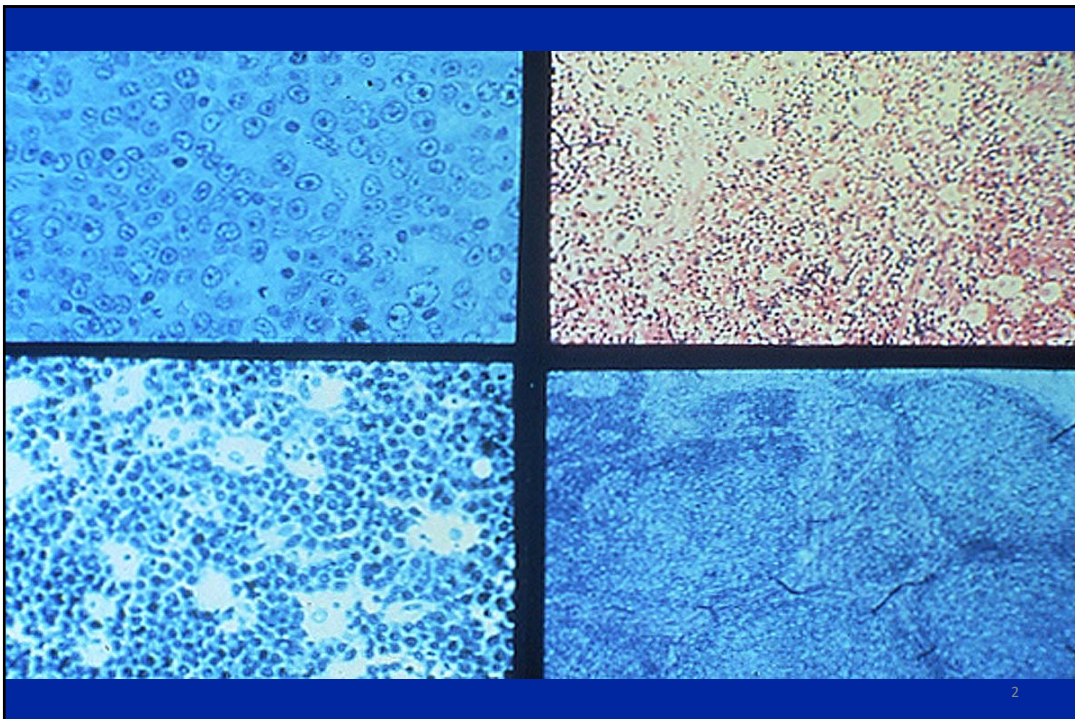


# Non-Hodgkin Lymphoma – Know Your Subtype

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# NHL Types

## MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukaemia /small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- *Splenic B-cell lymphoma/leukaemia, unclassifiable*
- *Splenic diffuse red pulp small B-cell lymphoma*
- Hairy cell leukaemia-variant
- Lymphoplasmacytic lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- In situ follicular neoplasia
- Pediatric type follicular lymphoma
- *Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- In situ mantle cell neoplasia

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# NHL Types (cont'd)

- Diffuse large B-cell lymphoma (DLBCL), NOS
- T cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL, not otherwise specified
- *EBV+ Mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8 positive DLBCL, NOS*
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberrations*
- *High grade B-cell lymphoma, with BCL2 and/or BCL6 and MYC rearrangements*
- *High grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

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## NHL Types (cont'd)

### MATURE T-AND NK-NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK cell leukaemia
- Epstein-Barr virus (EBV) positive T-cell lymphoproliferative diseases of childhood
- Chronic Active EBV infection, Cutaneous
- Hydroa vacciniforme-like lymphoma
- Severe mosquito bite hypersensitivity
- Chronic Active EBV infection, Systemic
- Systemic EBV+ T-cell Lymphoma of childhood
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- *Indolent T-cell lymphoproliferative disorder of the GI tract*
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides

