prognostic factors
- New treatment modalities

Current Status Of Management of Adult Non-Hodgkin's Lymphoma

Classification:

- Pre Working Formulation
- Working Formulation
- REAL / WHO Classification

Morphologic

Immunologic

Genetic

Clinical

Features



Clinico-pathologic profile of adult NHL at NCI, Egypt

**Pathologic Classification According to the previously adopted
Working Formulation (Pathology Department) :**

Low Grade	142	10.97 %
Intermediate Grade	726	56.11 %
High Grade	352	27.20 %
Miscellaneous	74	5.72 %
<hr/>		
Total	1294	100 %

REAL CLASSIFICATION --- DISTRIBUTION

Diffuse Large B-Cell Lymphoma	31%
Follicular Lymphoma	22%
Small Lymphocyte Lymphoma	6%
Mantle Cell Lymphoma	6%
Peripheral T. Cell Lymphoma	6%
Marginal Zone B-Cell Lymphoma (MALT type)	5%
Primary Mediastinal L B C Lymphoma	2%
Anaplastic Large T/Null C Lymphoma	2%
Lymphoblastic Lymphoma (T/B)	2%
Burkitt's Like Lymphoma	2%
Marginal Zone B-Cell Lymphoma (Nodal type)	1%
Lymphoplasmocytic Lymphoma	1%
Burkitt's Lymphoma	<1%

Table. The relative frequency of non-Hodgkin's lymphoma types at the Department of Pathology Registry, NCI during the period 1998-2000 (n=1095).

Type	%	Average Age	Male:Female
B-cell lymphomas			
Diffuse large B-cell lymphoma	49	47.5	1.3:1
Burkitt's lymphoma	6.9	11.9	4.4:1
Small lymphocytic lymphoma	6	58.3	5.3:1
Follicular lymphoma	5.2	49.3	1.5:1
Plasmacytoma/Myeloma	4.8	52.1	1.1:1
Marginal zone lymphoma	4.5	44.1	1.3:1
Mantle cell lymphoma	4.3	52	2.1:1
Hairy cell leukemia	0.2	36	-
T-cell lymphomas			
Lymphoblastic lymphoma	4.6	17	2.3:1
T-cell lymphoma NOS	3.7	39.9	3.7:1
Anaplastic lymphoma	1.8	28.2	1.6:1
Mycosis fungoides	1	47.5	1.8:1
Unspecified	8	44.9	1:1
Total	100	40.7	2.3:1



Clinical Profile of NHL Patients

At National Cancer
Institute , Egypt



Clinical Profile of NHL , Cairo NCI (427 patients)

- Age :

Range : 18 – 80 years
(median 47 years)

- Sex :

Male / Female : 1.96 / 1



Clinical Profile of NHL , Cairo NCI (427 patients)

- B-symptoms : 40 % positive
- Cervical nodal affection : 64 %
- Splenomegaly : 28 %
- Hepatomegaly : 11 %
- BM involvement : 4 % ?
- Extranodal presentation : 38 %



Clinical Profile of NHL , Cairo NCI (427 patients)

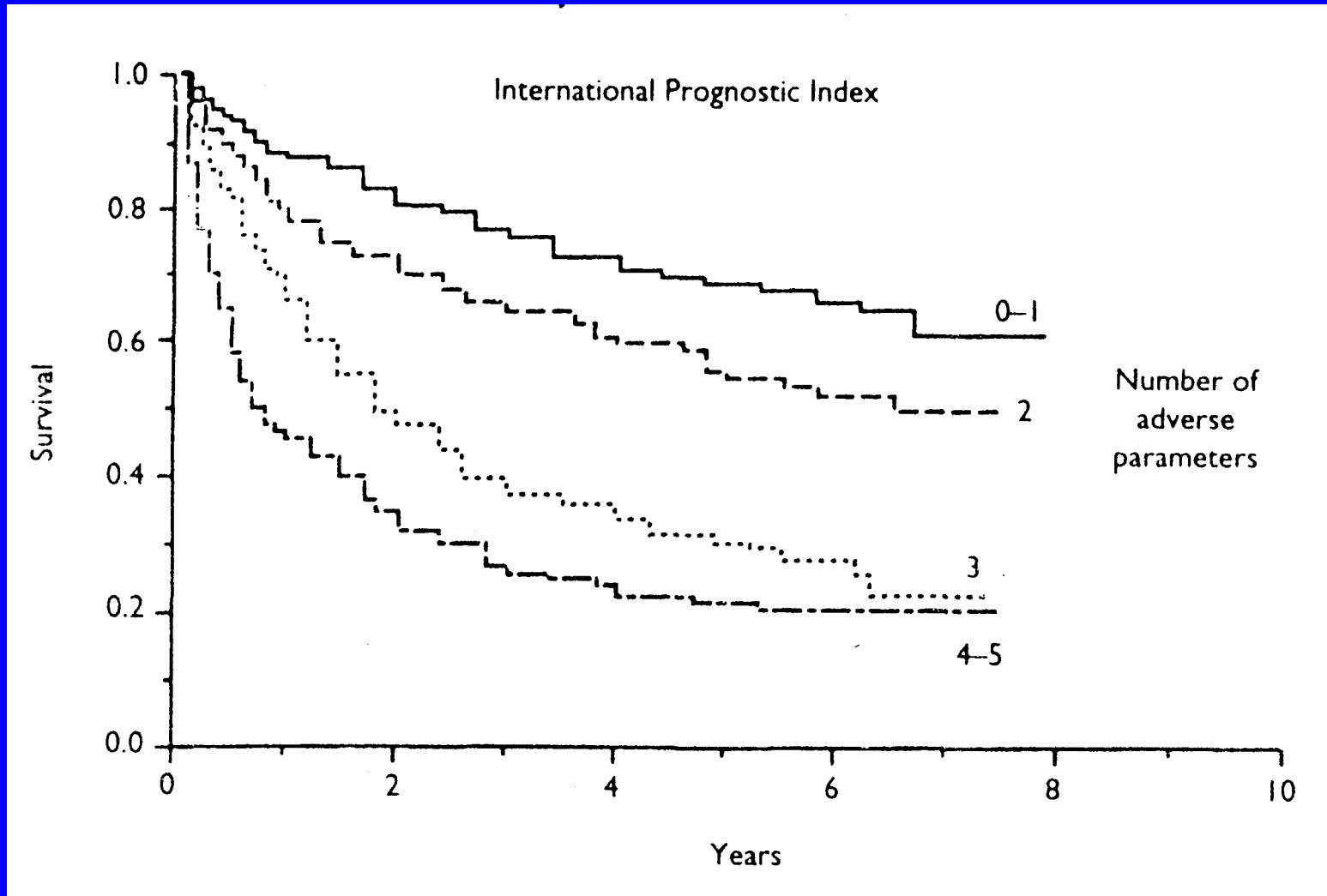
AN ARBOR STAGING SYSTEM

- Stage I : 8 %
- Stage II : 22 %
- Stage III: 40 %
- Stage IV : 30 %

The International Prognostic Index^a

Factor	Adverse prognosis
Age	≥60 years
Ann Arbor stage	III or IV
Serum LDH	Above normal
Number of extranodal sites of involvement	≥2
Performance status	≥ECOG 2 or equivalent

^aInternational Non-Hodgkin's Lymphoma Prognostic Factors Project, A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329**: 987–94.



