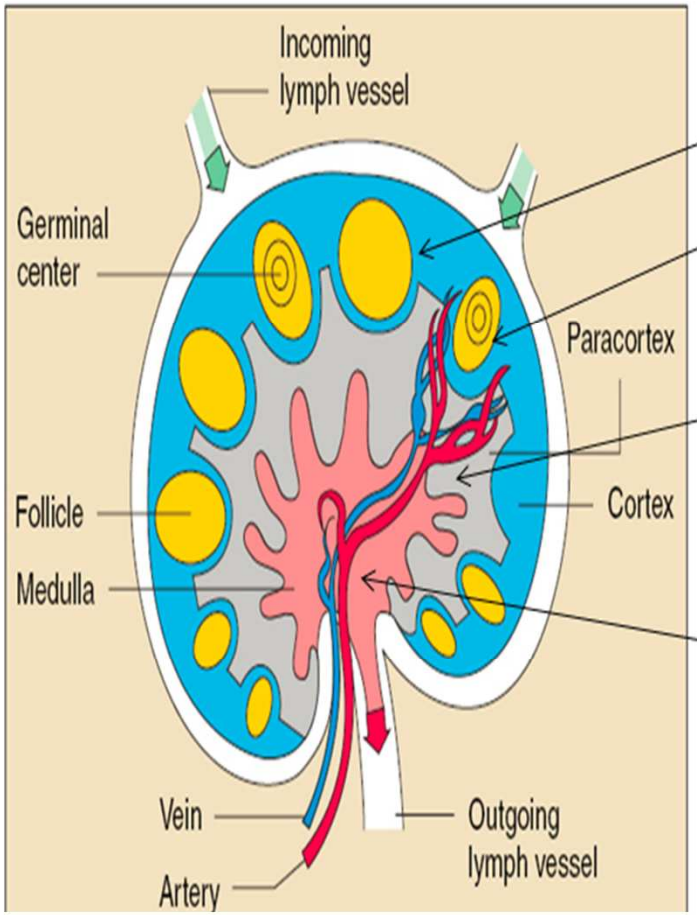
ROLE OF RADIATION IN PAEDIATRICS NON HODGKINS LYMPHOMA

DR S.N.SENAPATI
PROF & HOD
DEPT.OF RADIATION ONCOLOGY,
AH REGIONAL CANCER CENTRE,
CUTTACK

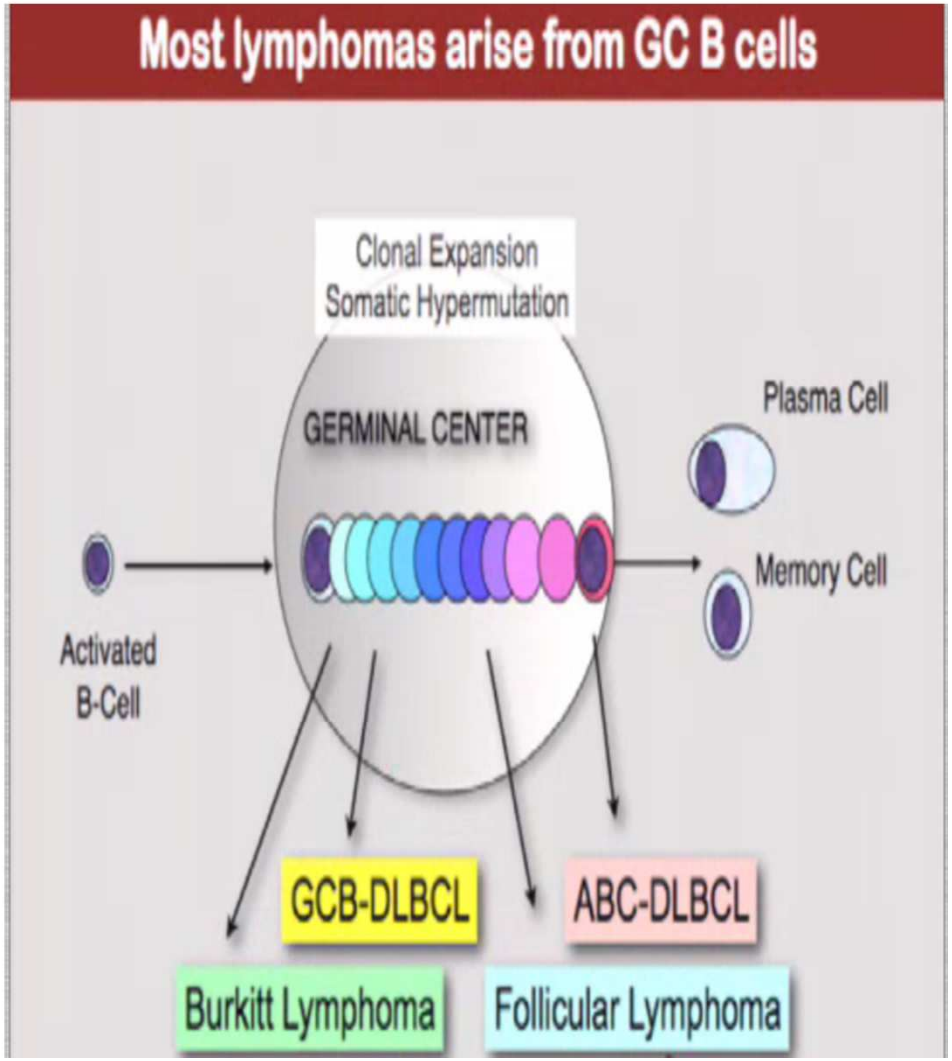


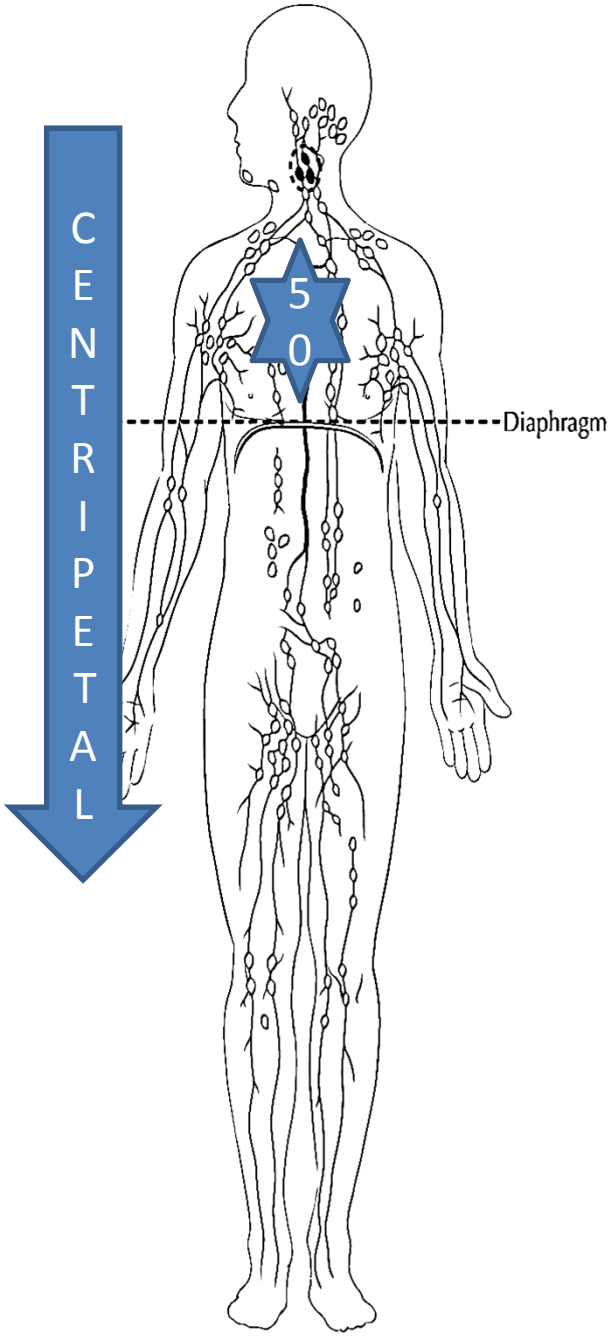
Perifolicular area
(**mantle zone lymphoma**)

Cortex
(B cell zone)

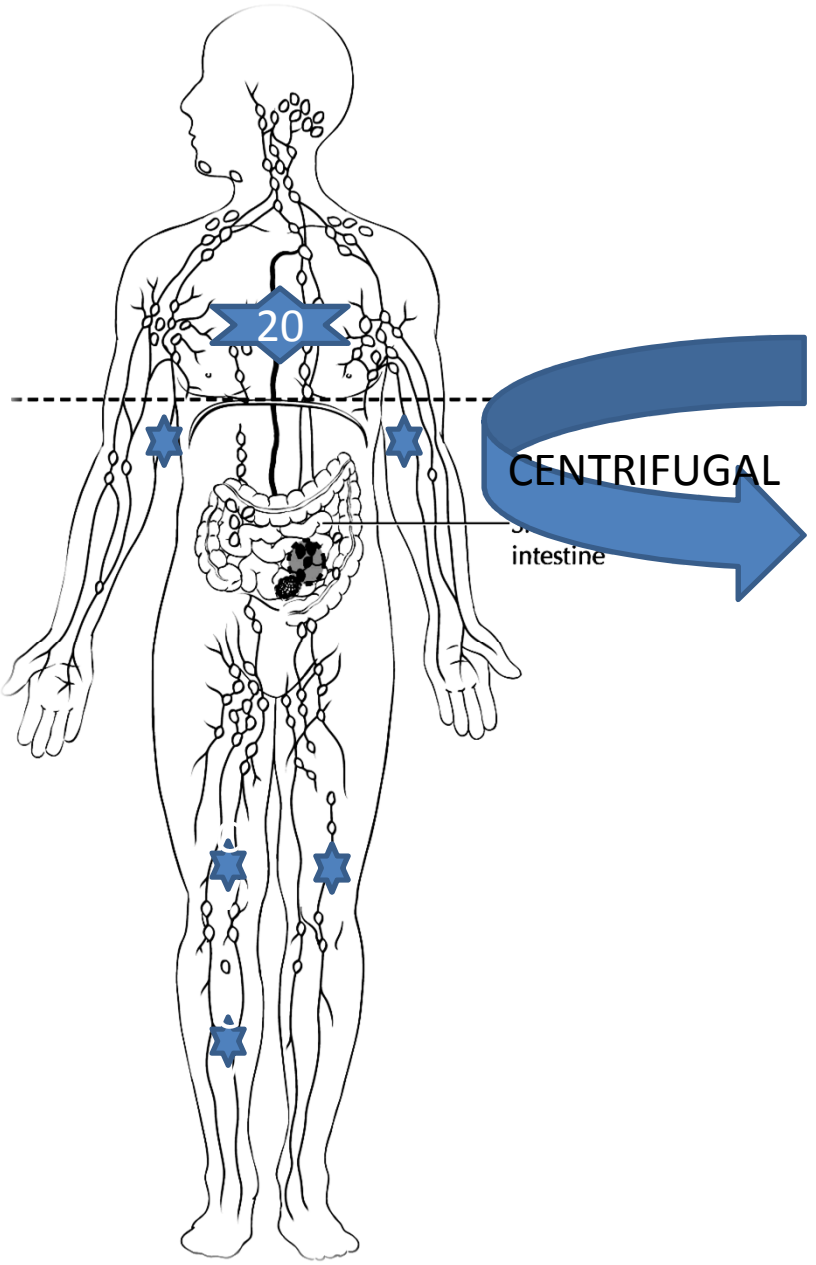
Paracortex
(T cell zone)

