

Treatment of childhood NHL in Brazil.

INCTR – march 2007

L.N.H. no Brasil

- Although data base is still not comprehensive, the incidence of childhood NHL in Brazil seems to be very similar to those observed in Europe and United States.
- Approximately 10% of all pediatric oncology diagnosis

Treatment of childhood NHL in Brazil.

- Until 1990 the childhood NHL in Brazil were treated in the various services with different therapeutic schemes.
- From 1990 onwards, the Brazilian Cooperative Group for NHL treatment has proposed therapeutic protocols aiming a standardization of diagnosis and treatment.

Treatment of childhood NHL in Brazil.

- Main objectives:
 - understand the Brazilian reality considering the different types of NHL and respective behavior.
 - Propose a viable and modern protocol that could offer a chance of cure similar to the reality experienced in developed countries.

Treatment of childhood NHL in Brazil.

- Group's first ten years:
 - A great number of services, mainly small teams, joined the Group and found basic orientation and conduct in the protocol proposed.
 - Mistakes in diagnosis, mainly among distinct histological subtypes.
 - High level of protocol violation.
 - Difficulties in data collection. There is no data manager.
 - Unsatisfactory results, but an improvement in survival, probably due to therapeutic orientation and support for the proposed protocol.

Treatment of childhood NHL in Brazil.

- NHL 2000 Protocol-new concepts and requirements:
 - Must have: Pathology diagnosis with immunohistochemistry /immunophenotyping is an obligation.
 - If possible: Molecular genetics.
 - Staging and risk group classification.
 - Different combination regimens for different groups of lymphomas. Different intensities, according to each risk group.

Summary of histologic categories(world health organization classification),immunophenotype,and major clinical features of childhood NHL

HISTOLOGIC-category	Immunophenotype	Sites of presentation	Cytogenetics abnormalities
Burkitt's lymphoma,burkitt's like.	B cell ; sIgM+, CD19+, CD20+, CD10+/, CD5-, CD23-, Cig+/-, slg+, Antígeno B+	Abdomen-GI, bone's face, Ovary, renal L3	LgH-R, IgH-R, IgL-R, t(8;14), t(8;22) ou t(2;8) (c-myc)
Lymphoblastic lymphoma	B Cel precursor, TdT+, CD19++, CD79a+, CD10+/-, HLADR+, Sig-	Bone marrow, Lymph-nodes L1 e L2	LgH-R, TCR-G ou R
	Precursor T Cell, TdT, CD1a+, CD3+, CD7+, CD4+, CD8+	Mediastinal Lympho-nodes, Bone marrow – Blood L1/L2	TCR-R maioria ou G, IgH-R ou G (maioria), t(8;14), t(11;14), t(10;14), t(1;14)
Anaplastic Large cell Lymphoma (KI1/ CD30+)	T cell, Positive T cell Antígenos or null, CD30+, EMA+	Lympho-nodes, skin, soft tissue,bone	T(2;5)
Large B cell Lymphomas	Células B, Sig+/-, CD19+, CD20+, CD45+, CD10+/-	Mediastinal, Tymus or others	LgH-R, IgL-R

BCNHLG- 2000 PROTOCOL

NHL GENERAL CLASSIFICATION:

Burkitt'S Lymphoma :

Low risk

Standart risk

Intermedian risk

High Risk

Lymphoblastic Lymphoma:

Low Risk

High Risk

Large Cell Anaplastic and diffuse:LG1,LG2 e LG3

NHL-2000

Total doses by risk group

	VCR	CTX	MTX	VP16	ARAC	IFO	ADRIA
L.R.	12 mg/m ²	4,8g/ m ²	8g/ m ²	-----	-----	-----	-----
S. R.	7 mg/m ²	5,1g/ m ²	4g/ m ²	600mg/m ²	1,8 g/m ²	-----	-----
I.R.	4 mg/m ²	5,1g/ m ²	10 g/m ²	600mg/m ²	6 g/m ²	-----	-----
H.R.	8,5 mg/m ²	7,5 g/ m ²	15 g/m ²	800 mg/m ²	12,25 g/ m ²	12,5 g/ m ²	60 mg/m ²

L.R. = LOW RISK S.R. = STANDARD RISK I.R. = INTERMEDIATE RISK H.R. = HIGH RISK

NHL 2000 PROTOCOL

General scheme protocol:

Every new patient must be located in one of the following groups:

1-Low risk T - COMP - PVD - Maintenance(18 months)

2-Low risk B –four cycles of COMP with Pred. No 1 and no 3.