Principles of management:

- Age , performance , and physiologic status of the patient
- Stage , and IPI Score
- Clinical behavior of the tumor

Indolent

Aggressive

Highly aggressive

Indolent Lymphomas

- *B Cell*

1-CLL/SLL

2-Lymphoplasmacytoid

3-FCC grade I – II

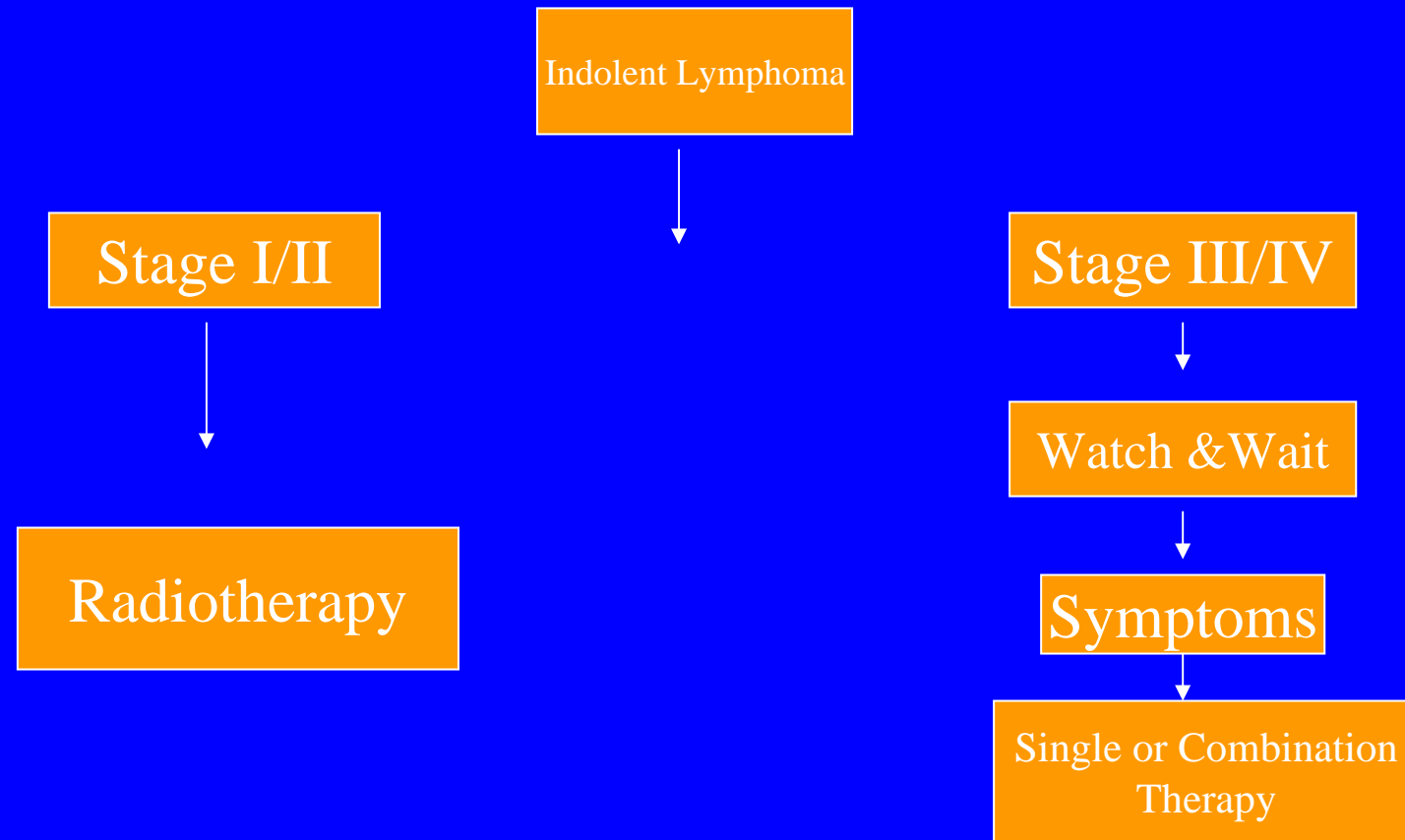
4-MZ

- *T Cell*

1-T-CLL/T-PLL

2-MF

Indolent Lymphomas



Aggressive Lymphomas

- B cell:

- 1- Mantle cell lymphoma
- 2-FCC , grade III
- 3-DLBC
- 4-Primary mediastinal large cell

- T cell:

- 1- Peripheral T cell lymphoma
- 2- Intestinal T cell lymphoma
- 3- Angiocentric Lymphoma
- 4- Angioimmunoblastic lymphoma
- 5- ATLL
- 6- Anaplastic large cell lymphoma

Management of Diffuse Large B Cell Lymphomas

First Generation Chemotherapy

CHOP

CR : 44 %

5-years survival : 35 % - 40 %

(De Vita VT Jr , 1975 Lancet)

Management of Diffuse Large B Cell Lymphomas

Second Generation Chemotherapy

m-BACOD

pro-MACE-MOPP

CR : 65 %

5-year survival : 57 %

(Longo DL , 1991 JCO ; Connors JM , 1988 Sem.Hematol.)

Management of Diffuse Large B Cell Lymphomas

Third Generation Regimen

pro-MACE-CytaBOM
MACOP-B

CR : 51%-86%

5-year survival : 62%-69%

(Longo DL , 1991 JCO ; Klimo P , 1985 Ann. Int. Med.)