Medulla
Plasma cell

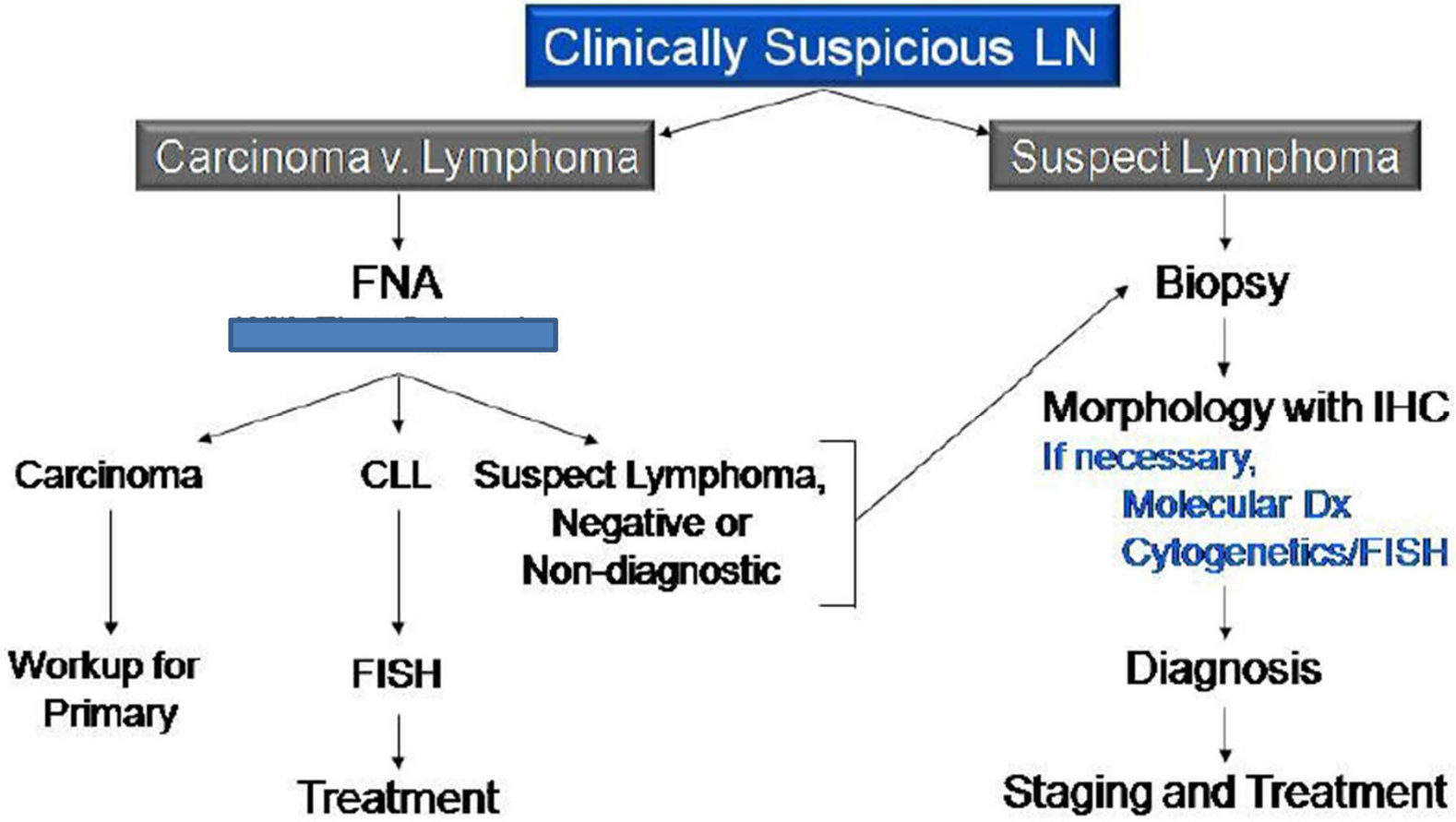




HODGKINS DISEASE



NON HODGKINS LYMPHOMA


Clinically Suspicious LN
Carcinoma v. Lymphoma
Suspect Lymphoma
FNA
Biopsy
Carcinoma
CLL
Suspect Lymphoma, Negative or Non-diagnostic
Morphology with IHC
If necessary,
Molecular Dx
Cytogenetics/FISH
Workup for Primary
FISH
Diagnosis
Treatment
Staging and Treatment

Biopsy Guidelines

- **Optimal biopsy is an excision or incisional biopsy at least 1 x 1 x 1 cm, adequate morphology**
  - **Adequate tissue enables associated studies if necessary**
    - **Flow, cytogenetics/FISH, molecular diagnosis**
    - **In the future: sequencing, GEP, proteomics**
- **Fine needle aspiration is NOT adequate for the diagnosis of lymphoma**
  - **Finding diagnostic cells (even confirmed by flow cytometry) is often not enough**
  - **Architecture is lost**
  - **Associate prognostic information is lost**
- **Core needle biopsy is often adequate**
  - **Multiple passes should be provide to enhance sampling**
  - **Do not accept a non-diagnostic result**
- **Consult with your pathologist**

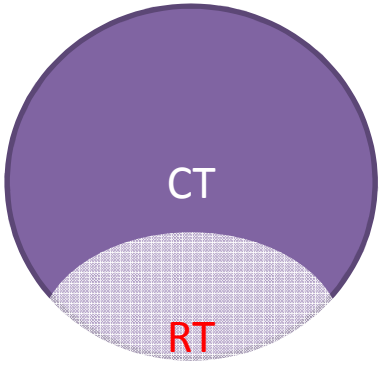
NHL

ADULT		PAEDIATRIC
+	EXTRA-NODAL INVOLVEMENT	++ (PREPONDERANCE)
+	TENDENCY FOR LEUKEMIC CONVERSION	++
+	CNS INVOLVEMENT	++
FOLLICULAR /DIFFUSE LOW /INTERMEDIATE GRADE	HISTOPATHOLOGY	DIFFUSE (FOLLICULAR <5%) INTERMEDIATE / HIGH GRADE
80% B CELL LINEAGE	PHENOTYPE	B & T CELL LINEAGE
ANN ARBOR	STAGING	ST. JUDE CHILDREN'S RESEARCH HOSPITAL
UNCOMMON, UNFAVOURABLE	C-MYC	PRESENT, FAVOURABLE OUTCOME
LESS COMMON, POOR PROGNOSIS	ALK REARRANGEMENT	FAVOURABLE

COMPARISON OF HODGKIN LYMPHOMA AND NON-HODGKIN LYMPHOMA IN PEDIATRIC PATIENTS		
FEATURE	HODGKINS LYMPHOMA	NON-HODGKIN LYMPHOMA
AGE	MOSTLY >10 Y	ANY AGE IN CHILDREN
STAGE AT DIAGNOSIS	MOSTLY LOCALISED	COMMONLY WIDESPREAD
CONSTITUTIONAL SYMPTOMS	ALTER PROGNOSIS	DO NOT AFFECT PROGNOSIS
CNS INVOLVEMENT	RARE	OCCRRENCE INCREASES WITH AIDS
MEDIASTINAL INVOLVEMENT	MOST COMMON WITH NODULAR SCLEROSING HODGKIN LYMPHOMA	MOST COMMON WITH LYMPHOBLASTIC LYMPHOMA
GASROINTESTINAL INVOLVEMENT	RARE	OCCUR
ABODMINAL NODAL INVOLVEMENT	CAN BE SMALL OR LARGE, MESENTERIC RARE	USUALLY ENLARGED MESENTERIC COMMON
BONE INVOLVEMENT	RARE	OCCUR
MARROW INVOLVEMENT	RARE	COMMON

ADULT NHL

- NODAL
- LOW & INTERMEDIATE GRADE
- LESS DISSEMINATION

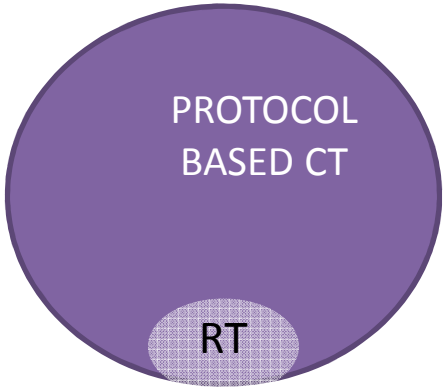


PAEDIATRIC NHL

- DIFFUSE
- EXTRA NODAL
- POORLY DIFFERENTIATED
- HIGH GRADE
- AROUND 2/3RD HAVE EARLY DISSEMINATION
- CELLS FROM THE PAEDIATRIC NHL USUALLY TRAFFIC THROUGH OUT THE BLOOD & TEND TO BE SYSTEMIC DISEASE AT THE OUTSET.

Extranodal disease

- Mediastinum
- Abdomen
- Head & Neck
- Bone marrow
- CNS



INDICATIONS OF RADIOTHERAPY IN NHL

- RADICAL RT
- INVOLVED FIELD RADIOTHERAPY
- CRANIAL IRRADIATION
- PALLIATIVE

ROLE OF RADIATION IN PAEDIATRIC LYMPHOMA

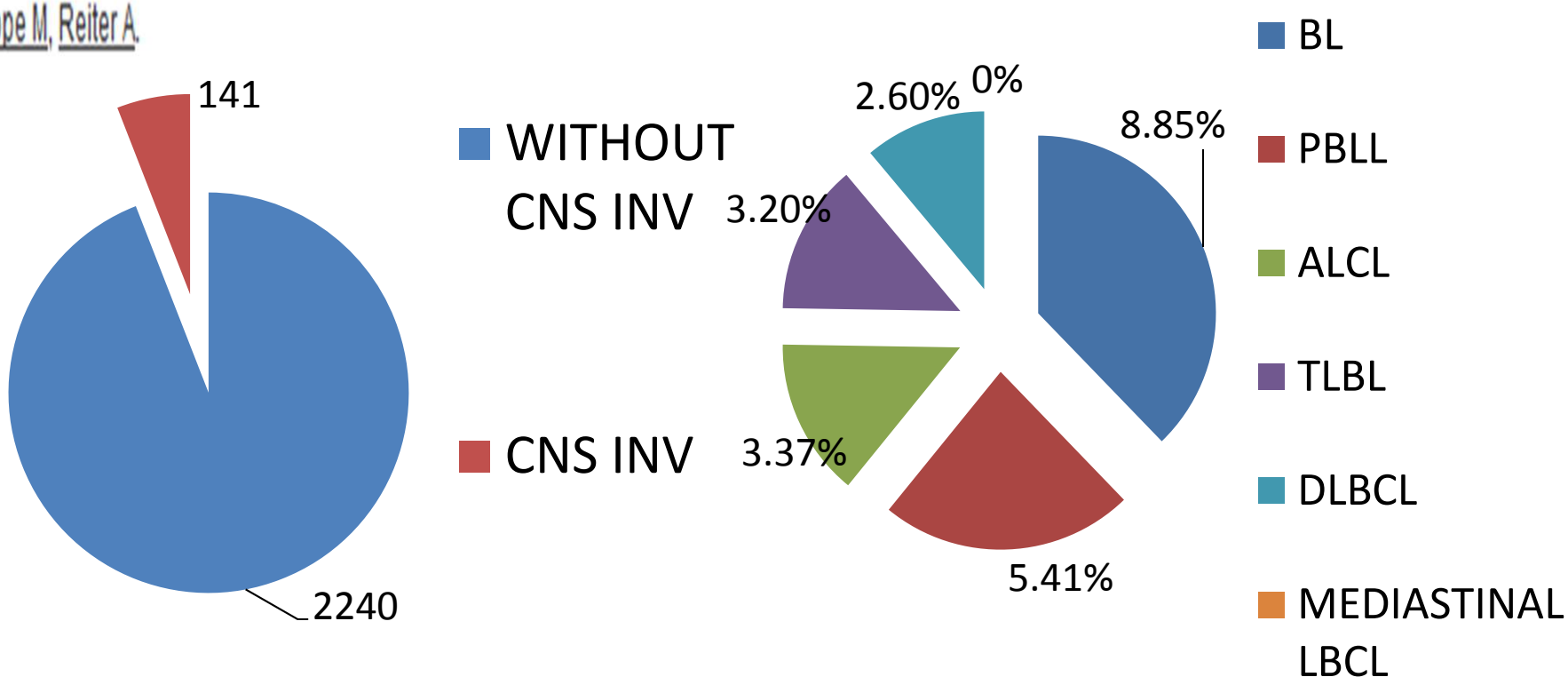
RADICAL RT	NO	NO EVIDENCE
PROPHYLACTIC CRANIAL RT	NO	Bukhardt B et al.JCO2006;24:491-99 Cairo MS et al.Blood 2007;109:2736-43
CNS INVOLVEMENT,CRANIAL NERVE INVOVEMENT	YES	Bukhardt B et al.JCO2006;24:491-99
CNS LYMPHOMA	YES	
IFRT EARLY STAGE DISEASE ADVANCED STAGE DISEASE LOCAL RESIDUAL /RELAPSE	 NO ROLE OF RT IFRT ELIMINATED YES	 Link M et al,NEJM1990;322:1169-74 Schwenn M et al,JCO1991;9:133-38
PALLIATION Mediastinal Mass Spinal Cord compression	YES	
PRIMARY BONY LYMPHOMA	NO YES	Lones M,JCO2002;20:2293-2301 Dai Maruyama et.al,JJCO;(2007) 37 (3):216-223

CNS INVOLVEMENT

J Clin Oncol. 2007 Sep 1;25(25):3915-22.

Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report.

Salzburg J[1], Burkhardt B, Zimmermann M, Wachowski O, Woessmann W, Oschlies I, Klapper W, Wacker HH, Ludwig WD, Niggli F, Mann G, Gadner H, Riehm H, Schrappe M, Reiter A.



NHL IN PAEDIATRIC
SURVIVAL VS MORBIDITY

- 5YYR SURVIVAL INCREASED FROM <15YRS = 45-87%
- 15-19YRS=48-82%

SMITH MA ET AL : CANCER 120(16): 2497-506, 2014

HOWEVER, CRT CARRY SIGNIFICANT LATE RISKS SUCH AS
NEUROPSYCHOLOGICAL DEFICITS,
MOOD DISTURBANCES,
SHORT STATURE,
SECONDARY MALIGNANCIES

WHAT IS THE SCENARIO OF RADIATION IN PAEDIATRICS NON HODGKINS LYMPHOMA ??????

INCIDENCE

- **3RD** MOST COMMON CHILDHOOD MALIGNANCY
- **8%** PAEDIATRIC MALIGNANCIES
- **GEOGRAPHIC LOCATION** –
- . USA- 10PTS/1 MILLION/YR NEW PATIENTS
- AFRICA – 10-20% HIGHER INCIDENCE OF BURKITTS LYMPHOMA.
- **AGE**– INCIDENCE INCREASES WITH AGE COMMON AT **2ND DECADE**.
  INFREQUENT IN <3YRS AGE GROUP.
  - ✓ BL- 5-15YRS
  - ✓ LL- CONSTANT
  - ✓ DLBCL & ALCL– 15 -19YRS
- **RACE**– HIGHER IN WHITES THAN AFRICAN AMERICANS (1.5:1)
  BL IS MORE IN NONHISPANIC WHITES THAN HISPANIC WHITES.
- **GENDER**– MALE > FEMALES (3:1)
  PRIMARY MEDIASTINAL B CELL LYMPHOMA M = F

EPIDEMIOLOGY

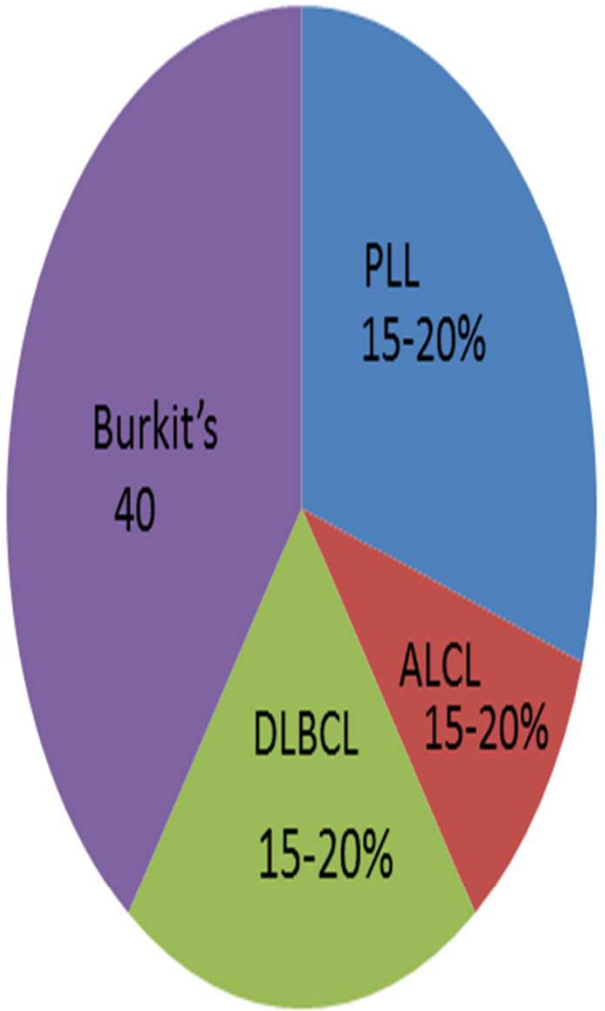
- EBV
- IMMUNODEFICIENCY
  - INHERITED– WISKOT-ALDRICH SYNDROME
    X-LINKED LYMPHOPROLIFERATIVE DISORDER
    ATAXIA TELAGECTASIA
  - ACQUIRED – HIV,POST TRANSPLANT

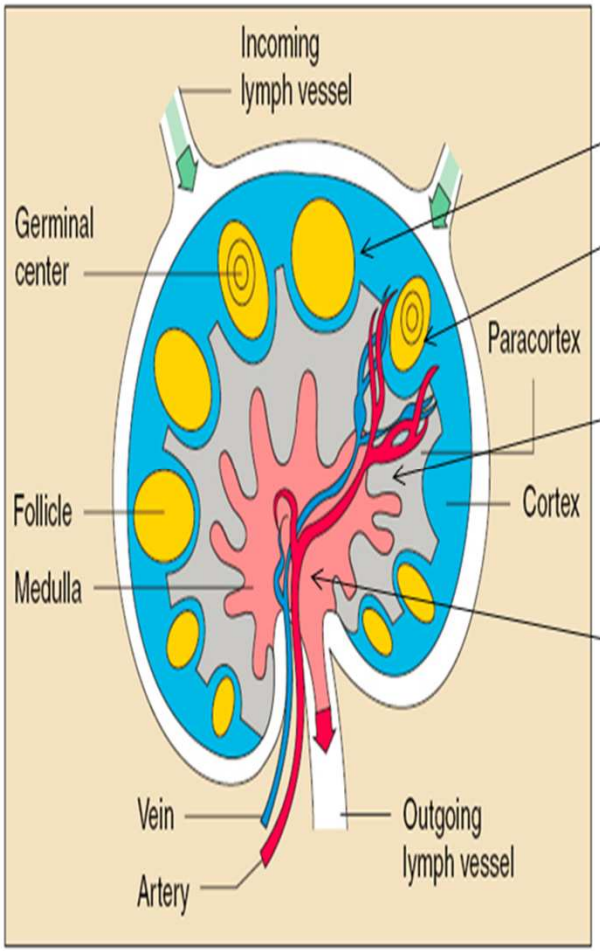
- PESTICIDES
- PREVIOUS NEOPLASMS

MAIN SUBTYPES OF PEDIATRIC NHL (2008 WHO CLASSIFICATION)

Subtype of lymphoma	Frequency
Precursor lymphoid neoplasms	
T-lymphoblastic lymphoma	15%–20%
B-lymphoblastic lymphoma	3%
Mature B-cell neoplasms	
Burkitt lymphoma	35%–40%
Diffuse large B-cell lymphoma	15%–20%
Primary mediastinal B-cell lymphoma	1%–2%
Pediatric follicular lymphoma	Rare
Pediatric nodal marginal zone lymphoma	Rare
Mature T-cell neoplasms	
Anaplastic large cell lymphoma, ALK positive	15%–20%
Peripheral T-cell lymphoma (NOS)	Rare

ALK, anaplastic lymphoma kinase; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.





Perifolicular area
(mantle zone lymphoma)

Lymphoblastic Lymphoma

Cortex
(B cell zone)

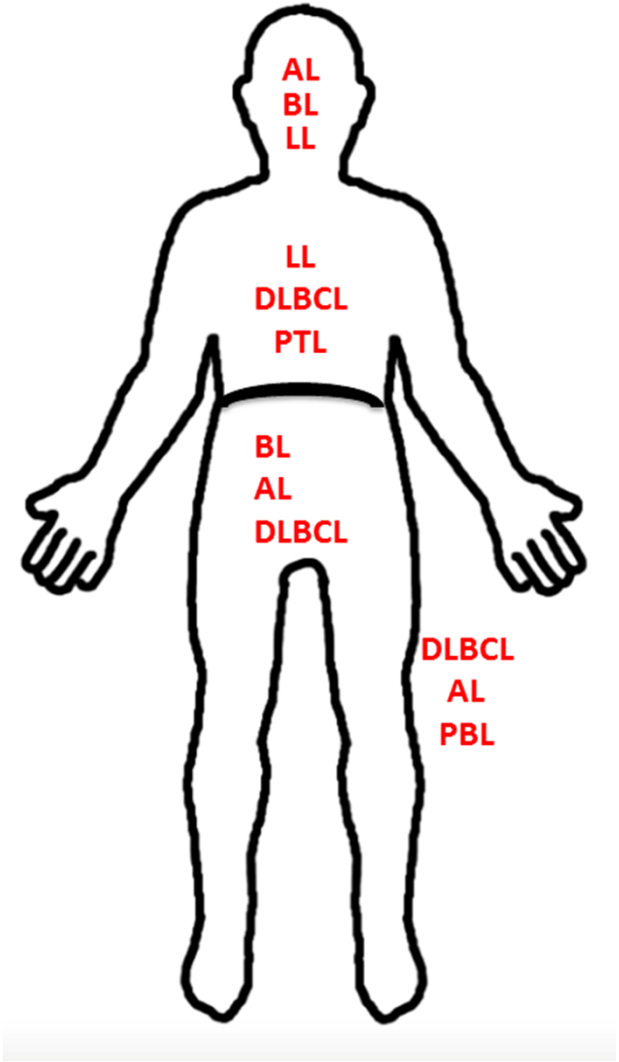
- BURKITT lymphoma
- Diffuse large B cell lymphoma
- Primary mediastinal B cell lymphoma

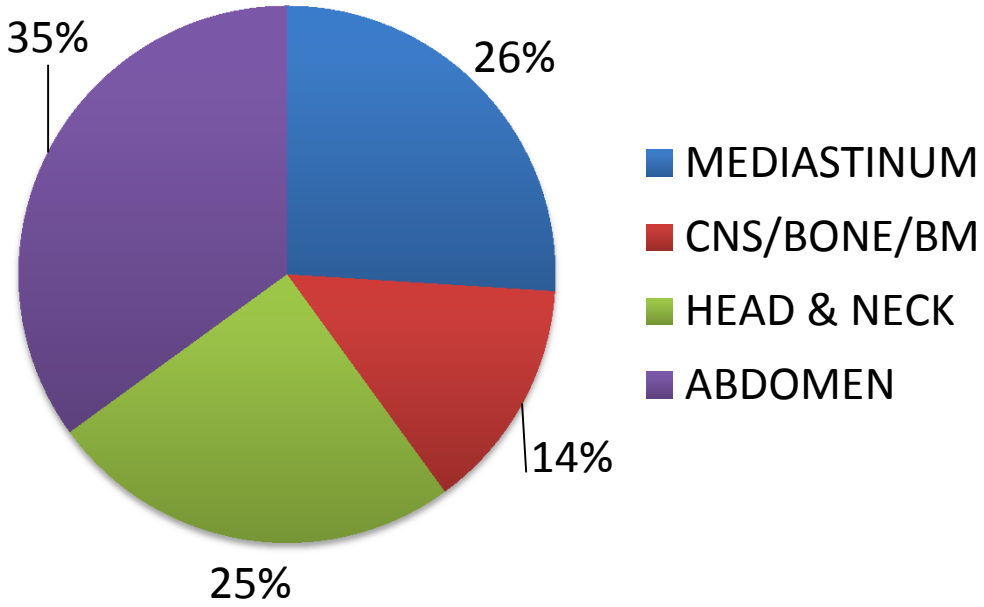
Paracortex
(T cell zone)