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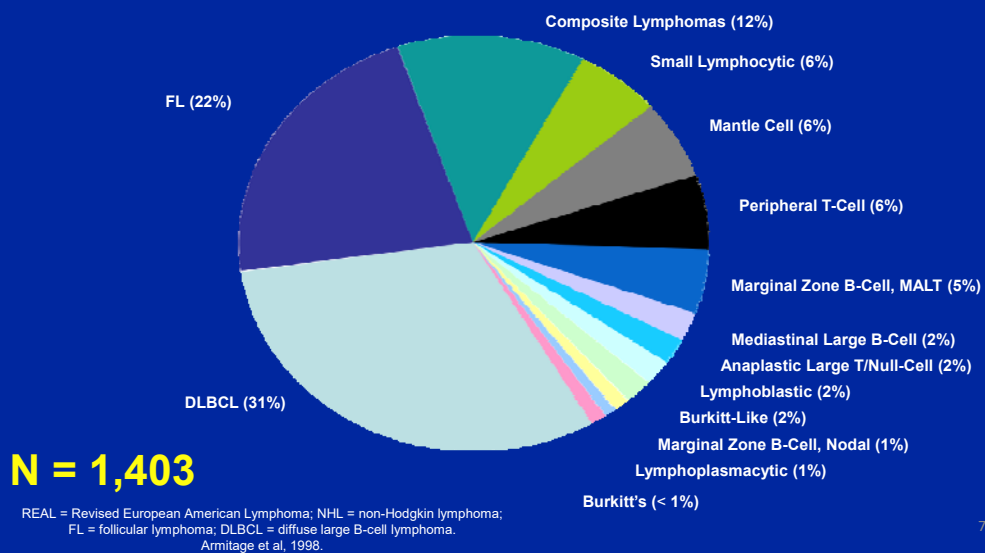
## NHL Types (cont'd)

### MATURE T-AND NK-NEOPLASMS

- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8+ T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma*
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative
- *Breast implant-associated anaplastic large cell lymphoma*

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## Frequency of REAL Classification NHL Subtypes



## Diffuse Large B-cell Lymphoma

## As We Learn More About the Biology of Lymphomas, it is Clear That Diffuse Large B-Cell Lymphoma is Not Just One Disease

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### Subtypes of Diffuse Large B-Cell Lymphoma In The 2008 WHO Classification

<u>Morphological</u> Centroblastic Immunoblastic Anaplastic Plasmablastic	<u>Genetic</u> GCB Non GCB (includes ABC) Double hit	<u>Other</u> EBV positive in elderly With chronic inflammation In lymphomatoid granulomatous In HHV-8 associated Castlemans Interface lymphomas DLBCL/Burkitt NSHD/DLBCL
<u>Immunological</u> ALK positive CD5 positive	<u>By Primary Site</u> CNS Cutaneous leg type Mediastinal Intravascular Effusion	

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## It is Possible That Some “Subtypes” Might Benefit From Specific Treatments

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## Conclusion

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- Diffuse large B-cell lymphoma is not just one disease
- There is not one “best” regimen for all patients, although CHOP-R remains the “standard”
- New drugs and a better understanding of molecular subtypes will almost certainly change the therapy for these patients

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# Follicular Lymphoma

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**Follicular Lymphoma  
is a Much More  
Complex Disorder  
Than is Sometimes  
Recognized**

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## Can Follicular Lymphoma Be Accurately Sub-typed (Graded)?

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<u>Type</u>	<u>Accuracy of Diagnosis</u>
Follicular Small Cleaved (Grade 1)	72%
Follicular Mixed (Grade 2)	61%
Follicular Large Cell (Grade 3)	60%

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## What About Distinguishing FL 3A vs. FL 3B??