Management of Diffuse Large B Cell Lymphomas

Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced NHLs

(Fisher RI et al . NEJM 1993 , 328 : 1002)

Study design

RANDOM

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graph TD; A[RANDOM] --> B[CHOP]; A --> C[MACOP-B]; A --> D[m-BACOD]; A --> E[ProMACE  
Cyta-BOM];
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CHOP

MACOP-B

m-BACOD

ProMACE
Cyta-BOM

Management of Diffuse Large B Cell Lymphomas

(Fisher RI et al . NEJM 1993, 328 : 1002)

- 1138 advanced patients (G II & III) , 899 eligible
- Median age 56 years , with 25% over 64
- Bulky 40% , elevated LDH 46%

NO DIFFERENCE in

Response Rate (50%-55%)

Six years Overall Survival (32%-36%)

Management of Diffuse Large B Cell Lymphomas

How to improve on these largely unsatisfactory results – Future Directions :

- New active agents
- CSFs and dose escalation
- Pediatric-like NHL protocols
- Strategies to overcome drug resistance
- The combination of monoclonal antibodies with chemotherapy
- Continuous infusion regimens
- High dose therapy and PBSCT



Treatment Policy of Adult NHL National Cancer Institute , Cairo

- First Generation (1975 – 1985) :
 - COP
 - IOP
 - CHOP
- Second Generation (1985 – 1995) :
 - BECOP-I
 - BECOP-II
 - BECOP-III
- Third Generation
 - Continuous infusion (EPOCH - CODBLAM)
 - MIME
 - CHOP-Interferon

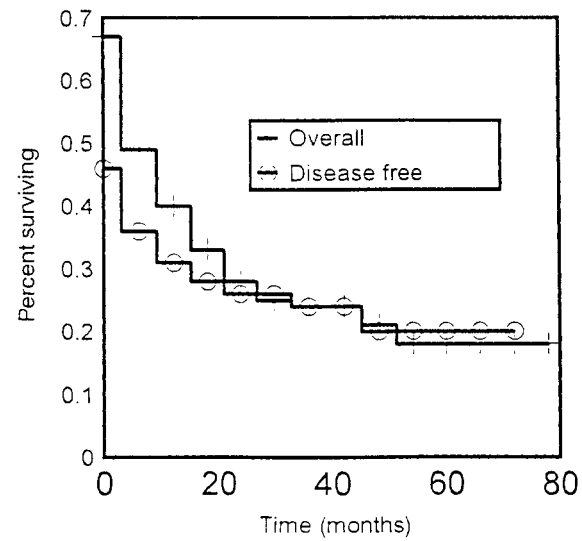


International Cooperation

- SWOG
- NCI , Bethesda , USA
- IOSG
- EORTC



First Generation (1975-1985)





BECOP REGIMENS

- BECOP I:

VCR 1.4 mg/sm iv days 1 , 8

Epirubicin 40 mg/sm iv days 1, 8

CTX 650 mg/sm iv days 1, 8

Bleomycin 5 un/sm iv days 15,22

Pred. 60 mg/sm po days 15-28

Courses are repeated every 4 weeks



BECOP - I

42 patients

- advanced stages III and IV
- grades II and III

CR rate 67 % (28/42)

3-year survival rates

- overall 48 %
- disease free 36 %



BECOP REGIMENS

- BECOP II:

VCR 1.4 mg/sm iv days 1, 8

Epirubicin 40 mg/sm iv days 1, 8

CTX 650 mg/sm iv days 1, 8

Bleomycin 10 un/sm iv day 15

Pred. 60 mg/sm po days 15-21

Courses are repeated every 3 weeks



BECOP - II

- Number of Patients 108
- M/F 76/32 (2.4)
- Age range 16-70 years
median 42 years
- Pathologic grade II 82 (76%)
III 26 (24%)
- Stage at presentation I 11 (10%)
II 19 (18%)
III 64 (59%)
IV 14 (13%)



BECOP - II

Out of 101 evaluable patients :

Response Rate CR 79 78 %

 PR 10 10 %

3- Survival Rate Overall 55 %

 Disease Free 50 %



BECOP - III

- As BECOP II but with 25 % dose increase of CTX and Epirubicin with GM-CSF given days 9-18.
- Higher CR rate for BECOP III (90% vs 80%)

A Prospective Randomized Study of Chop Versus Chop Plus Alpha-2B Interferon in Patients with Intermediate and High Grade Non-Hodgkin's Lymphoma: the International Oncology Study Group NHL1 Study

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Leukaemia and Lymphoma, 2000, Vol. 40 (1-2), pp.95-103

Intermediate and High Grade Non-Hodgkin's Lymphoma
According to Treatment Group

<i>Response</i>	<i>CHOP (N=214)</i>	<i>CHOP-INF (N=221)</i>
	no. of patients (%)	
Response		
Complete	118 (55)	119 (54)
Partial	56 (26)	57 (26)
Stable disease	9 (4)	4 (2)
Progression/Relapse	32 (15)	40 (18)

CHOP AND ALPHA INTERFERON IN NHL

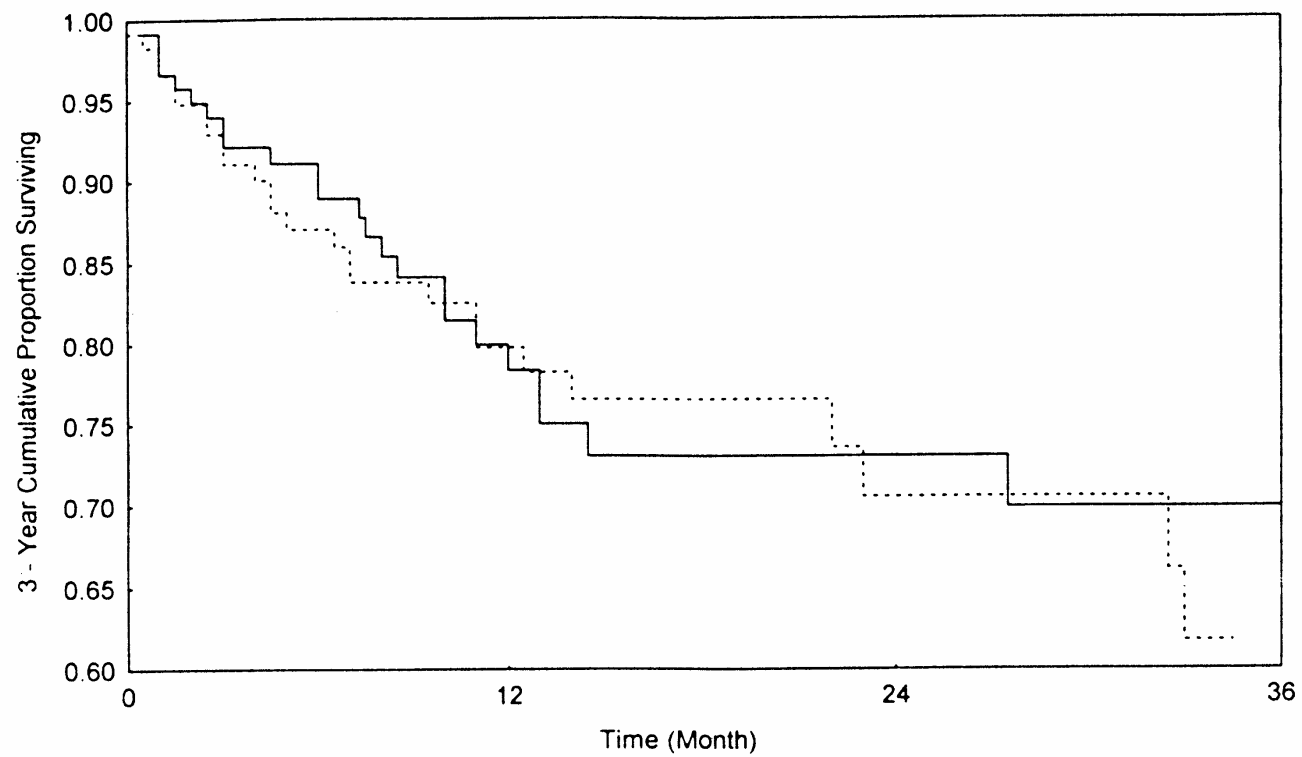


FIGURE 1 Three year cumulative proportion surviving curve (----- CHOP, - CHOP - INF)



Continuous Infusion Regimens (EPOCH)

- Phase III randomized clinical trial vs. CHOP
- Continuous infusion of E,V,D over 4 days
- 78 patients were randomized between the 2 arms
- All patients' clinico-pathologic characteristics were balanced between both arms including the IPI.