Anaplastic Large Cell Lymphoma

Medulla
Plasma cell

CLINICAL PRESENTATION





2/3RD have widespread disease at presentation

CORRELATION OF HISTOPATHOLOGY, IMMUNOPHENOTYPE, CLINICAL FEATURES, CYTOGENETICS, AND MOLECULAR FEATURES IN CHILDHOOD NON-HODGKIN LYMPHOMA

Histology	Immunology	Clinical features	Cytogenetics	Genes involved
Burkitt and Burkitt-like	B cell (sIg+)	Abdominal masses, gastrointestinal tract tumors, involvement of Waldeyer's ring	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	IgH-cMYC Igκ-cMYC Igλ-cMYC
Diffuse large B cell	B cells of germinal center or postgerminal center	Nodes, abdominal masses, bone		
Mediastinal large B cell	B cells of medullary thymus	Mediastinum		
Anaplastic large cell	T cell (mostly), null cell, or NK cell (CD30+)	Skin, nodes, bone	t(2;5)(p23;q35) t(1;2)(q21;p23) t(2;3)(p23;q21) t(2;17)(p23;q23) t(X;2)(q11–12;p23) inv 2(p23;q35)	NPM-ALK TPM3-ALK TFG-ALK CLTC-ALK MSN-ALK ATIC-ALK
Precursor T lymphoblastic	T cell (thymocyte phenotype)	Anterior mediastinal mass with upper torso adenopathy	t(1;14)(p32;q11) t(11;14)(p13;q11) t(11;14)(p15;q11) t(10;14)(q24;q11) t(7;19)(q35;p13) t(8;14)(q24;q11) t(1;7)(p34;q34)	TCRαδ-TAL1 TCRαδ-RHOMB2 TCRαδ-RHOMB1 TCRαδ-HOX11 TCRβ-LYL1 TCRαδ-MYC TCRβ-LCK
Precursor B lymphoblastic	B-cell precursors	Cutaneous masses, isolated lymph node masses, primary bone lymphoma		

NK, natural killer.

PERCENTAGE DISTRIBUTION

PLL(PRECURSOR T/B CELL LYMPHOMA)

- 15-25%
- **CLINICAL & BIOLOGICAL FEATURES OF ALL**
- **> 90% HAVE PRECURSOR T IMMUNOPHENOTYPE**
- NECK NODES & MEDIASTINAL ADENOPATHY
- CERVICAL ADENOPATHY, SVC SYNDROME, RESPIRATORY SYMPTOMS
- **PBL IS LIMITED DISEASE AT SKIN(SCALP), BONE, PERIPHERAL NODES**

BURKITT'S LYMPHOMA

- 40%
- INCLUDES BURKITT'S & ATYPICAL BURKITT'S LYMPHOMA
- **ENDEMIC**-- JAW INVOLEMENT , MESENTERIC,OMENTAL AND CNS INVOLMENTN IS COMMON
- **SPORADIC**- MOSTLY IN ABDOMEN I.E ILEOCAECAL INTUSUCCEPTION, HEAD & NECK(PHARYNX, PNS), JAW INVOLVEMENT.
- **LYMPHOMA INVOLVING ILEOCAECAL REGION OF CHILDREN IS INVARIABLY BURKITT'S LYMPHOMA**

COMPARISON OF ENDEMIC AND SPORADIC BURKITT LYMPHOMA

Feature	Endemic	Sporadic
Clinical features	5–10 years Males > females	6–12 years Males > females
Most common distribution of disease	Equatorial Africa, New Guinea, Amazonian Brazil, Turkey	North America, Europe most common
Annual incidence	10 in 100,000	0.2 in 100,000
Common tumor sites	Jaw, abdomen, central nervous system, cerebrospinal fluid	Abdomen, marrow, lymph nodes, ovaries
Histopathologic features	Diffuse growth pattern, monomorphic intermediate-sized cell, starry-sky pattern	Same
Immunologic features	CD20+, usually IgM, κ or λ CD10+, BCL2−	CD10+, usually IgM, κ or λ CD10+, BCL2−
Presence of Epstein-Barr virus DNA in tumor cells	95%	15%
Presence of t(8;14), t(2;8), or t(8;22)	Yes	Yes
Chromosome 8 breakpoints	Upstream of *cMYC*	Within *cMYC*

DLBCL

- 15-20%
- NODAL AS WELL AS BONE INVOLVEMENT
- IN IMMUNOCOMPROMISED PATIENTS EXTRA NODAL DISEASE IS COMMON
- LOCALLY INVASIVE i.e INVOLVE THE PERICARDIUM

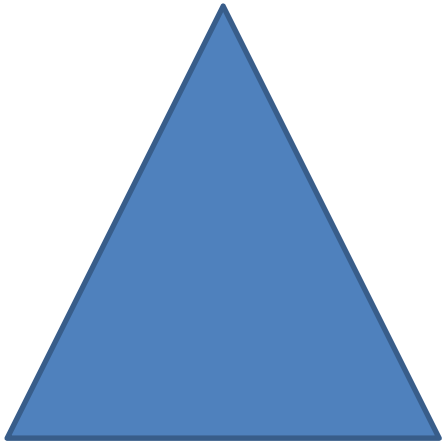
ANAPLASTIC LARGE CELL LYMPHOMA

- 15 – 20%
- INVOLVE LYMPH NODE, EXTRA NODAL SITES I.E SKIN, SOFT TISSUE, BONE
- MOSTLY PRIMARY CUTANEOUS / SYSTEMIC ALCL
- CONSTITUTIONAL SYMPTOMS LIKE FEVER, BONE PAIN PRESENT
- SKIN INVOLVEMENT MORE COMMON
- **SPONTANEOUS REGRESSION / WAXING & WANING SKIN DISEASE**
- **MULTIFOCAL BONE DISEASE**
- CD30/ALK MAY BE POSITIVE

DIAGNOSIS

- HISTORY & PHYSICAL EXAMINATION
- PATHOLOGICAL EXAMINATION OF TUMOR CELLS
- IHC- IMMUNOPHENOTYPING
- BONE MARROW ASPIRATION AND CYTOLOGY
- PERIPHERAL SMEAR
- LUMBAR PUNCTURE & CSF CYTOLOGY
- SERUM ELECTROLYTES, UREA, CREATININE, URIC ACID, LFT
- SERUM LDH

HISTOLOGY



IMMUNO PHENOTYPING
(antibody directed against surface antigen)

CYTOGENETIC STUDY
(molecular markers)

FEW CRITERIAS TO REMEMBER

- MDD(MINIMAL DISSEMINATED DISEASE)– DEFINED AS SUB-MICROSCOPIC BONE MARROW INVOLVEMENT THAT IS PRESENT AT DIAGNOSIS. MDD IS GENERALLY DETECTED BY SENSITIVE METHODS SUCH AS RT-PCR
- LEUKEMIC INVOLVEMENT IS WHEN >25% BLASTS OR MALIGNANT CELLS IN MARROW.
- STAGE IV NHL– 5-25% MARROW INVOLVEMENT
- NORMAL -- < 5% BLASTS IN MARROW
- ANY IDENTIFIABLE TUMOR CELLS IN CSF– CNS DISEASE

DIAGNOSIS

- NEED EARLY DIAGNOSIS TO START PROMPT TREATMENT DUE TO RAPID GROWTH OF THE TUMOR.
- ADEQUATE TISSUE(OPEN/CORE NEEDLE) FOR BIOPSY, IHC, KARYOTYPING
- BILATERAL BONE MARROW BIOPSY DUE TO PATCHY DISTRIBUTION OF NHL.
- CT SCAN THORAX FOR MEDIASTINAL DISEASE.
- FDG –PET IS UNDER EVALUATION
- NO LAPAROTOMY FOR STAGING/ TUMOR DEBULKING
- MRI- NOT ROUTINELY USED, HAS ROLE IN CNS LYMPHOMA
- NO BIOPSY UNDER GA
- NO PREBIOPSY STEROID/ RT

(IF NECESSARY ON EMERGENCY PREDNISOLONE 40-60 MG/M2 /DAY FOR 2 DAYS RESULT IN RAPID CLINICAL IMPROOVEMENT & PRESERVATION OF DIAGNOSTIC TISSUE)

PROGNOSTIC FACTORS

1. RESPONSE TO THERAPY
2. STAGE AT DIAGNOSIS
3. SITE OF DISEASE

   BONE MARROW
   CNS INVOLVEMENT
   MEDIASTINAL INVOLVEMENT
   } Poor prognosis
   HEAD & NECK – HIGHER DISSEMINATION

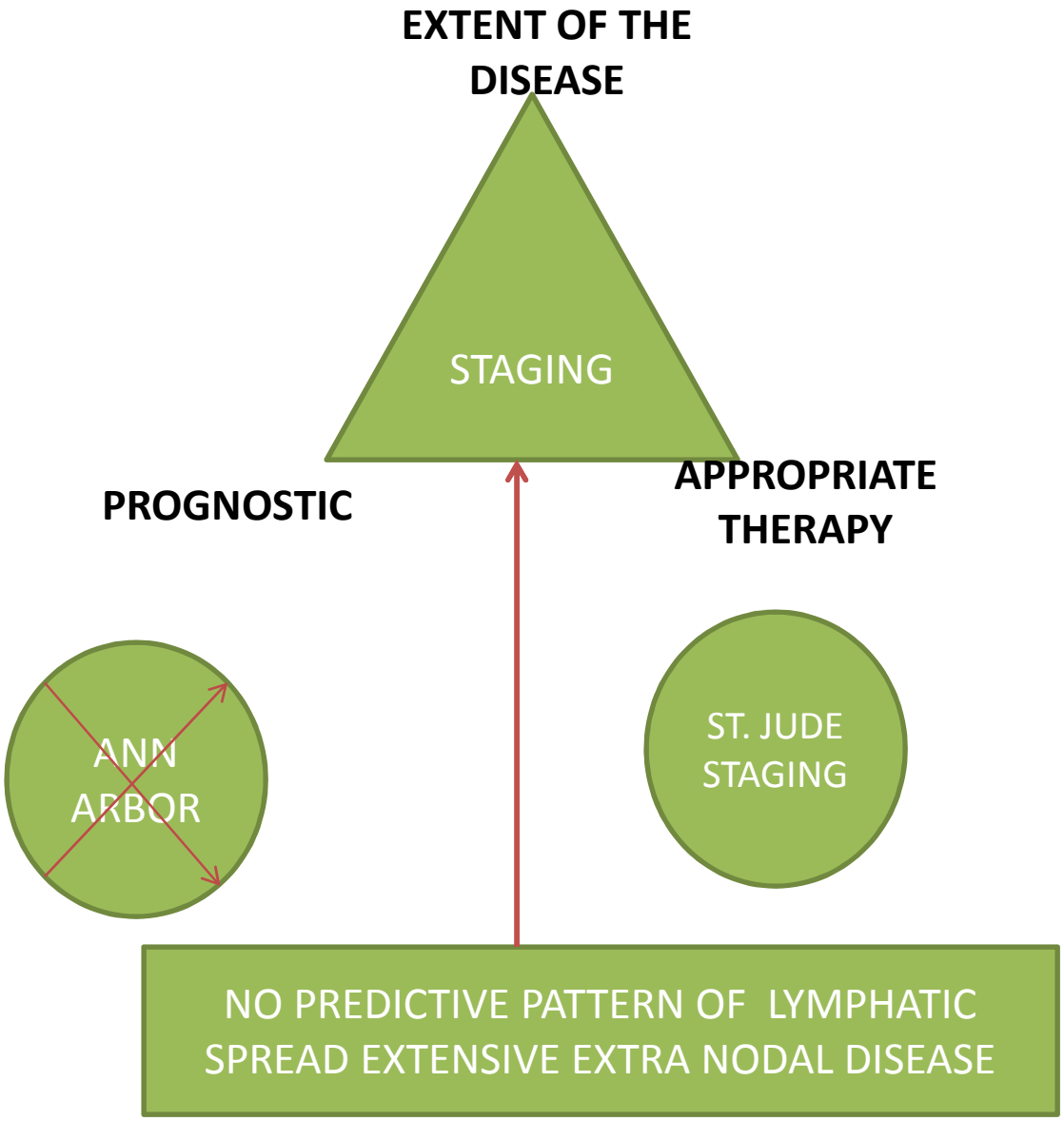
4. **TUMOR BIOLOGY**-

- MATURE B CELL LYMPHOMA- CYTOSMEAR ABNORMALITY OTHER THAN C-MYC IMPLIES INFERIOR OUTCOME.
  C-MYC – FAVOURABLE OUTCOME
- T- LYMPHOBLASTIC LYMPHOMA– LOSS OF HETEROZYGOSITY AT CHROMOSOME 6Q– UNFAVOURABLE PROGNOSIS
- ANAPLASTIC LARGE CELL LYMPHOMA—ALK +VE GOOD PROGNOSIS