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## **Should Follicular Lymphoma Grade 3 Be Treated Differently?**

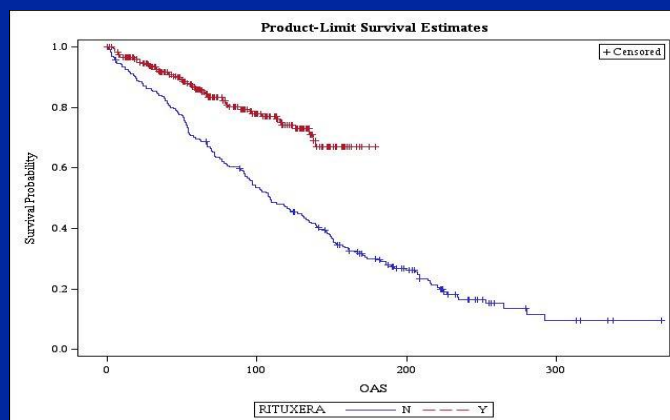
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## **Is Survival Improving for Low Grade Follicular Lymphoma?**

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## Patients With Low Grade Follicular Lymphoma Treated in the NLSG



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## Mantle Cell Lymphoma

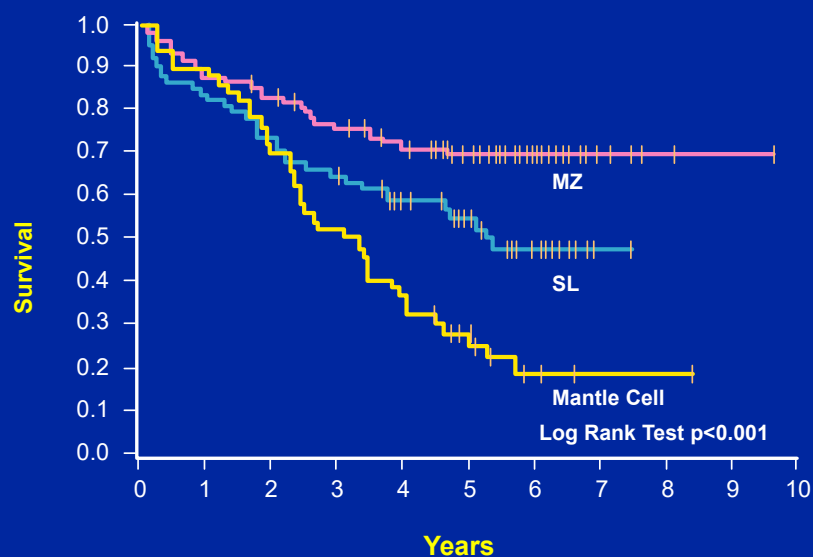
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## Mantle Cell Lymphoma History

- 1974, lymphocytic lymphoma of intermediate differentiation (Berard, et al)
- 1974, centrocytic lymphoma (Lennert, et al)
- 1982, mantle zone lymphoma (Weisenburger, Rappaport)
- 1987, association of intermediate lymphocytic lymphoma with t(11;14)
- 1990, association of intermediate lymphocytic lymphoma with Bcl-1 (cyclin-D1)
- 1992, mantle cell lymphoma