Continuous Infusion Regimens (EPOCH)

	CHOP	EPOCH
CR	27 (68%)	19 (50%)
PR	10 (25%)	11(29%)
ID	1 (2.5%)	7 (18.4%)

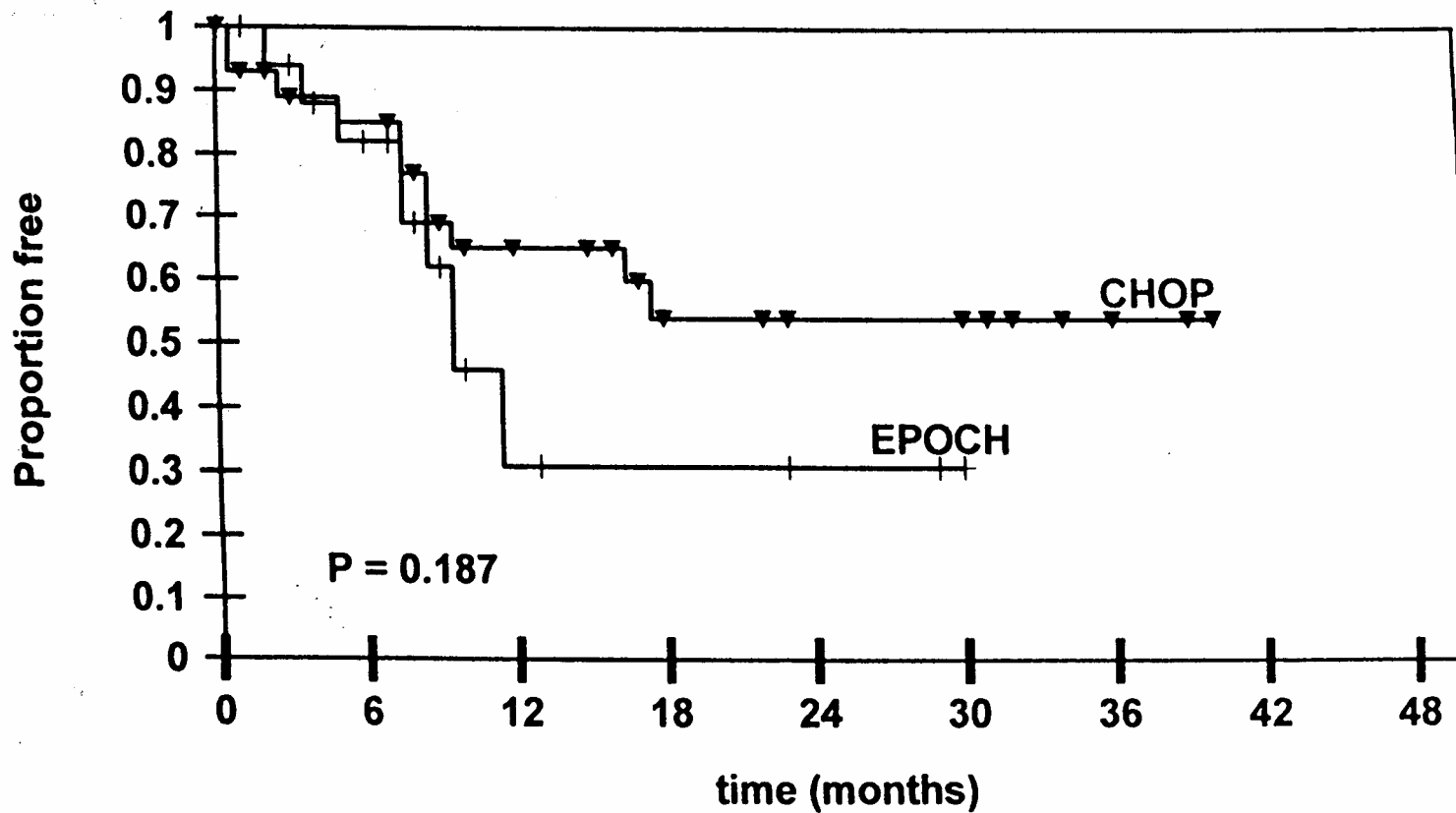


Fig. (1) Event free survival of the 78 NHL patients who received CHOP and EPOCH regimens.