5. **AGE**- OUTCOME IN INFANTS IS POOR.
   ADOLESCENTS HAVE INFERIOR OUTCOME COMPARED TO YOUNG CHILDREN.
6. IMMUNE RESPONSE TO TUMOR
7. GENETIC ABNORMALITY

STAGING

ST. JUDE STAGING SYSTEM



ST JUDE STAGING SYSTEM

I	**A SINGLE TUMOR(EXTRANODAL) OR SINGLE ANATOMIC AREA(NODAL), EXCLUDING THE MEDIASTINUM AND ABDOMEN**
II	A SINGLE TUMOR(EXTRANODAL) WITH REGIONAL LYMPH NODE INVOLVEMENT ON THE SAME SIDE OF DIAPHRAGM a) 2 OR MORE NODAL AREAS b) 2 SINGLE EXTRA NODAL TUMORS WITH/ WITHOUT REGIONAL NODE INVOLVEMENT A PRIMARY GIT TUMOR (ILEOCAECAL) WITH / WITHOUT ASSOCIATED MESENTERIC NODE INVOLVEMENT, GROSSLY COMPLETELY RESECTED
III	ON BOTH SIDES OF DIAPHRAGM: a) TWO SINGLE TUMORS (EXTRA NODAL) b) TWO OR MORE NODAL AREAS c) ALL PRIMARY INTRATHORACIC TUMORS d) ALL EXTENSIVE PRIMARY INTRA-ABDOMINAL DISEASES; UNRESECTABLE ALL PRIMARY PARASPINAL OR EPIDURAL TUMORS REGARDLESS OF OTHER SITES.
IV	ANY OF THE ABOVE WITH INITIAL CNS OR BONE MARROW INVOLVEMENT (< 25% BLASTS)

RISK STRATIFICATION SCHEMA

B-cell NHL (FAB/LMB)

Stratum	Disease manifestations
A	Completely resected stage I and abdominal stage II
B	Multiple extra-abdominal sites. Nonresected stage I and II, III, IV (marrow <25% blasts, no CNS disease)
C	Mature B ALL (>25% blasts in marrow) and/or CNS disease

B-cell NHL (BFM)

Stratum	Disease manifestations
R1	Completely resected stage I and abdominal stage II
R2	Nonresected stage I/II and stage III with LDH <500
R3	Stage III with LDH 500 –999 Stage IV, B-ALL (>25% blasts), no CNS disease and LDH <1,000
R4	Stage III, IV, B-ALL, and LDH ≥1,000 Any CNS disease

ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; CNS, central nervous system; FAB, French-American-British; LDH, lactic dehydrogenase; NHL, non-Hodgkin lymphoma.

RECOMMENDED THERAPY FOR LOCALIZED NHL

WHO classification	Regimen	EFS (%)
Burkitt	CODOX-M/I-VAC FAB/LMB[151, 152] (Group A, B) BFM 90/95[145] (R1, R2)	90–95
Lymphoblastic (mostly precursor B)	BFM 90/95[107]	85–90
DLBCL	CHOP[106] FAB/LMB (Group A, B)[151,152] BFM 90/95 (R1, R2)[107]	90–95
ALCL	CHOP[106] BFM 90[168]	90

ALCL, anaplastic large cell lymphoma; BFM, Berlin-Frankfurt-Munster; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FAB, French-American-British; WHO, World Health Organization.

RECOMMENDED THERAPY FOR DISSEMINATED NHL

WHO classification	Regimen	EFS (%)
Burkitt	FAB/LMB (Group B, C)[138,152] BFM 90/95[144,145] No craniospinal irradiation	70–90
Lymphoblastic (mostly precursor T)	BFM–NHL 90/95[107,108] Craniospinal irradiation for CNS (+) only	80–90
DLBCL	FAB/LMB (Group B, C)[138,155] BFM 90/95[144,145] No craniospinal irradiation	85–90
ALCL	APO[170], NHL BFM 90[168] ALCL 99[109] No craniospinal irradiation	70–75

ALCL, anaplastic large cell lymphoma; APO, Adriamycin (doxorubicin), prednisone, and vincristine; BFM, Berlin-Frankfurt-Munster; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FAB, French-American-British; WHO, World Health Organization.

PRECURSOR LYMPHOBLASTIC LYMPHOMA

- ALL LIKE TREATMENT APPROACH
- CRANIAL RADIATION CAN BE SAFELY OMITTED, HOWEVER IF CRANIAL INVOLVEMENT PRESENT THEN CRANIAL IRRADIATION IS NECESSARY
- MOST RELAPSE WITHIN TWO YEARS, IF RELAPSE CONSIDER ALLOGENIC BMT

INDICATIONS OF RADIATION

- RT FOR LOCAL CONTROL OF PRIMARY DISEASE & CNS PROPHYLAXIS HAS BEEN VIRTUALLY ELIMINATED
  1. EMERGENCY MANAGEMENT OF MEDIASTINAL DISEASE
  2. SPINAL CORD COMPRESSION
  3. PALLIATION OF PAIN & MASS EFFECT
  4. CONSOLIDATION BEFORE BONEMARROW TRANSPLANT IN CASE OF RECURRENT DISEASE
  5. TREATMENT OF CNS LYMPHOMAS AT DIAGNOSIS

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RADICAL RT	NO	NO EVIDENCE
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PALLIATION Mediastinal Mass Spinal Cord compression	YES	
PRIMARY BONY LYMPHOMA	NO YES	Lones M,JCO2002;20:2293-2301

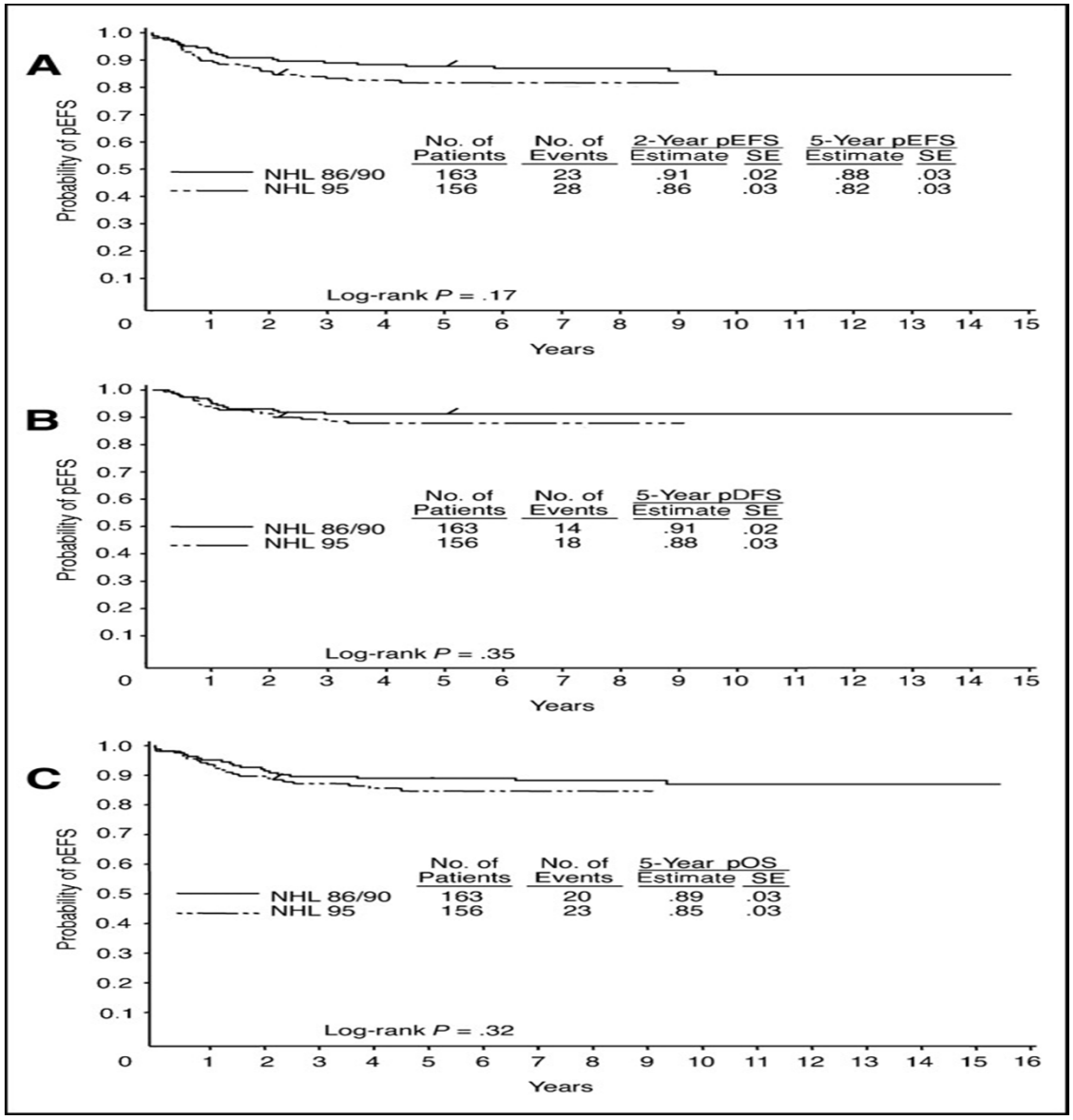
Impact of Cranial Radiotherapy on Central Nervous System Prophylaxis in Children and Adolescents With Central Nervous System–Negative Stage III or IV Lymphoblastic Lymphoma

Birgit Burkhardt, Wilhelm Woessmann, Martin Zimmermann, Udo Kontny, Josef Vormoor, Wolfgang Doerffel, Georg Mann, Guenter Henze, Felix Niggli, Wolf-Dieter Ludwig, Dirk Janssen, Hansjoerg Riehm, Martin Schrappe and Alfred Reiter