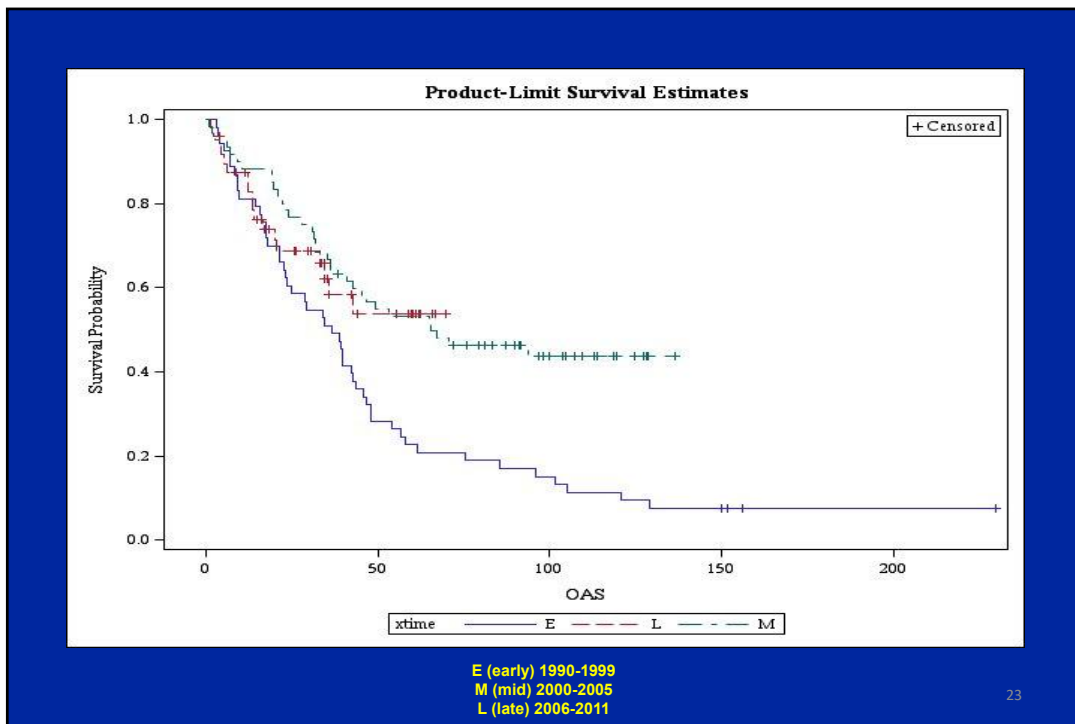
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## Overall Survival Small Round Cell Tumors



JCO 1998; 16: 2780

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## Mantle Cell Histological Appearance

- Diffuse
- Nodular
- Blastic

## Mantle Cell Lymphoma Presenting as “CLL”

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- Often splenomegaly without lymphadenopathy
- Frequently asymptomatic
- Reported median survival ~6 years
- Some patients go  $\geq 5$  years without therapy

Blood 2003; 101:4975

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## Conclusion

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The survival of patients with mantle cell lymphoma has improved considerably with better understanding of the disease, the advent of rituximab, and clinical trials studying comparative effectiveness of available regimens. Several active new agents make it likely that the outcome will continue to improve.

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# Marginal Zone Lymphoma

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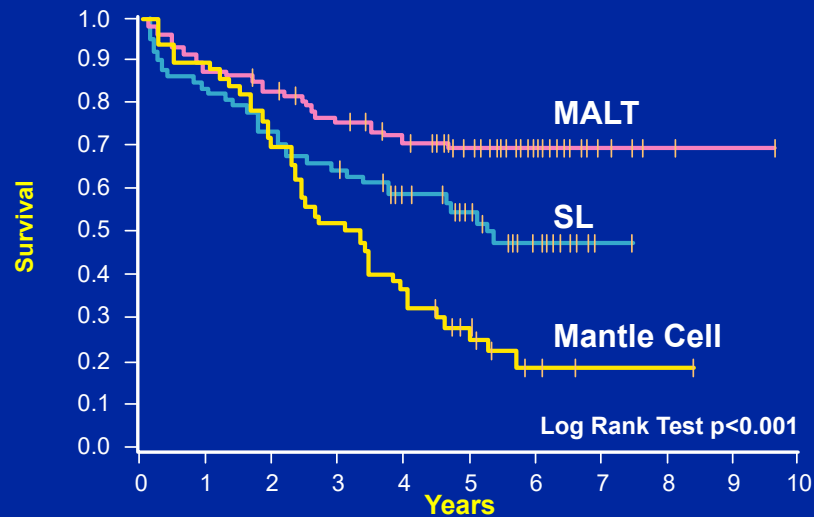
## Marginal Zone Lymphomas as a Percent of All Non-Hodgkin's Lymphoma

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<u>Type</u>	<u>Percent</u>
MALT	7.6%
Nodal	1.8%
Splenic	<1%

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## Overall Survival Small Round Cell Tumors