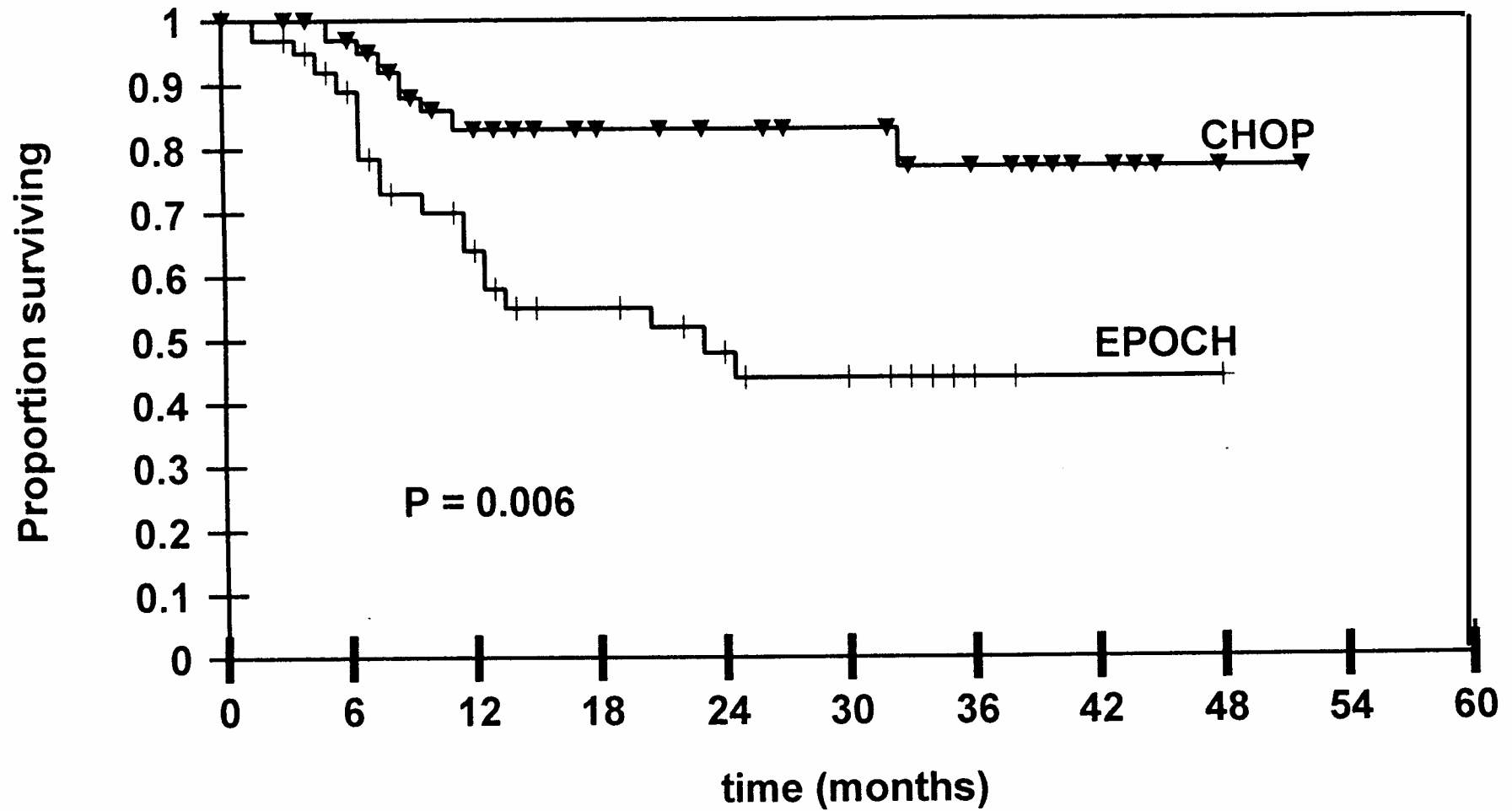


Fig. (2) Overall survival of the 78 NHL patients who recieved CHOP and EPOCH regimens.

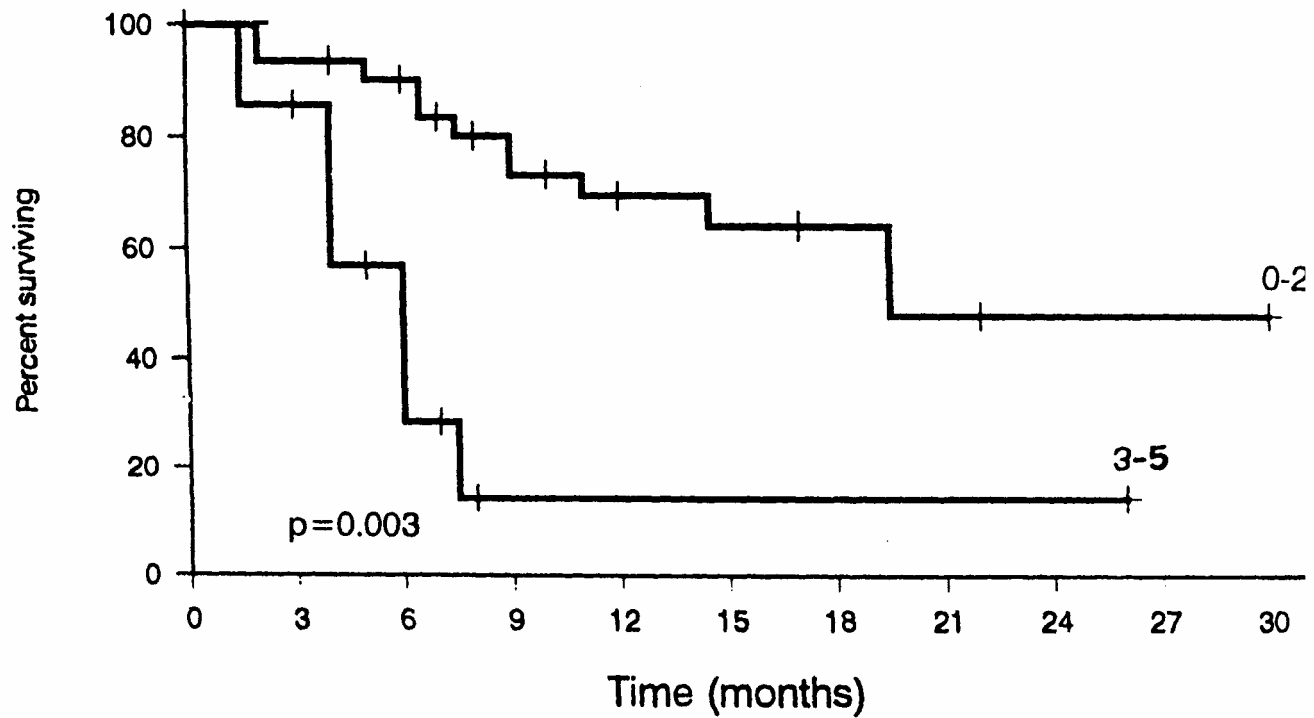


Fig. (3) Overall survival in relation to international index for the EPOCH group.



Continuous Infusion Regimens (COD BLAM)

- Phase III randomized clinical trial vs. CHOP
- 89 patients were randomized between the 2 arms
- All patients' clinico-pathologic characteristics were balanced between both arms including the IPI.



Continuous Infusion Regimens (COD BLAM)

	CHOP	COD BLAM
CR	39 (87%)	33 (78%)
No CR	6	10
No. of relapses	11(28%)	7 (21%)
Mortality	5	9