3-Standard risk B - COP - A - B - A - B.

4-Intermediate risk B - COP - AA - BB - AA - BB.

5-High risk B - COP - AA - D - AA - E - AA .

6-High risk T - COP - Induction - Consolidation - HDARAC - Reinduction - Maintenance (24 months)

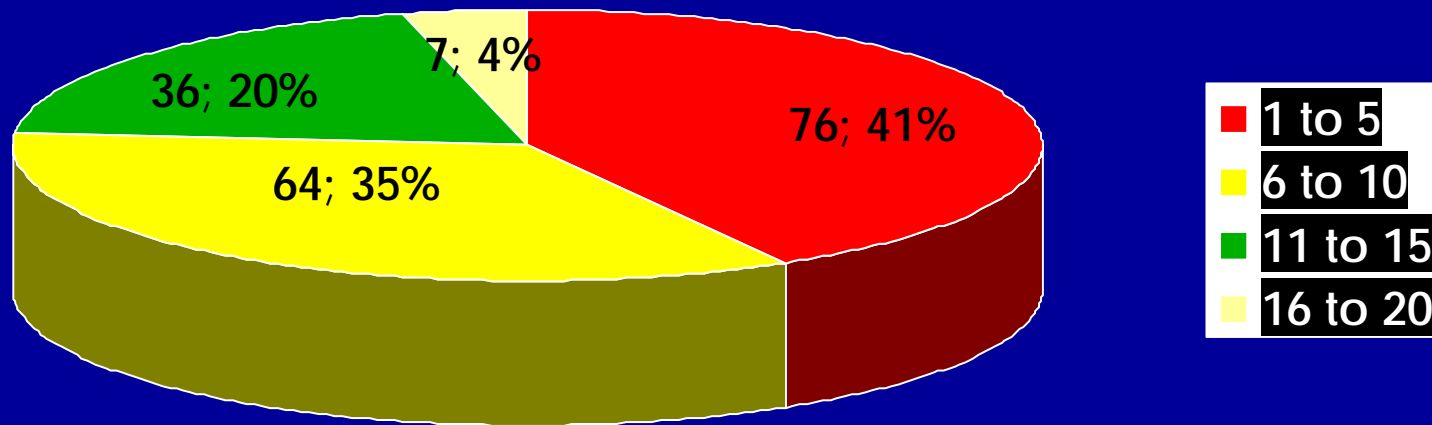
7-Anaplastic Large Cell or Diffuse Lymphoma - G1, G2 ou G3.