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## MALT Lymphoma

### An Antigen-dependent Process

Features suggesting an antigen-driven growth of MALT Lymphoma

- Histologic features
  - Reactive lymphoid follicles and follicular colonization
  - Scattered transformed cells in cell cycle
  - Plasma cell differentiation
  - Large amount of intratumoral T-cells
- Association with chronic infectious and acute-immune processes
- Mutation pattern of immunoglobulin gene
- Therapeutic efficacy of antibiotics

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# Small Lymphocytic/ Chronic Lymphocytic Leukemia

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## Virchow: Initial Description CLL



### Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weissen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Proteinmolekülen, gedehnten, förmigen, feizhälligen, farblosen Körperchen und granulierten Zellen mit einem rauhlichen, kugelförmigen oder fleckförmigen oder mit mehreren kernförmigen, blasseren Kerne. Die gedehnten dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältnis zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weissen Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weissen) Blutkörperchen eine umgekehrte ist, ohne daß eine Beimischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

ich würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen und, wie es mir scheint, nicht unbedeutenden Thatfache beizutragen zu haben. —

Dr. Virchow.

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## The Names Can Sometimes Be Confusing

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- CLL
- SLL
- Monoclonal B lymphocytosis

All typically Have CD5+, CD10-, CD20 dim, CD23+ Small Lymphocytes

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## Differential Diagnosis

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- Lymphoplasmacytic lymphoma
- Hairy cell leukemia
- MALT lymphoma
- Nodal marginal zone lymphoma
- Splenic marginal zone lymphoma
- B-cell prolymphocytic leukemia
- Mantle cell lymphoma
- Follicular lymphoma

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# Peripheral T-Cell Lymphoma

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## Indolent PTCLs

- Mycosis fungoides
- Chronic, smoldering ATL
- CD30+, primary cutaneous lymphoproliferative disorders

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## **Spectrum of CD30+ Cutaneous Lymphoproliferative Disorders**

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- Lymphomatoid papulosis (ALK-)
- Primary cutaneous ALCL (usually ALK-)
- Systemic ALCL with skin involvement (ALK+/-)
- All CD30+ and rearranged TCR genes

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## **Aggressive PTCLs**

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## **Anaplastic Large Cell Lymphoma**

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- Previously confused with other malignancies
- B-cell variant exists
- Sub-divided by ALK expression

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## **ALCL and Breast Implants**

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# NK/T Cell Lymphomas

## Nasal vs Nasal-type

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# Hepatosplenic Gamma/Delta T-cell Lymphoma

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- Difficult to diagnose
- Liver, spleen and marrow infiltrated
- Sinusoidal pattern – not tumors
- Poor prognosis

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## Enteropathy-Type Intestinal T-cell Lymphoma

