

***Lizette Figueroa-Rivera, MA***

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. James Armitage for sharing his time and expertise with us today. We have over 800 people participating in today's program from across the United States and several countries around the world, including Canada, Turkey, and the United Kingdom.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Chief Medical Officer, Dr. Gwen Nichols, who will share a few words. Dr. Nichols, please go ahead.

***Gwen Nichols, MD***

Thanks, Lizette. I'd like to add my welcome to patients, caregivers, and healthcare professionals that are on the phone today. The Leukemia & Lymphoma Society exists to find cures and to be sure that we have access to the best treatments for blood cancer patients. For more than 60 years, LLS has been involved not only in pioneering innovation, targeted therapies, immunotherapies that are improving the survival rates and the quality of life for blood cancer patients, but we've also invested over a billion dollars in research to advance these therapies to save lives. Until there's a cure for the various types of blood cancers, LLS will continue to fund promising research.

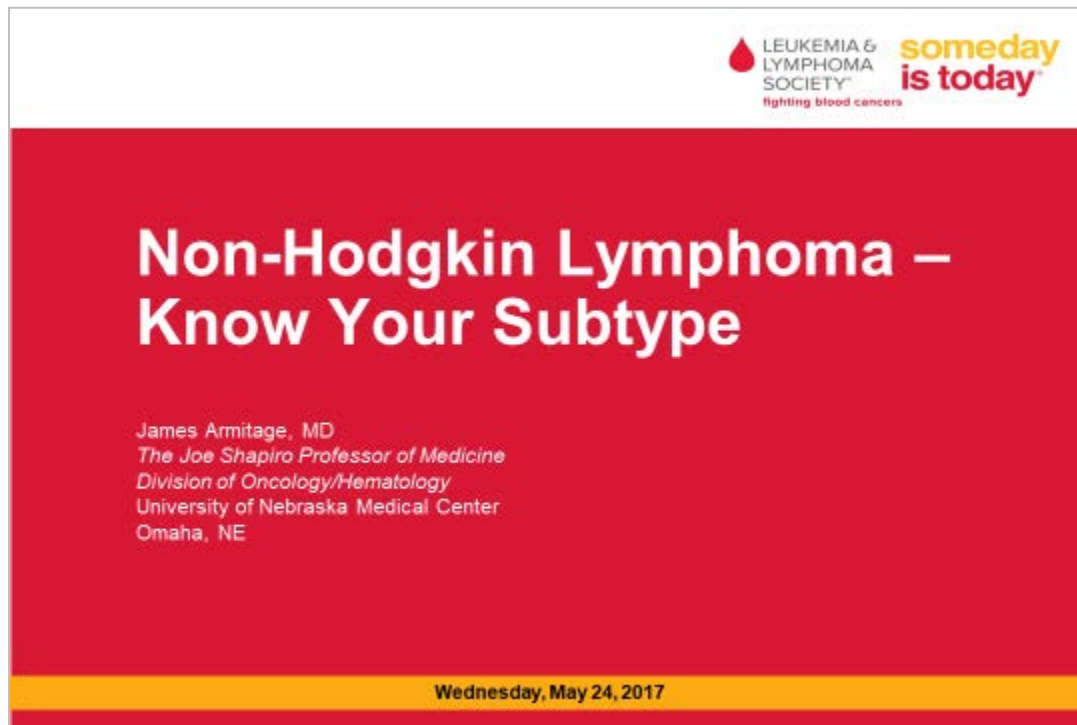
In addition, as this program is a great demonstration, we're the leading source of free information for blood cancer patients, for blood cancer educators and for professionals taking care of patients with blood cancer. And we touch the patients in their communities through our 56 chapters all across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors, helping them navigate their treatments and ensuring access.

We're fortunate that Dr. Armitage, Dr. James Armitage, who is one of the nation's leading experts in lymphoma, is here today to share his insights and his time. We appreciate his dedication to supporting our mission and our patients and his commitment for caring for patients living with blood cancers.