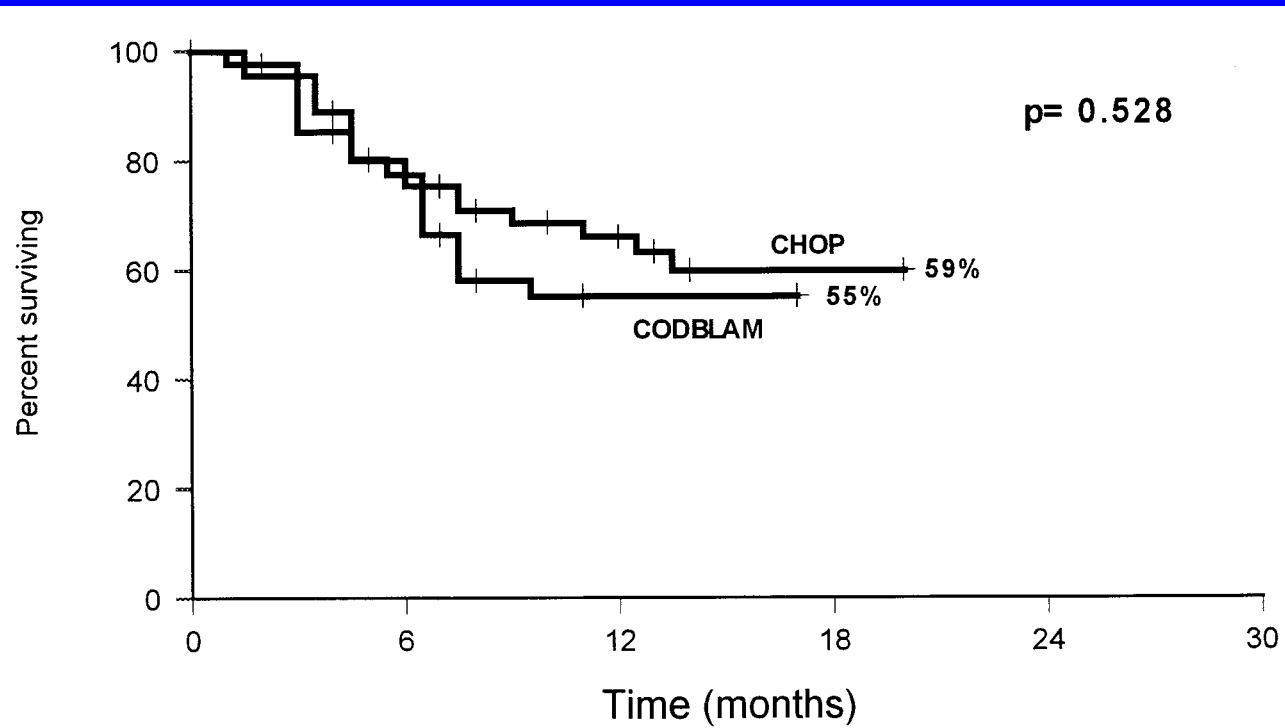


Fig (1): Event free survival rates of patients receiving the CODBLAM and CHOP regimens.

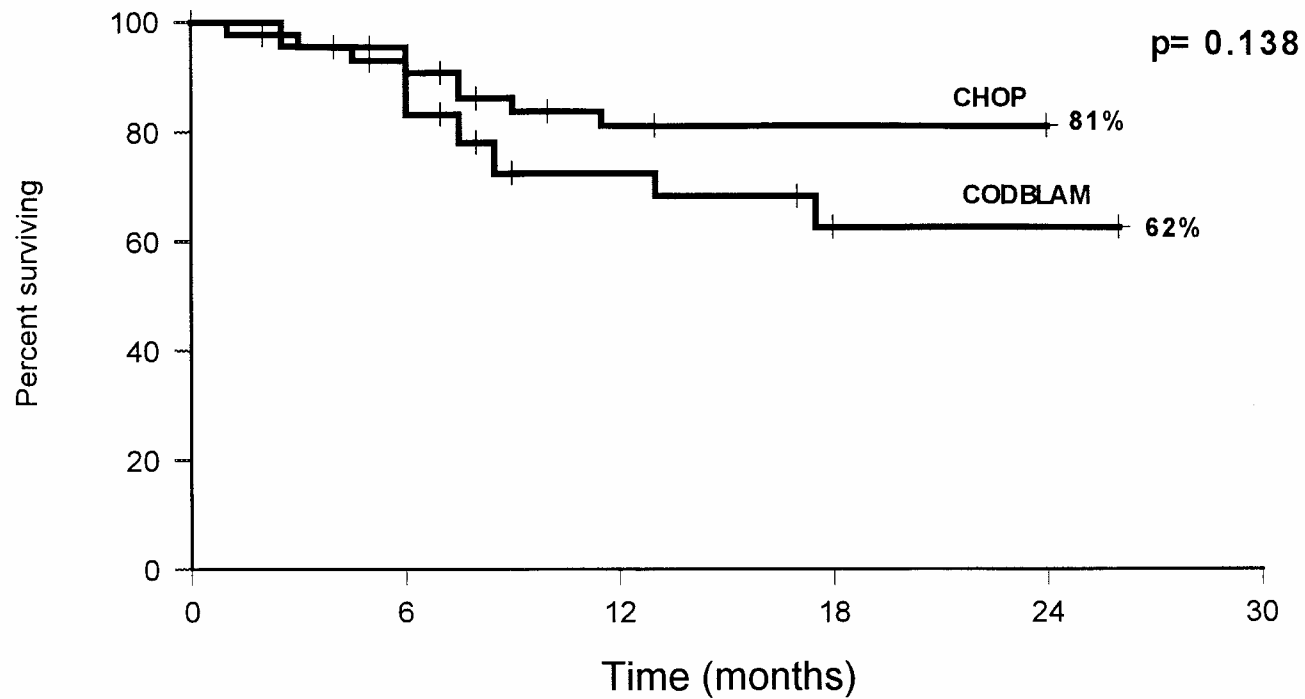


Fig (2): Overall survival rates of patients receiving the CODBLAM and CHOP regimens.