Participating Services

NHL-2000

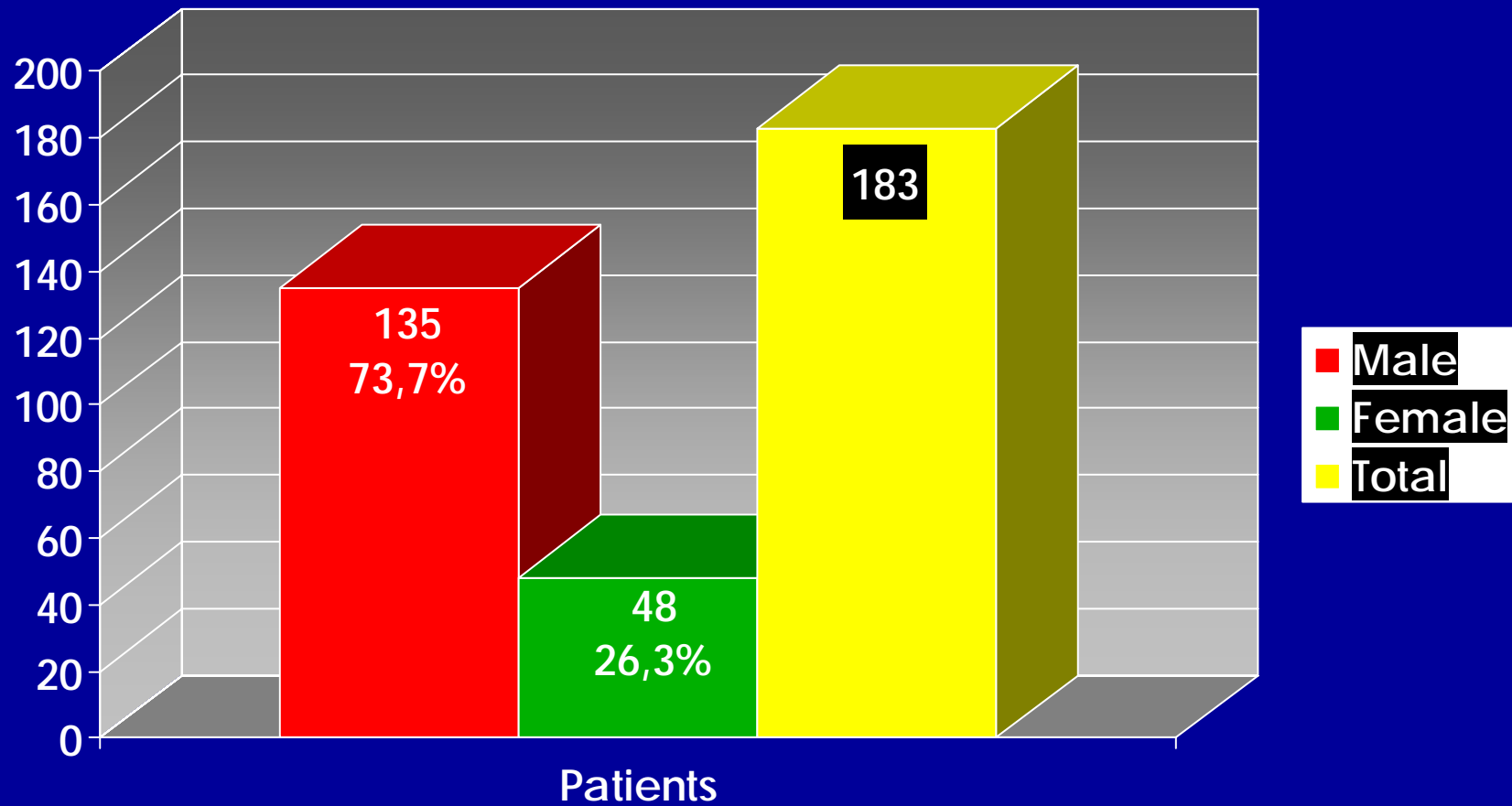
- **ONCOPEDSM - Hospital Santa Marcelina ***
- **OBH - ONCO - Sociedade de Oncologia da Bahia Ltda ***
- **Hospital Infantil Nossa Senhora da Gloria de Vitoria - HINSG ***
- **HIDV - Hospital Infantil Darcy Vargas ***
- **CACON-I - Hospital de Apoio - Hospital Público CACON-I**
- **FCECON - FUNDAÇÃO CENTRO DE CONTROLE DE ONCOLOGIA DO ESTADO DO AMAZONAS**
- **FMABC - Faculdade de Medicina do ABC**
- **GOP - GOP Grupo de Oncologia Pediátrica**
- **HC-UFPR - Hospital de Clínicas - UFPR**
- **HCSA - Irmandade da Santa Casa de Misericórdia de Porto Alegre**
- **HIJG - Hospital Infantil Joana de Gusmão**
- **HMK - PED - Hospital Mario Kroeff**
- **HNL - Hospital Napoleão Laureano**
- **HPP - Hospital Pequeno Principe**
- **NOHP HAB SE - Secretaria de Estado de Saúde GDF**
- **ONCO Pediatria - Hospital PRONTOBABY**
- **Santa Casa - Santa Casa de Misericórdia de São Paulo**
- **Serv.Hemato-Onc - Hospital Universitário de Santa Maria**
- **SPCC - Sociedade Piauiense de Combate ao Câncer**