Thank you, Dr. Armitage, and I'll turn the program back to Lizette.

***Lizette Figueroa-Rivera, MA***

Thank you, Dr. Nichols. And we would like to acknowledge and thank Bristol-Myers Squibb and Genentech for their support of this program.



## PRESENTATION

### ***Lizette Figueroa-Rivera, MA***

I'm now pleased to introduce Dr. James Armitage, the Joe Shapiro Professor of Medicine, Division of Oncology/Hematology at the University of Nebraska Medical Center in Lincoln, Nebraska. On behalf of The Leukemia & Lymphoma Society, thank you so much, Dr. Armitage, for volunteering your time and expertise with us today. And I'm now privileged to turn the program over to you.

### ***James Armitage, MD***

Thank you for that nice introduction. I must, however, point out that some of you will already know that the University of Nebraska Medical Center is not in Lincoln, Nebraska. It's actually Omaha, Nebraska.



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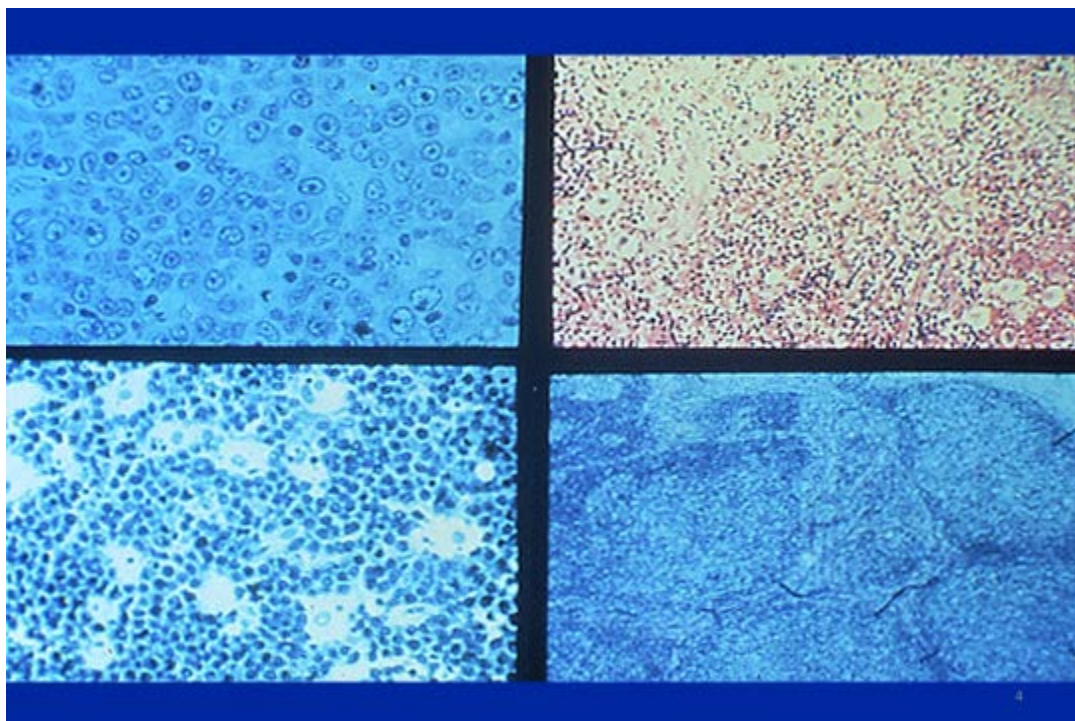
## Disclosure

James Armitage, MD has affiliations with:

- TESARO
- Samus Therapeutics

Wednesday, May 24, 2017

Now it is my pleasure to have a chance to give this presentation and to talk about this group of illnesses that can be sometimes really confusing. Before I actually begin the presentation, this slide is up here to have me remember to tell you that I am on the board of a company called Tesaro and a consultant to a company called Samus but have very few other, any possible conflicts.