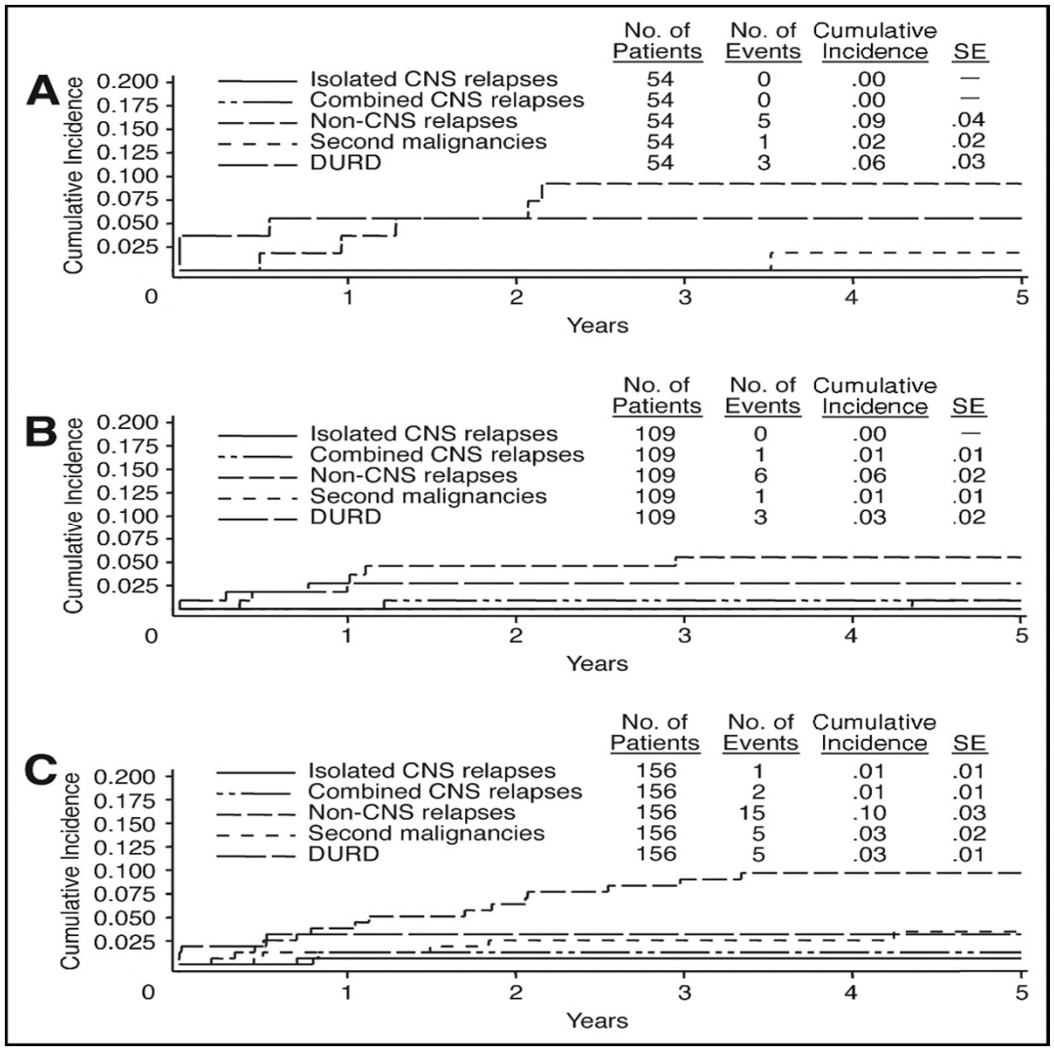
PURPOSE IN THE NON-HODGKIN'S LYMPHOMA–BERLIN-FRANKFURT-MUNSTER (NHL-BFM) 95 TRIAL, WE TESTED, AGAINST THE HISTORICAL CONTROL OF THE COMBINED TRIALS NHL-BFM90 AND NHL-BFM86, WHETHER PROPHYLACTIC CRANIAL RADIOTHERAPY (PCRT) CAN BE OMITTED FOR CNS-NEGATIVE PATIENTS WITH STAGE III OR IV LYMPHOBLASTIC LYMPHOMA (LBL) WITH SUFFICIENT EARLY RESPONSE.

RESULT**S** THE NUMBER OF TARGET PATIENTS WAS 156 IN NHL-BFM95 (MEDIAN AGE, 8.6 YEARS; RANGE, 0.2 TO 19.5 YEARS) AND 163 IN NHL-BFM90/86 (MEDIAN AGE, 8.4 YEARS; RANGE, 0.6 TO 16.6 YEARS). FOR THE TARGET GROUP, THE PEFS RATES AT 2 AND 5 YEARS WERE 86% ± 3% AND 82% ± 3%, RESPECTIVELY, IN NHL-BFM95 (MEDIAN FOLLOW-UP TIME, 5.1 YEARS; RANGE, 2.1 TO 9.1 YEARS) COMPARED WITH 91% ± 2% AND 88% ± 3%, RESPECTIVELY IN NHL-BFM90/86 (MEDIAN FOLLOW-UP TIME, 10.7 YEARS; RANGE, 5 TO 15.4 YEARS). THE LOWER LIMIT OF THE ONE-SIDED 95% CI FOR THE DIFFERENCE IN PEFS WAS −11% AT 2 YEARS AND −13% AT 5 YEARS**. IN NHL-BFM95, ONE ISOLATED AND TWO COMBINED CNS RELAPSES OCCURRED** COMPARED WITH ONE COMBINED CNS RELAPSE IN NHL-BFM90/86. FIVE-YEAR DISEASE-FREE-SURVIVAL RATE WAS 88% ± 3% IN NHL-BFM95 COMPARED WITH 91% ± 2% IN NHL-BFM90/86.

CONCLUSION FOR CNS-NEGATIVE PATIENTS WITH STAGE III OR IV LBL AND SUFFICIENT RESPONSE TO INDUCTION THERAPY, TREATMENT WITHOUT PCRT MAY BE NONINFERIOR TO TREATMENT INCLUDING PCRT.



Outcome of target patients in the Non-Hodgkin's Lymphoma (NHL) –Berlin-Frankfurt-Munster 95 trial (stage III or IV, CNS negative, sufficient response at induction day 33, and no prophylactic cranial radiotherapy) compared with the historical control of combined trials NHL-BFM90/86. (A) Event-free survival (pEFS) at 2 and 5 years, (B) disease-free survival (pDFS) at 5 years, and (C) overall survival (pOS) at 5 years. SE, standard error.



Cumulative incidences of isolated CNS relapses, combined CNS relapses, non-CNS relapses, second malignancies, and death unrelated to disease for (A) Non-Hodgkin's Lymphoma (NHL) –Berlin-Frankfurt-Munster 86 trial, (B) NHL-BFM90, and (C) NHL-BFM95.

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Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents

Mitchell S. Cairo, Mary Gerrard, Richard Sposto, Anne Auperin, C. Ross Pinkerton, Jean Michon, Claire Weston, Sherrie L. Perkins, Martine Raphael, Keith McCarthy, Catherine Patte and on behalf of the FAB LMB96 International Study Committee

Table 2. Summary of patient characteristics

	All patients		Reduced treatment*		Standard treatment*	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
National group						
Children's Oncology Group	101	43	40	43	44	46
Société Française d'Oncologie Pédiatrique	98	42	39	41	39	41
United Kingdom Children's Cancer Study Group	36	15	15	16	13	14
Sex						
Male	185	79	75	80	77	80
Female	50	21	19	20	19	20
Age, y						
0-4	47	20	15	16	22	23
5-9	97	42	39	41	44	46
10-14	64	27	31	33	20	21
15-19	27	12	9	10	10	10
Histology						
BL/BLL/B-ALL	204	87	84	90	84	88
Diffuse B-LC/TCRLCL	21	9	6	6	7	7
Other/NOS/pending	10	4	4	3	5	5
BM/CNS involvement						
BM^+/CNS^-	121	51	51	54	52	54
BM^-/CNS^+	46	20	14	15	21	22
BM^+/CNS^+	68	29	29	31	23	24
LDH level						
Unknown	16	—	6	—	7	—
Less than or equal to 2 times normal	41	19	16	18	15	17
More than 2 times normal	178	81	72	82	74	83

For all patients, N = 235; for reduced treatment, N = 94; and for standard treatment, N = 96.

BL indicates Burkitt lymphoma; BLL, Burkitt-like lymphoma; B-LC, B large cell; TCRLCL, T-cell–rich large-cell lymphoma; NOS, not otherwise specified; and –, not determined.

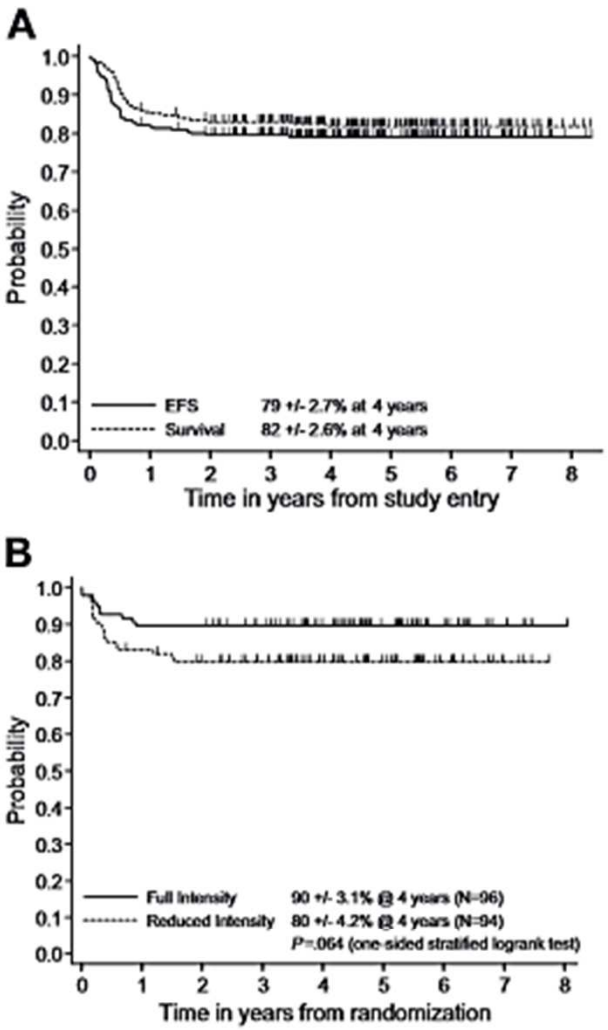


Figure 2. Probability of EFS and S of all patients and randomized patients. (A) Product-limit estimate of probability of EFS and S in all patients from study entry. EFS at 4 years, 79% ± 2.7%; S at 4 years, 82% ± 2.6%. (B) Product-limit estimate of probability of EFS from randomization of patients randomized to C1 versus C2 (mini CYVE and deletion M2, M3, M4 courses); EFS at 4 years 90% ± 3.1% versus 80% ± 4.2%, $P = .064$.

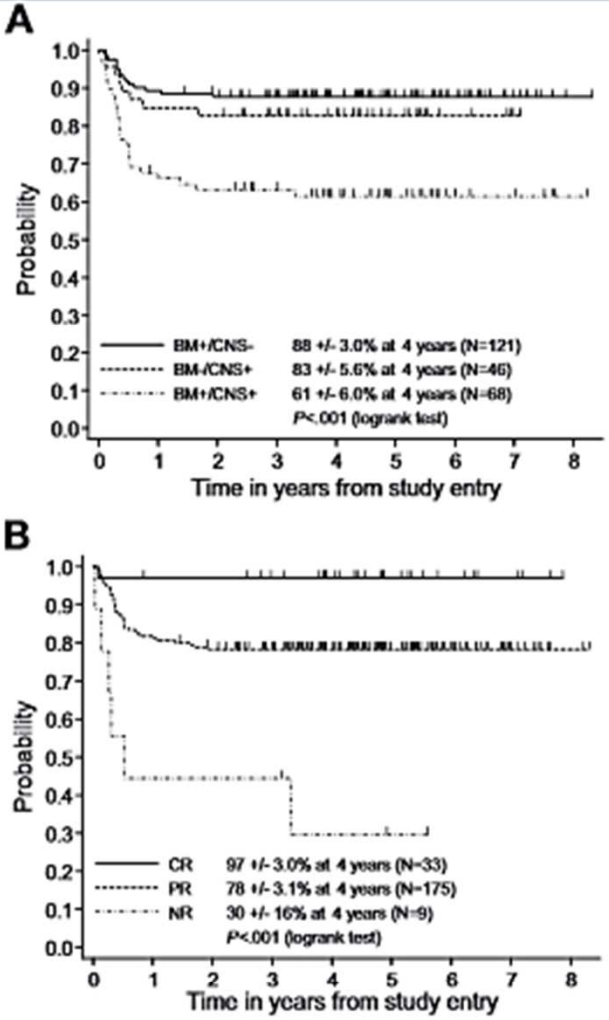


Figure 3. Stratified probabilities. Probability of EFS and S stratified by BM, CNS, or BM/CNS (A) and response to COP reduction (B). (A) Product-limit estimate of probability of EFS in patients with BM disease only (BM^+/CNS^-), CNS disease only (BM^-/CNS^+), and combined BM and CNS disease (BM^+/CNS^+) (88% ± 3.0% versus 82 ± 5.6% versus 61% ± 6.0%, $P < .001$). (B) Product-limit estimate of probability of EFS in patients with complete response (CR; 100%), incomplete response (IR; 20%-99%) and nonresponse (NR; < 20%) after COP reduction therapy (94% ± 3.8% versus 78 ± 3.1% versus 30% ± 16%, $P < .001$).