Age distribution

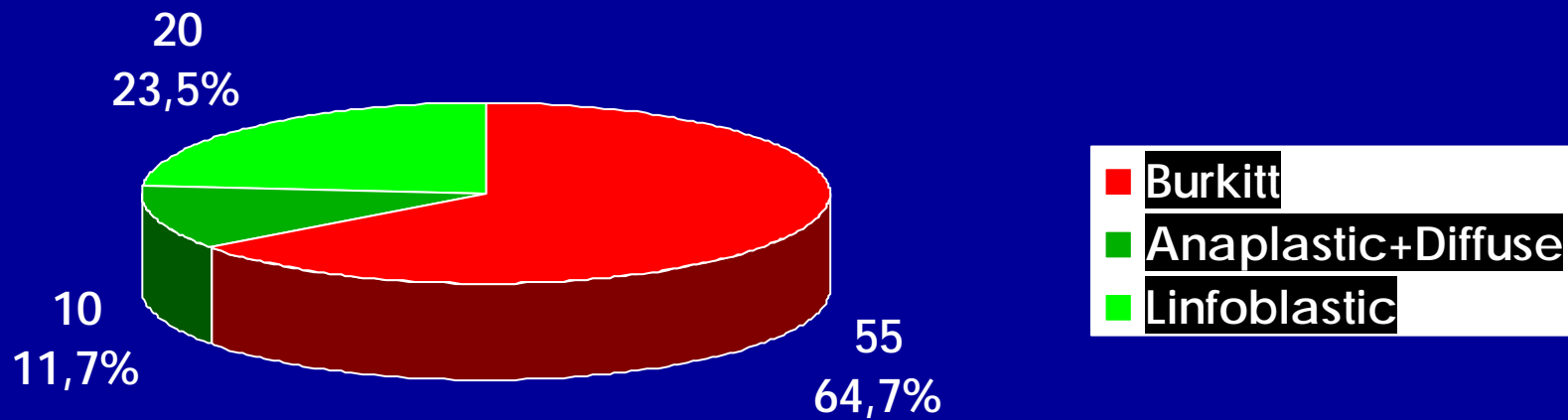


Total:183

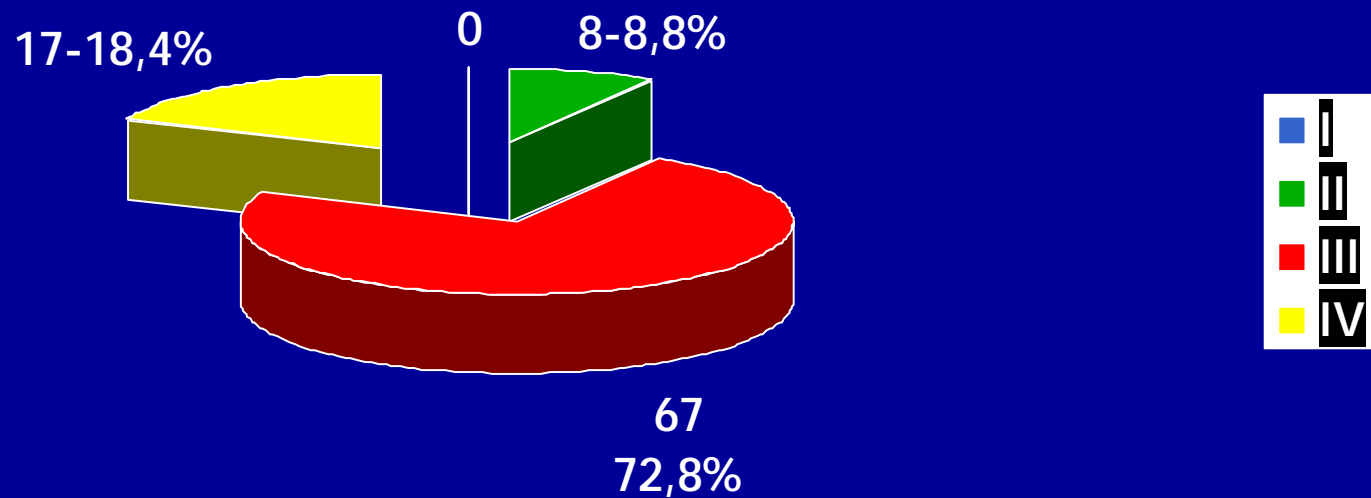