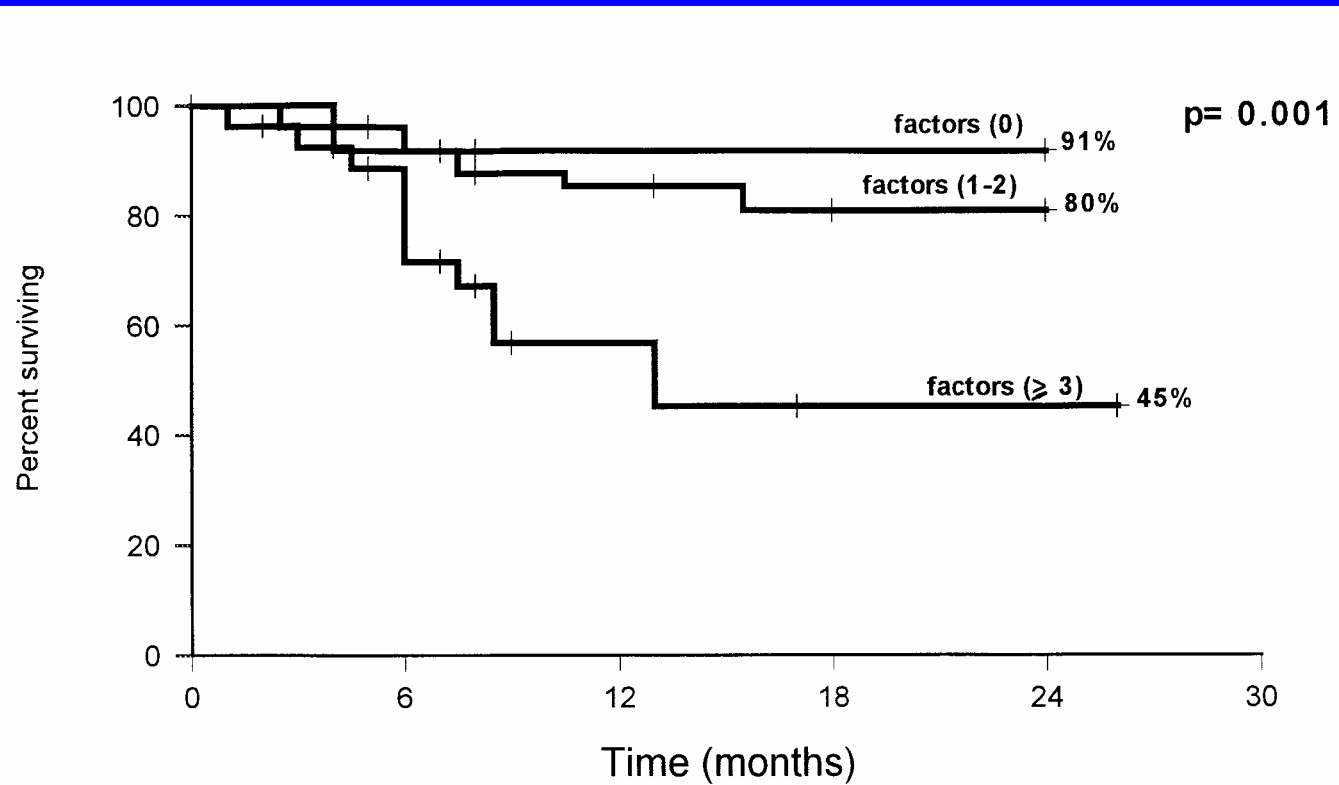


Fig (3): Overall survival rates of patients according to the international index risk factors.

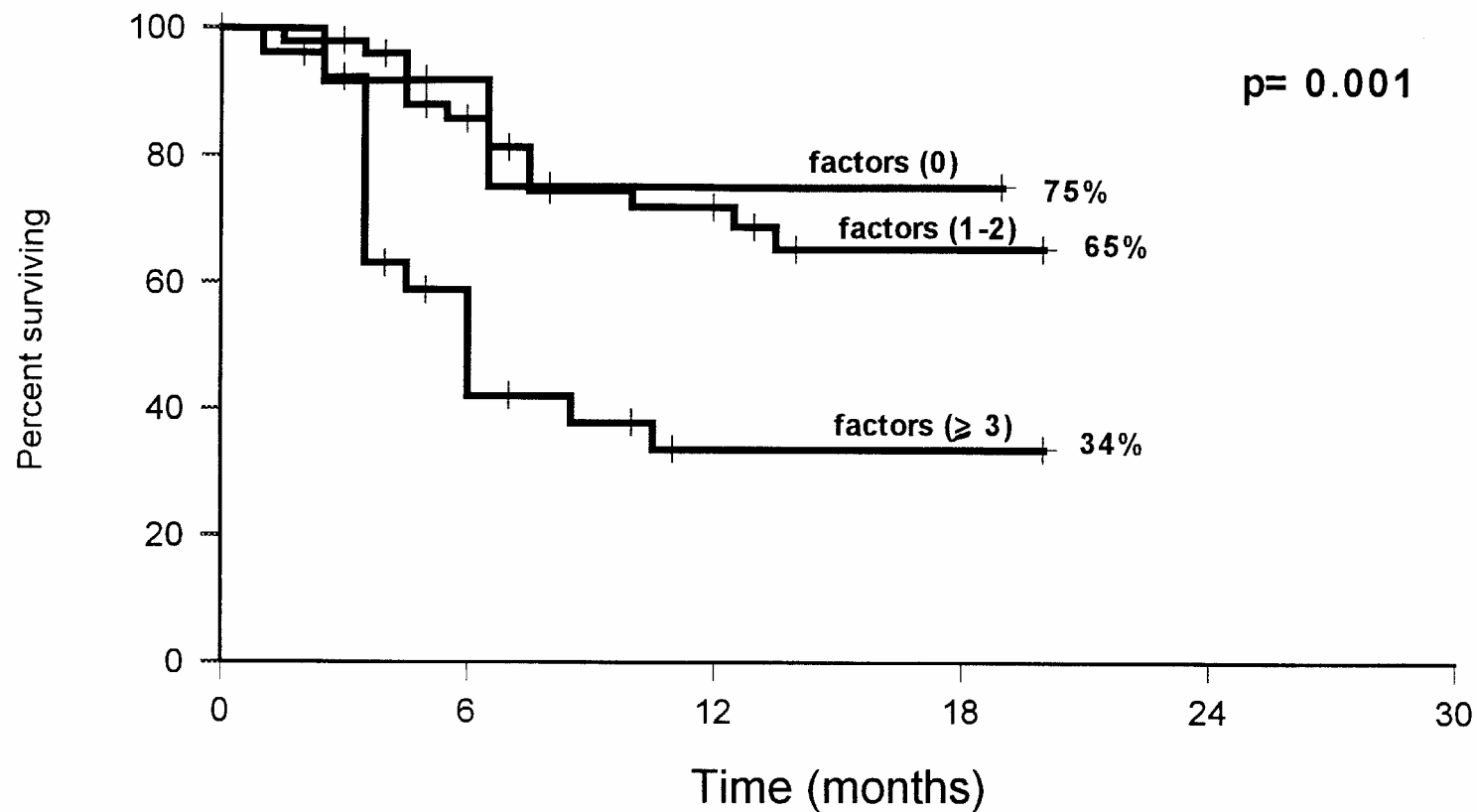
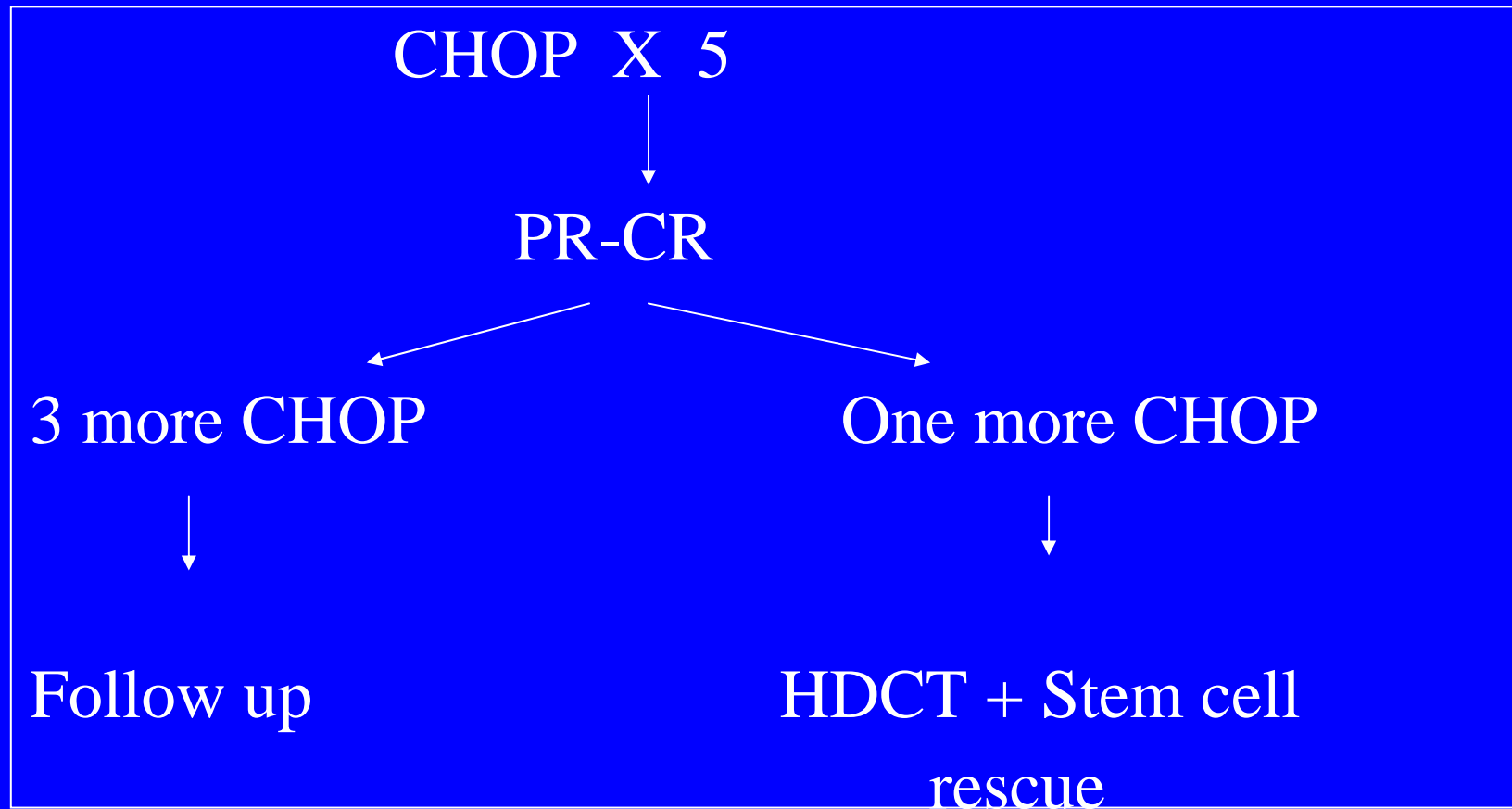