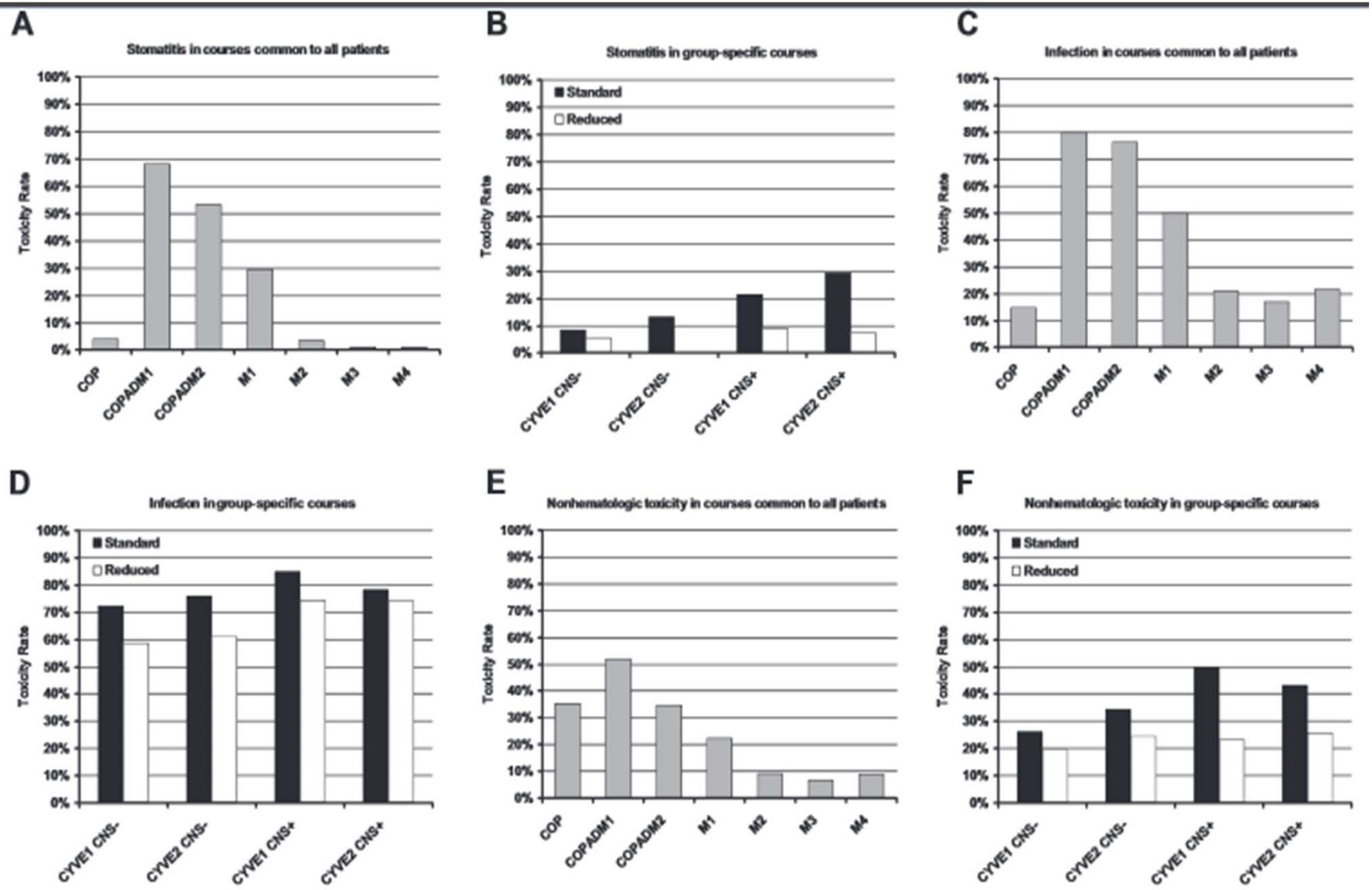


Figure 5. Percentage of grade III/IV toxicities. Rates of grade III/IV stomatitis, infection, and other nonhematologic toxicities, within therapy courses. The left column shows the rates of these toxicities during COP, COPADM1, COPAMD2, and maintenance course that were common treatments received by all patients. The right column shows the comparative rates of these toxicities for the CYVE (standard) or mini CYVE (reduced) course received by patients with (CNS^+) or without (CNS^-) CNS disease at diagnosis. Reductions in stomatitis, infection, and other nonhematologic toxicities during these courses were statistically significant ($P < .001$, $P < .01$, and $P < .005$, respectively).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

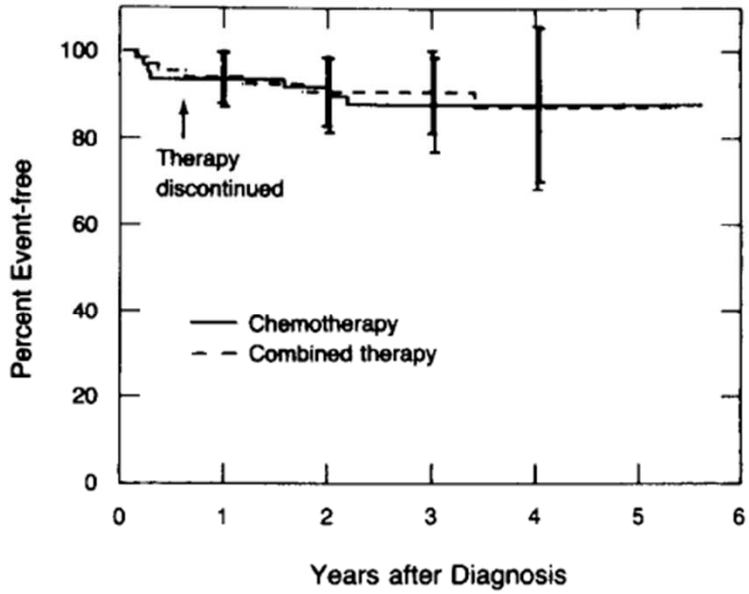
Results of Treatment of Childhood Localized Non-Hodgkin's Lymphoma with Combination Chemotherapy with or without Radiotherapy

Michael P. Link, M.D., Sarah S. Donaldson, M.D., Costan W. Berard, M.D., Jonathan J. Shuster, Ph.D., and Sharon B. Murphy, M.D.

N Engl J Med 1990; 322:1169-1174 | April 26, 1990 | DOI: 10.1056/NEJM199004263221701

THERAPY	SCHEDULE*
Induction (6 wk)	
Vincristine	1.5 mg/m^2 i.v. weekly for 6 doses
Doxorubicin	40 mg/m^2 i.v. days 1 and 22
Cyclophosphamide	750 mg/m^2 i.v. days 1 and 22
Prednisone	40 mg/m^2 p.o. daily for 28 days
Radiotherapy	27 Gy to the involved field, in 15 fractions of 180 cGy initiated with induction chemotherapy (only for patients assigned to combined therapy)
Consolidation (3 wk)	
Vincristine	1.5 mg/m^2 i.v. on day 1
Doxorubicin	40 mg/m^2 i.v. on day 1
Cyclophosphamide	750 mg/m^2 i.v. on day 1
Prednisone	40 mg/m^2 p.o. daily for 5 days
Maintenance (24 wk)	
Mercaptopurine	50 mg/m^2 p.o. daily
Methotrexate	25 mg/m^2 p.o. weekly
Central nervous system prophylaxis	
Methotrexate	12 mg/m^2 intrathecally on days 1, 8, and 22 of induction, day 1 of consolidation, and every 6 weeks during maintenance therapy only for patients with primary tumors in the head-and-neck region.

*m^2 Denotes square meters of body-surface area, i.v. intravenously, and p.o. orally.



No. at Risk						
Chemotherapy	62	57	47	32	12	1
Combined therapy	67	63	50	34	11	2

Figure 1. Event-free Survival after Diagnosis among Patients with Localized Non-Hodgkin's Lymphoma.

No difference in outcome was evident between patients receiving chemotherapy alone and those receiving combined chemotherapy and radiotherapy; there were seven treatment failures in each group. The bars denote 95 percent confidence intervals.

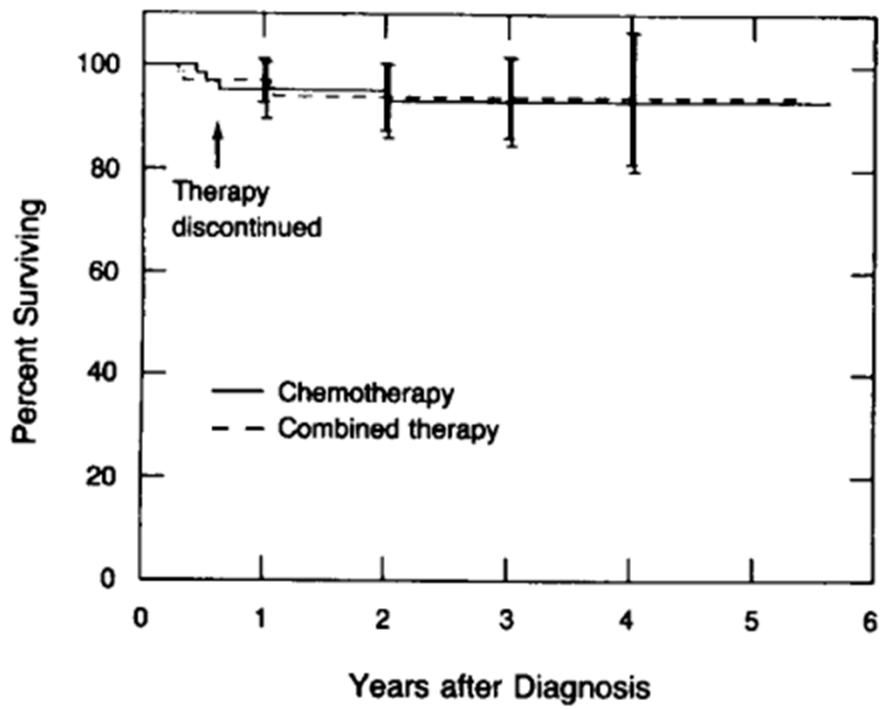
Table 4. Characteristics of Patients Who Had Treatment Failure.