Gender distribution



Hystologic sub type distribution

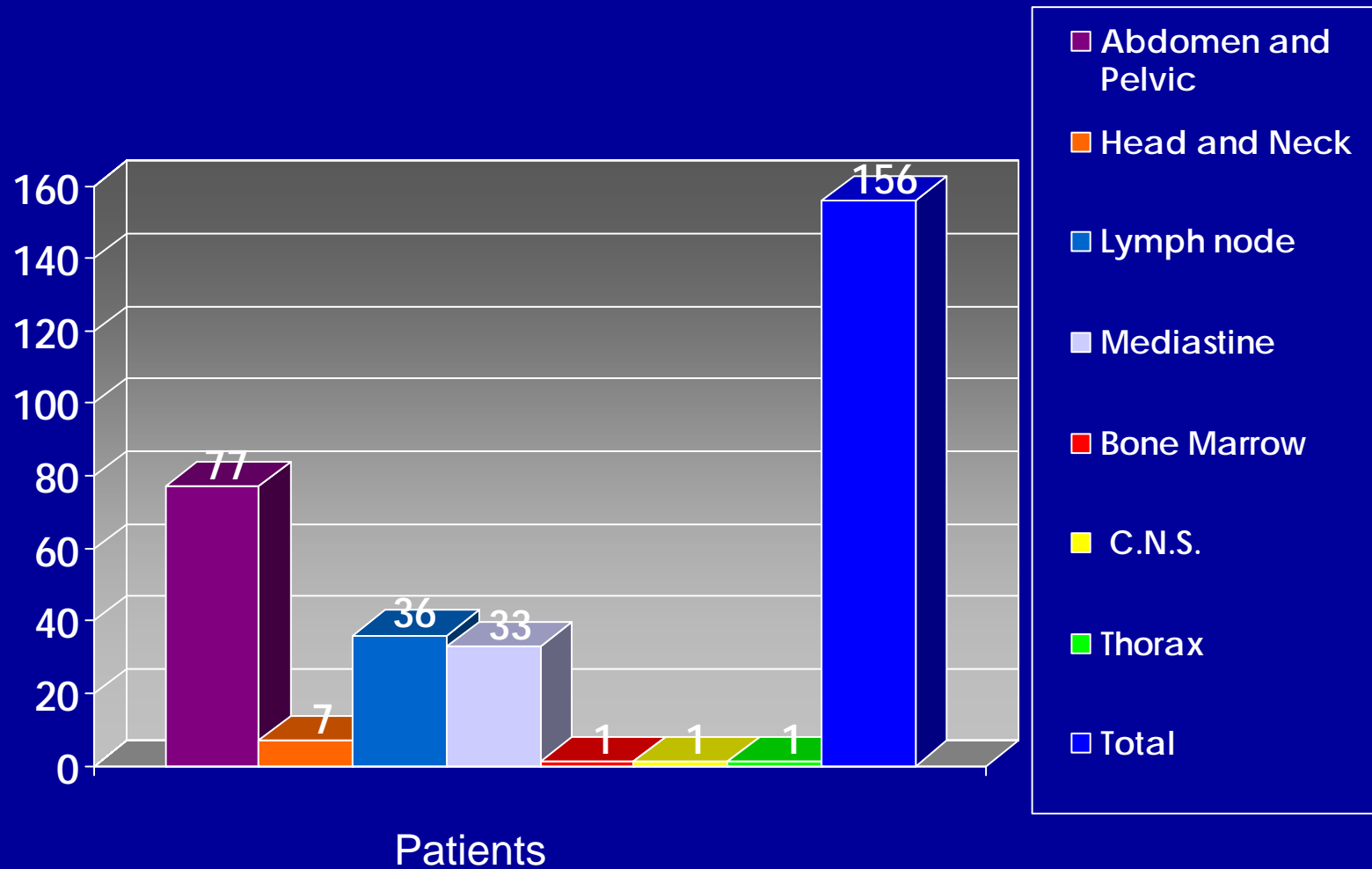