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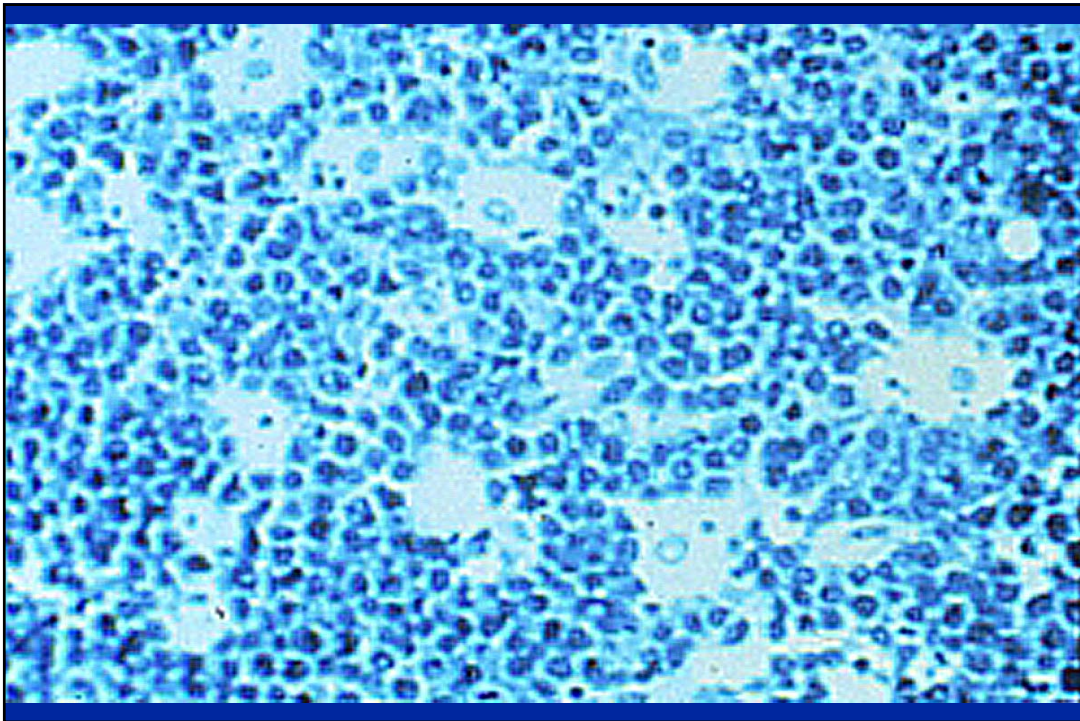
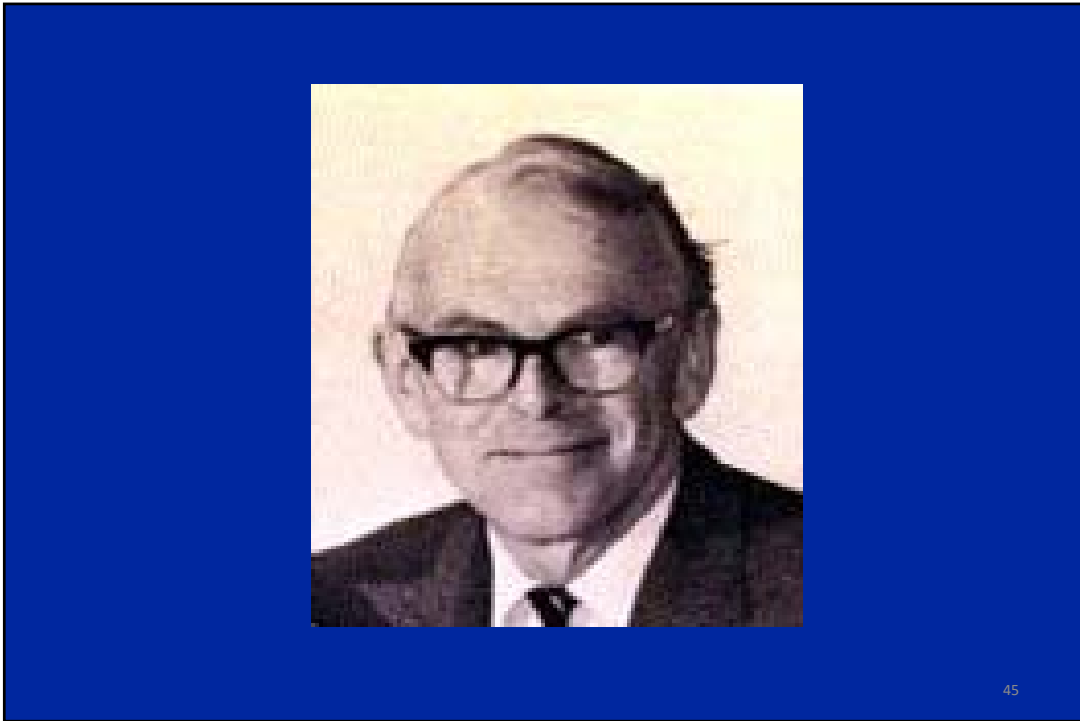
- Often gluten-sensitive enteropathy (32% in International Study)
- Treating celiac disease seems to prevent lymphoma
- Poor prognosis

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## Burkitt Lymphoma

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# Burkitt Lymphoma Was the First Malignancy to Be Cured With Chemotherapy