Fig (4): Event free survival rates of patients according to the international index risk factors.



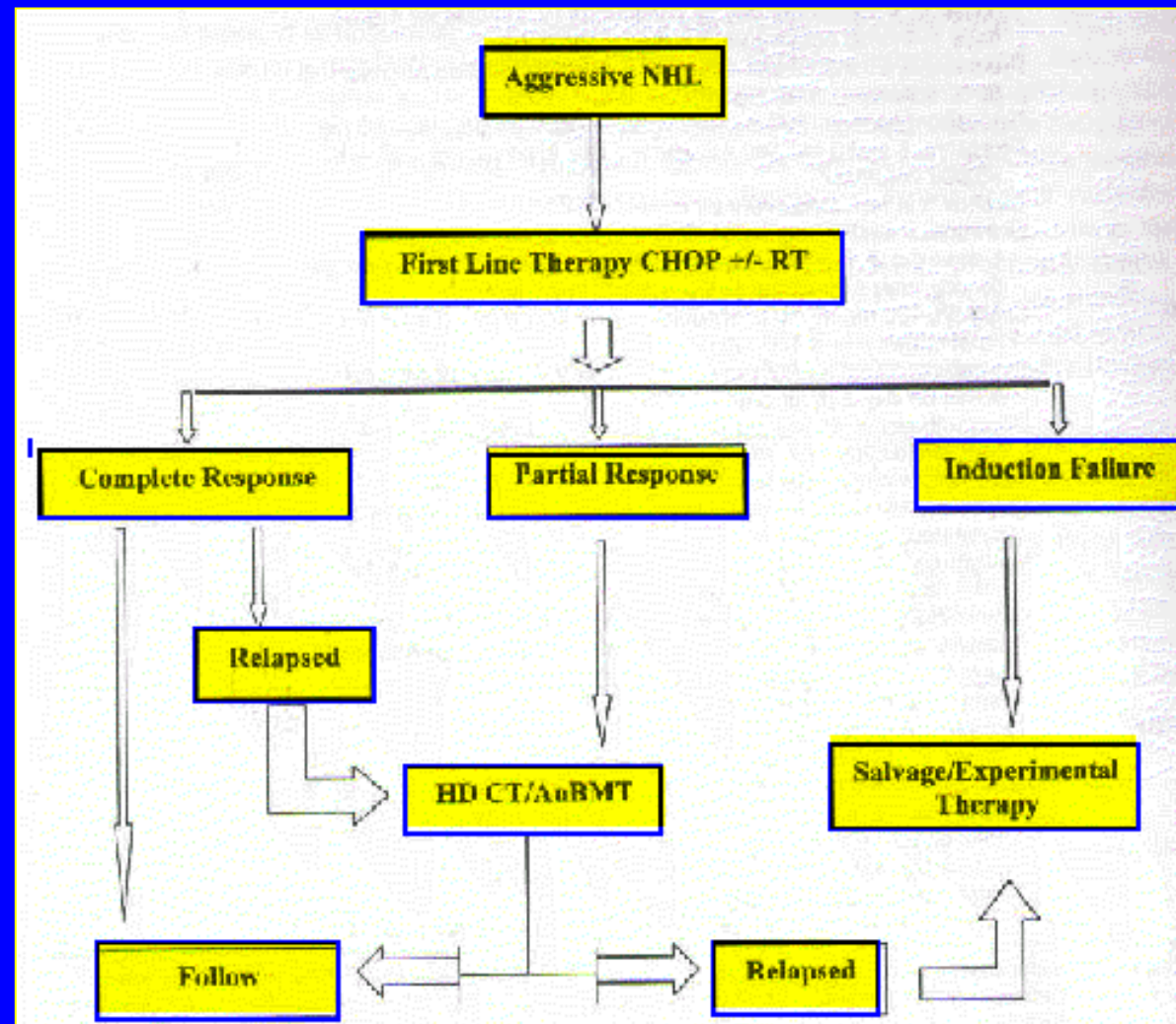
High Dose Chemotherapy and Autologous Stem Cell Transplantation vs. CHOP in Poor Risk NHL Patients.





High Dose Chemotherapy and Autologous Stem Cell Transplantation vs. CHOP in Poor Risk NHL Patients.

- 30 patients were included .
- CR : 6 cases only
- High dose arm : 3 patients , 2 relapsed
- CHOP arm : 3 patients , 1 relapsed





Treatment Policy of Adult NHL National Cancer Institute , Cairo

Current Ongoing Protocols

- High dose therapy in high risk cases
- Some EORTC trials