Staging distribution



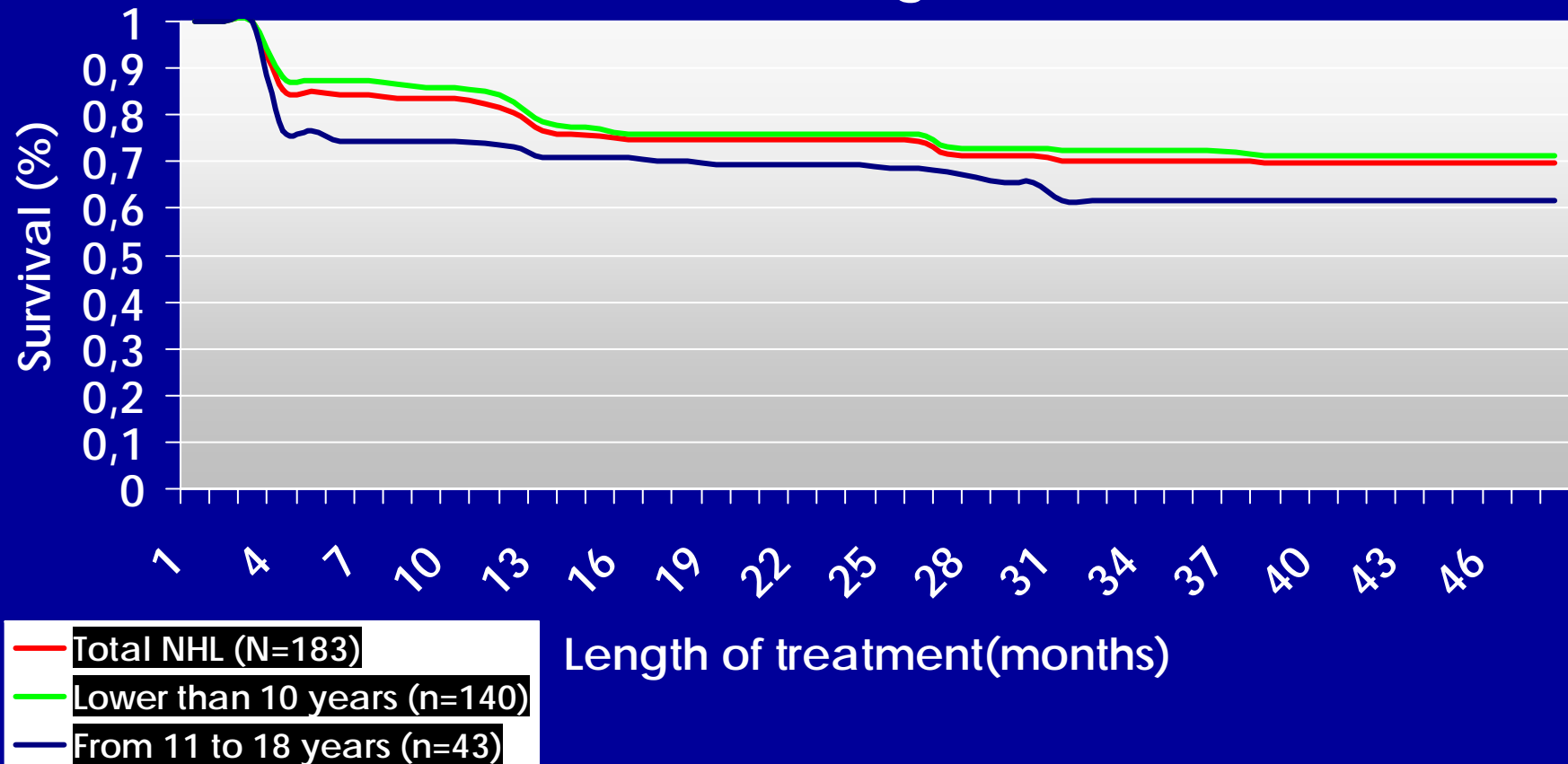
Note: 91 patients without staging information