## TRANSCRIPT

All right, now this slide shows you what pathologists see looking at a biopsy under the microscope. To give you an idea of the different appearances of lymphomas. Lymphomas are malignancies of the immune system, and they're all situations where a lymphocyte underwent some genetic change so it behaves in an abnormal way. It behaves like what we call cancer. That means the cells grow when they shouldn't, don't die when they should, and go places they shouldn't.

But lymphocytes, at various stages of development, can acquire lymphoma; and the lymphomas then are a reflection of that stage of lymphocyte development. And it leads to, as we'll see here in a minute, quite an impressive array of different diseases. They're all cancers of lymphocytes, but they're quite different illnesses.

And so, in this slide, you see in the upper left-hand corner an example of diffuse large B-cell lymphoma, the most common lymphoma. In the upper right, you see a lymphoma with these large funny looking cells, and this is a Hodgkin lymphoma. In the lower left, you see a lymphoma that has these, what's been called, starry sky appearance with lots and lots of dense, little blue cells and then these open areas and that's a Burkitt lymphoma. And the lower right, you can see a lymph node with these big, clear things surrounded by a darker edge, and this is a follicular lymphoma. All different types of lymphoma. And you can see how pathologists might be able to just use the appearance to make that diagnosis, but today they use all sorts of other sophisticated techniques to tell these apart, not just the appearance of the cell itself under the microscope. They do immunological studies and genetic studies that help more precisely make a diagnosis.

Now currently today, the World Health Organization (WHO) classification of lymphomas has about 80 subtypes. So the next four slides are going to be those subtypes.

## NHL Types

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### 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

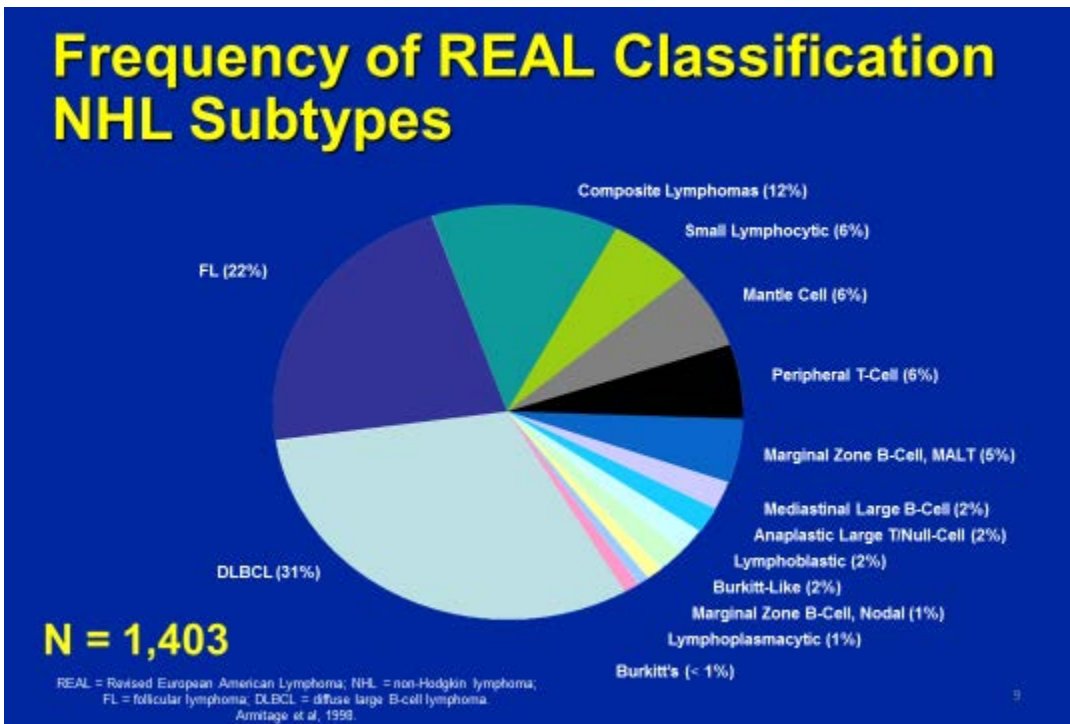
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## NHL Types (cont'd)