Primary Site	Histology	Site of Failure*	Mo to Failure†	St
Chemotherapy				
Neck	Small non-cleaved cell	Local	2	
Neck	Large cell	Local	3	
Nasopharynx	Small non-cleaved cell	Local and CNS	3	
Neck	Small non-cleaved cell	CNS	4	
Scalp	Lymphoblastic	Bone marrow	19	
Inguinal node	Lymphoblastic	Mediastinum	20	
Parotid gland	Lymphoblastic	Pelvis	26	
Combined therapy				
Nasopharynx	Small non-cleaved cell	Local	2	
Sinuses	Small non-cleaved cell	—‡	4	
Tonsil	Small non-cleaved cell	Bone marrow and testis	5	
Nasopharynx	Small non-cleaved cell	Kidney and thigh	8	
Gastrointestinal tract	Small non-cleaved cell	Secondary ANLL	14	
Scalp	Lymphoblastic	Testis	21	
Neck	Lymphoblastic	Talus	41	

*Local denotes local recurrence, CNS central nervous system, and ANLL acute nonlymphocytic leuk

†From the start of therapy.

‡The patient died of severe granulocytopenia and sepsis while in remission.



No. at Risk						
Chemotherapy	62	58	48	33	12	1
Combined therapy	67	65	51	35	11	2

Figure 2. Overall Survival after Diagnosis of Localized Non-Hodgkin's Lymphoma.

No difference in overall survival was evident between patients receiving chemotherapy alone and those receiving combined chemotherapy and radiotherapy; there were four deaths in each group. The bars denote 95 percent confidence intervals.

IS THERE ANY ROLE OF IFRT

- LOCALIZED EARLY STAGE DISEASE– NO ROLE OF RT
- ADVANCED STAGE DISEASE– IFRT ELIMINATED
- LOCAL RESIDUAL/RELAPSE AFTER COMPLETE REMISSION– LOCAL FIELD RT

Non-Hodgkin's Lymphoma Arising in Bone in Children and Adolescents Is Associated With an Excellent Outcome: A Children's Cancer Group Report

Mark A. Lones, Sherrie L. Perkins, Richard Sposto, Nicole Tedeschi, Marshall E. Kadin, Carl R. Kjeldsberg, John F. Wilson, David L. Zwick and Mitchell S. Cairo

- PURPOSE: Non-Hodgkin's lymphoma (NHL) arising in bone is a heterogeneous histologic type of NHL that includes large-cell lymphoma, lymphoblastic lymphoma, and small noncleaved-cell lymphoma. NHL arising in bone is well recognized in adults but is less well characterized and infrequent in children and adolescents.
- PATIENTS AND METHODS: We performed a retrospective review of Children's Cancer Group (CCG) studies treating children and adolescents with NHL over a 20-year period (CCG-551, CCG-501, CCG-502, CCG-503, CCG-552, CCG-5911, and CCG-5941) and determined the response and event-free survival (EFS) rates in 31 patients with NHL arising in bone.
- RESULTS: The patients ranged in age from 3 to 17 years (median, 11 years; mean, 11 years), and 64.5% were male. All 31 (100%) patients achieved complete response. For 31 patients with NHL arising in bone, the product-limit estimated 5-year EFS was 83.8% ± 6.7%. ***EFS in 17 patients with localized disease (Murphy stages I and II) was 94.1% ± 5.7%, and EFS in 14 patients with disseminated disease (Murphy stage III) was 70.7% ± 12.4% (log-rank P = .10). EFS in 17 patients treated with chemotherapy and radiation was 70.1% ± 11.2%, and EFS in 14 patients treated with chemotherapy without radiation was 100% (P = .03).*** EFS in 26 patients with histology-directed treatment (LSA2-L2 or ADCOMP for lymphoblastic, other therapy for nonlymphoblastic) was 92.2% ± 5.3%, and in five patients with nonhistology-directed treatment it was 40.0% ± 21.9% ($P < .001$).
- CONCLUSION: NHL arising in bone is a heterogeneous type of NHL that makes up approximately 2.0% of NHL in children and adolescents on CCG studies. Response and survival in this young age group seem superb, with histology-directed treatment protocols without radiation in both localized and disseminated diseas

OXFORD JOURNALS
Japanese Journal of Clinical Oncology

Primary Bone Lymphoma: A New and Detailed Characterization of 28 Patients in a Single-Institution Study

Dai Maruyama,Takashi Watanabe,Yasuo Beppu,Yukio Kobayashi,Sung-Won Kim,Kazuki Tanimoto,Atsushi Makimoto,Yoshikazu Kagami,Takashi Terauchi,Yoshihiro Matsuno,Kensei Tobinai1

- Several studies have suggested that a combination of chemotherapy and radiotherapy was the best treatment for patients with PBL. Zinzani *et al.* conducted a retrospective analysis of 52 patients with stage I to stage IV PBL. The CR rates for patients treated by radiotherapy alone and chemotherapy with or without radiotherapy were 64% and 85%, respectively. The relapse rates between the two groups were 57% and 6%, respectively. These previous reports confirmed the superiority of chemotherapy to radiotherapy alone as the initial treatment for PBL patients. Beal *et al.* concluded that PBL patients treated with a combination of chemotherapy and radiotherapy were found to have a significantly better survival than the patients treated with single modality therapy (chemotherapy or radiotherapy alone), but the 5-year OS rate for patients treated with combined modality therapy versus chemotherapy alone was not significantly different. The addition of radiotherapy did not affect the survival rate in either the total of all PBL patients or those with early stage disease (data not shown) in our univariate analysis. Bacci*et al.* reported that four of six patients who underwent radiotherapy of less than 30 Gy had a relapse in their radiation fields and that a combination of chemotherapy and radiotherapy of more than 40 Gy was needed

J Clin Oncol. 2007 Sep 1;25(25):3915-22.

Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report.

Salzburg J[1], Burkhardt B, Zimmermann M, Wachowski O, Woessmann W, Oschlies I, Klapper W, Wacker HH, Ludwig WD, Niggli F, Mann G, Gadner H, Riehm H, Schrappe M, Reiter A.

Author information

Abstract

PURPOSE: We analyzed the prevalence, clinical pattern, and prognostic impact of CNS involvement in a large cohort of children and adolescents diagnosed with non-Hodgkin's lymphoma (NHL), with special attention to differences according to NHL subtype.

PATIENTS AND METHODS: From October 1986 to December 2002, 2,381 patients (median age, 9.37 years; range, 0.2 to 23.8 years; female-to-male ratio, 1:2.7) from Germany, Austria, and Switzerland were registered. A total of 2,086 patients were eligible for the consecutive multicenter protocols NHL-Berlin-Frankfurt-Münster [BFM] -86, NHL-BFM-90, and NHL-BFM-95, and could be evaluated for outcome.

RESULTS: CNS involvement was diagnosed in 141 (5.9%) of 2,381 patients and was associated with an advanced stage of NHL. The percentage of CNS-positive patients was 8.8% for Burkitt's lymphoma/Burkitt's leukemia (BL/B-ALL), 5.4% for precursor B-lymphoblastic lymphoma (pB-LBL), 3.3% for anaplastic large-cell lymphoma, 3.2% for T-cell-LBL, 2.6% for diffuse large B-cell lymphoma, and 0% for primary mediastinal large B-cell NHL ($P < .001$). Most CNS-positive patients with pB-LBL, T-LBL, or BL/B-ALL had meningeal disease. The probability of event-free survival (pEFS; +/- SE) at 5 years was 85% +/- 1% for the 2,086 protocol patients (median follow-up, 6.5 years; range, 0.3 to 17.7 years). For the 112 CNS-positive patients, pEFS was 64% +/- 5%, compared with 86% +/- 1% for the 1,927 CNS-negative patients ($P < .001$). Although CNS disease had no impact on pEFS for advanced-stage T-LBL patients, CNS-positive patients with BL/B-ALL had a worse average outcome than CNS-negative patients with stage IV BL/B-ALL (60% +/- 5% v 81% +/- 3%; $P < .001$). In multivariate analysis, CNS disease was the strongest predictor for relapse in BL/B-ALL patients with advanced-stage disease.

CONCLUSION: Six percent of childhood/adolescent NHL patients were CNS positive. However, the prevalence, pattern, and prognostic impact of CNS involvement differed among NHL subtypes.

RT DOSE

- SMALL CELL LYMPHOBLASTIC/LYMPHOCYTIC LYMPHOMA– 30GY
- LARGE CELL HISTOLOGY- 45GY
- PRIMARY BONE LYMPHOMA- 45-55 GY
- PALLIATION-10GY
  - SVC SYNDROME
  - ACUTE RESPIRATORY DISTRESS
  - SPINAL CORD COMPRESSION
  - ORBITAL PROPTOSIS
- PROPHYLAXIS FOR CNS DISEASE– NO RT

Treatment Protocol for NHL-BFM95 for Advanced-Stage Lymphoblastic Lymphoma

Drug	Dose	Days Administered
Induction protocol I, weeks 1-9		
Prednisone, oral	60 mg/m^2*	1-28, then taper over 3 × 3 days
Vincristine, IV	1.5 mg/m^2; max, 2 mg	8, 15, 22, 29
Daunorubicin, IV over 1 hour	30 mg/m^2	8, 15, 22, 29
Escherichia coli L-asparaginase, IV over 1 hour†	5,000 U/m^2	12, 15, 18, 21, 24, 27, 30, 33
Cyclophosphamide with mesna, IV over 1 hour	1,000 mg/m^2	36, 64
Cytarabine, IV	75 mg/m^2	38-41, 45-48, 52-55, 59-62
Mercaptopurine, orally	60 mg/m^2	36-63
MTX, IT‡	12 mg	1, 12, 33, 45, 59§
Protocol M, starting 2 weeks after the end of protocol I		
Mercaptopurine, orally	25 mg/m^2	1-56
MTX‖	5 g/m^2	8, 22, 36, 50
MTX, IT‡	12 mg	8, 22, 36, 50
Reinduction protocol II, starting 2 weeks after the end of protocol M		
Dexamethasone, orally	10 mg/m^2	1-21, then taper over 3 × 3 days
Vincristine, IV	1.5 mg/m^2; max, 2 mg	8, 15, 22, 29
Doxorubicin, IV over 1 hour	30 mg/m^2	8, 15, 22, 29
E coli L-asparaginase, IV over 1 hour†	10,000 U/m^2	8, 11, 15, 18
Cyclophosphamide with mesna, IV over 1 hour	1,000 mg/m^2	36
Cytarabine, IV	75 mg/m^2	38-41, 45-48
Thioguanine, orally	60 mg/m^2	36-49
MTX, IT‡	12 mg	38, 45

TAKE HOME MESSAGE

- LEUKEMIC TRANSFORMATION AND CNS INVOLVEMENT ARE MORE COMMON
- BOTH B AND T CELL LINEAGE ARE COMMON
- ST JUDES STAGING SYSTEM IS USED
- MEDIASTINUM IS MORE COMMONLY INVOLVED IN DLBCL, ANAPLASTIC LARGE CELL LYMPHOMA, LYMPHOBLASTIC LMPHOMA AND HODGKINS DISEASE.
- THE THREE MAIN SUBTYPES ARE PRECURSOR LYMPHOID NEOPLASM, MATURE B CELL LYMPHOMA, MATURE T CELL LYMPHOMA.
- PRECURSOR T CELL LYMPHOBLASTIC LYMPHOMA HAVE CLINICAL & BIOLOGICAL FEATURES OF ACUTE LYMPHOBLASTIC LEUKEMIA.
- MORE THAN 25% BLAST IN MARROW SUGGESTIVE OF LEUKEMIC INVOLVEMENT.

- MORE THAN 5% BLAST IN MARROW SUGGESTIVE OF STAGE IV DISEASE.
- DUE TO UNPREDICTABLE PATTERN OF LYMPHATIC SPREAD & EXTENSIVE EXTRANODAL DISEASE ST JUDES STAGING SYSTEM INSTEAD OF ANN ARBOR STAGING SYSTEM IS ADOPTED.
- NO ROLE OF RADIOTHERAPY IN CNS PROPHYLAXIS & NO ROLE OF IFRT IN LOCALISED AND ADVANCED STAGE DISEASE.
- RT IS INDICATED IN RELAPSE, RESIDUAL DISEASE, CNS INVOLVEMENT & IN PALLIATIVE INTENT.