Distribution According to Primary Location

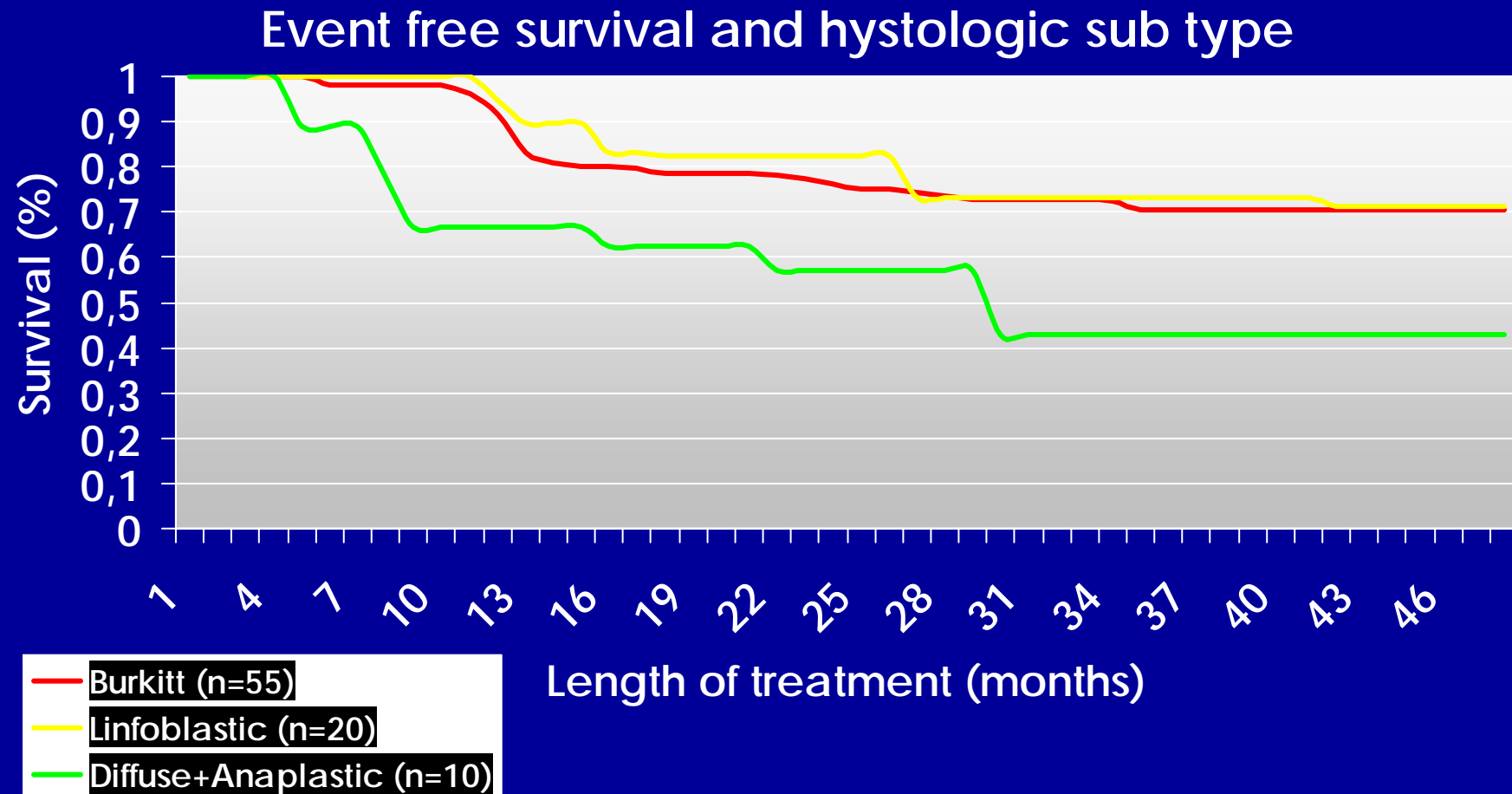


Event free survival for all patients ,less ten and greater eleven

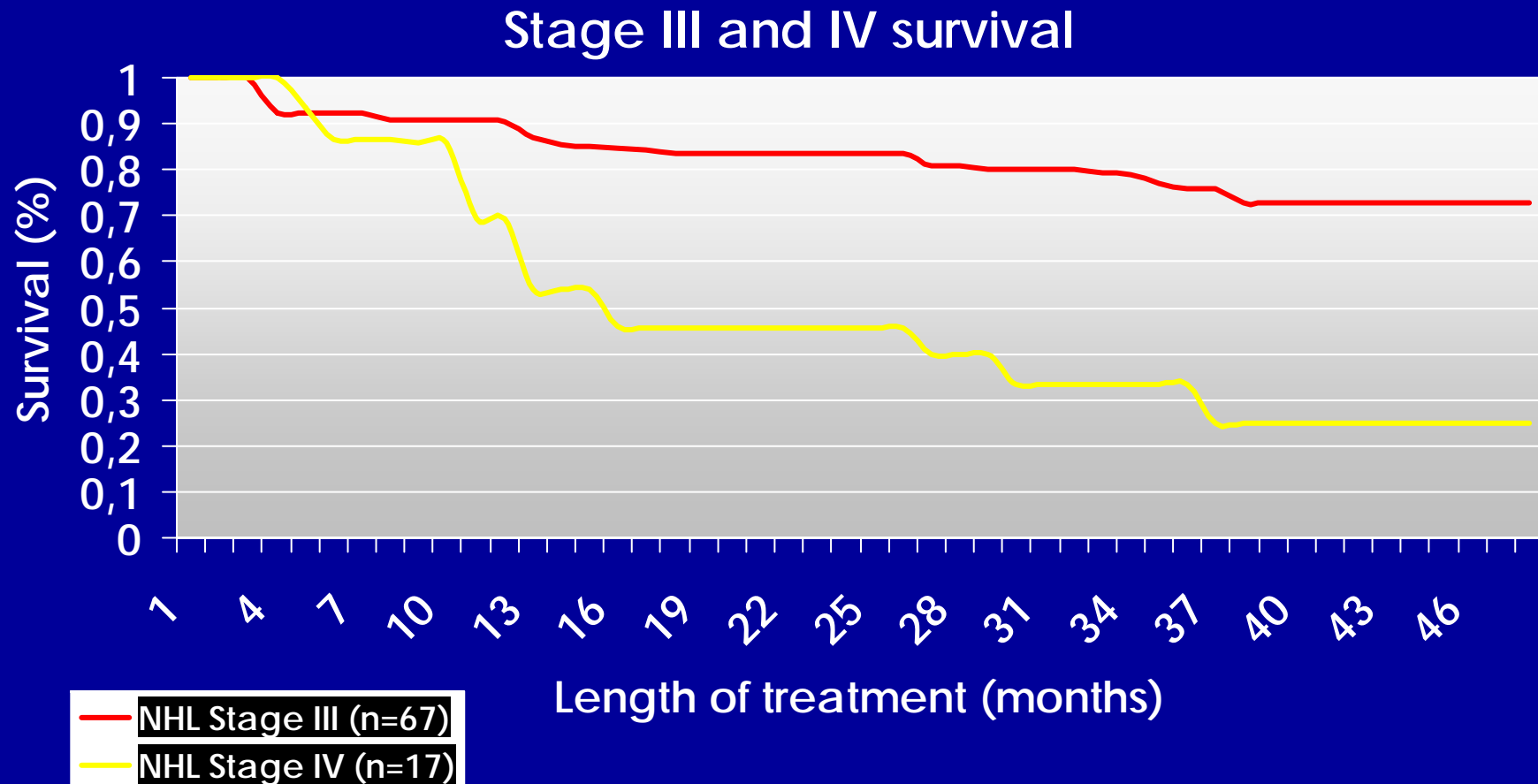
Event free survival - Age distribution



Survival for Different Sub-types



Event free survival for stages III and IV



Treatment of childhood NHL in Brazil.

- On going projects BCGNHL and SOBOPE-expected initiation in 2007.
 - Data Center -CIOPE/SOBOPE supported by Mc Donalds
 - BCGNHLI/SOBOPE Protocol on line-LSI(Integrate System Laboratory-São Paulo University)
 - Outstanding centralized pathology review-Prospective review of byopsies from NHL-2000 Dr.Bacchi/BCGNHL/SOBOPE
 - Fedex account established
 - Development of large scale analysis of lymphomas with tissue micro-array - Dr. Bacchi-supported by NCI grant PI Harrington./SOBOPE
 - Molecular analysis and Epi. Of EBV + BL in Bahia (Drs.Barreto,Araujo,Harrington,Bahia,Dittmer,Fonseca,Brites).support NCI RO1 grants,University of Miami Cancer center.