### 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*

And I'm not putting this up because I expect you to remember them. Just I want you to have an idea of here are some of the B-cell lymphomas. You can see all these different words. And this is the rest of them. Those are all lymphomas of maturing B lymphocytes. Lots and lots of different types. And here are mature T-cell lymphomas and the rest of them. You can see just again all sorts of different subtypes that are now recognized. And these are just the mature cell lymphomas, and you have to remember they're also the so-called progenitor cell lymphomas, precursor cell lymphomas that are another group. So many, many kinds. How do you make sense out of any of this?



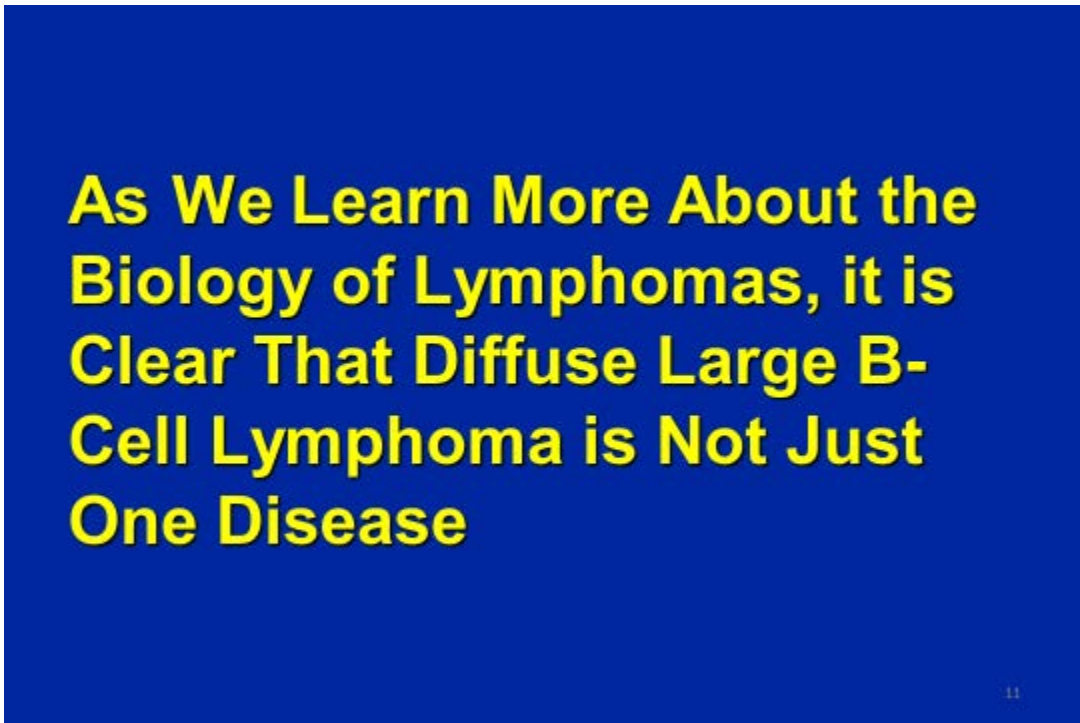
Well one thing, you can see on this slide. This gives you some idea of the relative proportions of these disorders. And this isn't all those names we just talked about, but a lot of them are important ones. And you can see that the biggest group here are diffuse large B-cell lymphomas which make up 30 plus percent of all lymphomas. Follicular lymphoma is the next biggest group. These are just non-Hodgkin's lymphomas. So if we had Hodgkin lymphoma on, it would be the next biggest group. And then there are a variety of different other subtypes, and you can see a bunch of them are in that 5 to 10% range. Composite lymphomas that you see there, that was from this study, those are lymphomas where more than one subtype of lymphoma was present in the same biopsy. So lots of different choices.