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## Treatment Outcome for Adult Burkitt Lymphoma Using Dose- Intensive Regimens

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<u>Investigators</u>	<u>Regimen</u>	<u>EFS</u>
NCI	Magrath	92%
NCI	Magrath	84%
MD Anderson	R-HyperCVAD	80%
NCI	R-EPOCH	93%

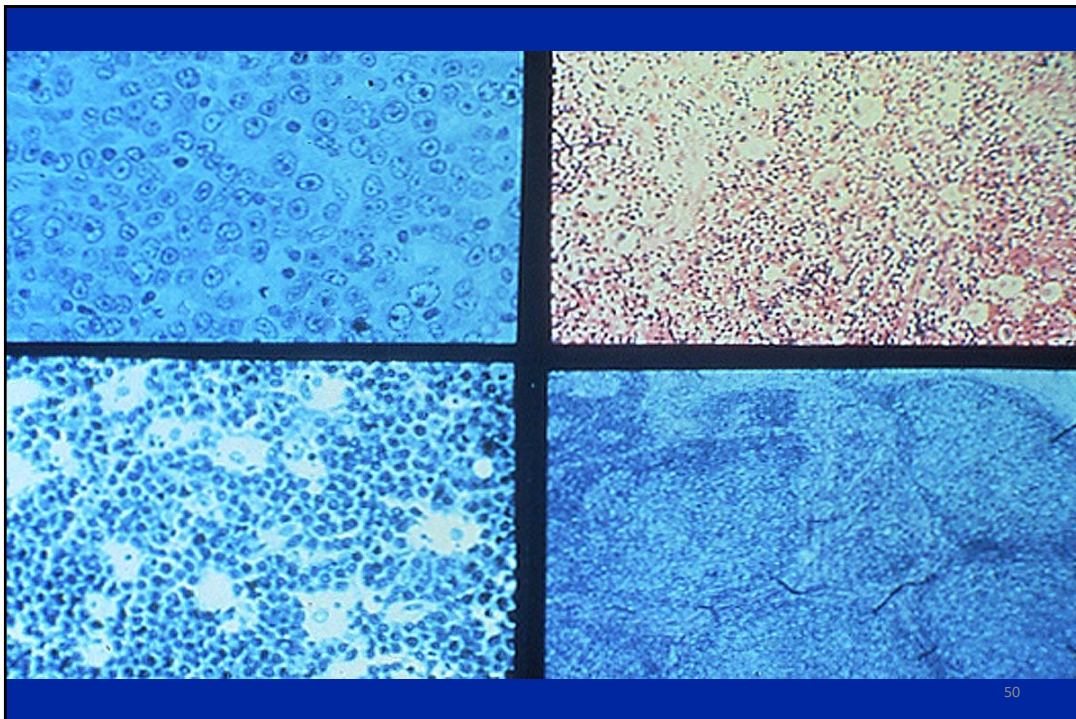
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## In Burkitt Lymphoma it is a Tragedy to:

1. Misdiagnose
2. Delay treatment
3. Not give correct doses of an intensive regimen on schedule

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## Non-Hodgkin Lymphoma – Know Your Subtype



# Q&A Session

### Ask a question by phone:

- Press star (\*) then the number 1 on your keypad.

### Ask a question by web:

- Click “Ask a question”
- Type your question
- Click “Submit”

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

## Non-Hodgkin Lymphoma – Know Your Subtype



### SUPPORT RESOURCES

- Online Chats: Online moderated chat forums: [www.LLS.org/chat](http://www.LLS.org/chat)
- Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)
- Free education materials: [www.LLS.org/booklets](http://www.LLS.org/booklets)
- Past NHL education programs: [www.LLS.org/programs](http://www.LLS.org/programs)
- Additional information on NHL: [www.LLS.org/NHL](http://www.LLS.org/NHL)
- Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - EMAIL: [infocenter@LLS.org](mailto:infocenter@LLS.org)
  - TOLL-FREE PHONE: (800) 955- 4572