 - EBV Viral load in BL(Drs.Klumb,Brites,Barreto)supported by NCI,INCA.

Phase II study Therapy Based in antiviral Agents (Zidovudine + Hydroxiurea) in combination with chemotherapy (Doxorubicyne, Methotrexate and Leucovoryn) for relapsed Burkitt's NHL EBV+

- **Population:**
 - 26 patients, age \leq 18 years relapsed Burkitt's NHL.
- **Treatment:**
 - Day 1 Doxorubicine 20 mg/m², IV administration.
 - Day 2 Methotrexate 5 gm/m², IV administration. Followed by leucovorin rescue.
 - Days 2-5 Zidovudine 750 mg/m², IV twice a day.
 - Days 2-5 Hidroxyurea 1000 mg, P.O.once a day.
 - Cycles repeated every 21 days,at least three,maximum 6.
 - The response will be evaluated after cycles 3 and 6.

Rationale for Chemotherapy Drugs in the Protocol

- Doxorubicin - induces the lytic cycle of EBV (Feng et al, *J Viro*)
- Methotrexate - potentiates intracellular level of AZT and induces EBV (Tosi et al, *BLOOD*)
- Hydrea - inhibits ribonucleotide reductase and increases AZT-MP (Hoggard et al, *AIDS*)

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