So what we're going to try to do today is, at least for many of the common ones, try to make sense out of them. Well, the most common lymphoma is diffuse large B-cell lymphoma.



# Diffuse Large B-cell Lymphoma

Originally this group of illnesses would have been lumped with what was called diffuse large cell lymphoma. Before then, diffuse histiocytic lymphoma as you go back in time. But even though we call it one disease, the diagnosis is diffuse large B-cell lymphoma, it is quite clear that this represents a variety of different clinical entities that can be subdivided based on sometimes appearance, more often on immunologic or genetic characteristics.



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



And all the different subtypes of diffuse large B-cell lymphoma don't have the same clinical characteristics and don't have the same likelihood for benefit. But overall, diffuse large B-cell lymphoma is one of the more curable lymphomas. When I see a new patient with diffuse large B-cell lymphoma, everything else equal, that person is more likely to get over their disease than not. Most of them are not going to die from this disease.

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

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

Here are the major subtypes of diffuse large B-cell lymphoma from the WHO (World Health Organization) classification, and I want you to see that the upper left hand has four different appearances, morphology, how they look. Below that are two different types, based on proteins that are expressed. In the upper middle are three different types—we could actually have more—but three different types based on which genes are expressed for the top two or the bottom one, which genes have specific abnormalities in them, double-hit lymphomas. And that's important because those patients have, their lymphoma has, a translocation or an abnormality involving the MYC gene and BCL2 usually. And those patients don't have as good an outlook.

The top part, the germinal center B and the nongerminal center B, reflects the expression of a whole variety of genes; but what we learned was the germinal center B, which is the more common, is more likely to be cured than the nongerminal center B or ABC or activated B-cell subtype.

We know that lymphomas that begin in different parts of the body, that's the lower middle, don't all have the same characteristics. And the most obvious one is central nervous system lymphoma where they begin in the brain and have to be treated in quite a different way. And then the right-hand side, show you that there's a lot of other subtypes, this is just some of them. And at the bottom, you'll notice that there are some diffuse large B-cell lymphomas that have characteristics of diffuse large B-cell lymphoma but also some characteristics of Burkitt lymphoma and another group that share

characteristics with Hodgkin lymphoma. So, complicated business. But the truth is, if you have a diffuse large B-cell lymphoma, if that's your diagnosis, you have a chance to be cured of the disease; and with most subtypes, a very good chance.



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

The thing that we're learning is that it may be that some subtypes of diffuse large B-cell lymphoma would be better treated differently than the common forms. The most obvious one of these is one I mentioned earlier, and that's the ones that begin in the brain where the drugs that we use typically don't penetrate into the brain and aren't likely to have as good a treatment effect. But there are other drugs we can use that make brain lymphoma still potentially curable. And we've learned that some of those that I showed you earlier that were called nongerminal center B or activated B, those subtypes seem to benefit from some different drugs like ibrutinib and lenalidomide, and we're learning to try to incorporate those new drugs into the care of patients with that particular subtype.

## 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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So, diffuse large B-cell lymphoma isn't really just one thing. Although CHOP-R is by far the most commonly used treatment, it's not necessarily best for every single patient with this type of lymphoma. And as we learn more about the biology of the disease and new drugs become available, we're going to have a continually improving chance for these patients to be cured.

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## Follicular Lymphoma

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TRANSCRIPT

The next most common kind of lymphoma is follicular lymphoma. This has had different names in the past, giant follicular, giant follicle lymphoma, a variety of other names in the distant past. But second most common kind of lymphoma, and everybody used to think of it as kind of a boring disease. Basically, everything's all the same.

But as we're learning more about the biology of the disease, it's not quite as simple as we thought.



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

For a long time now, we've tried to subdivide follicular lymphomas based on the number of big cells, large cells, transformed cells in the tumor.

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

<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%

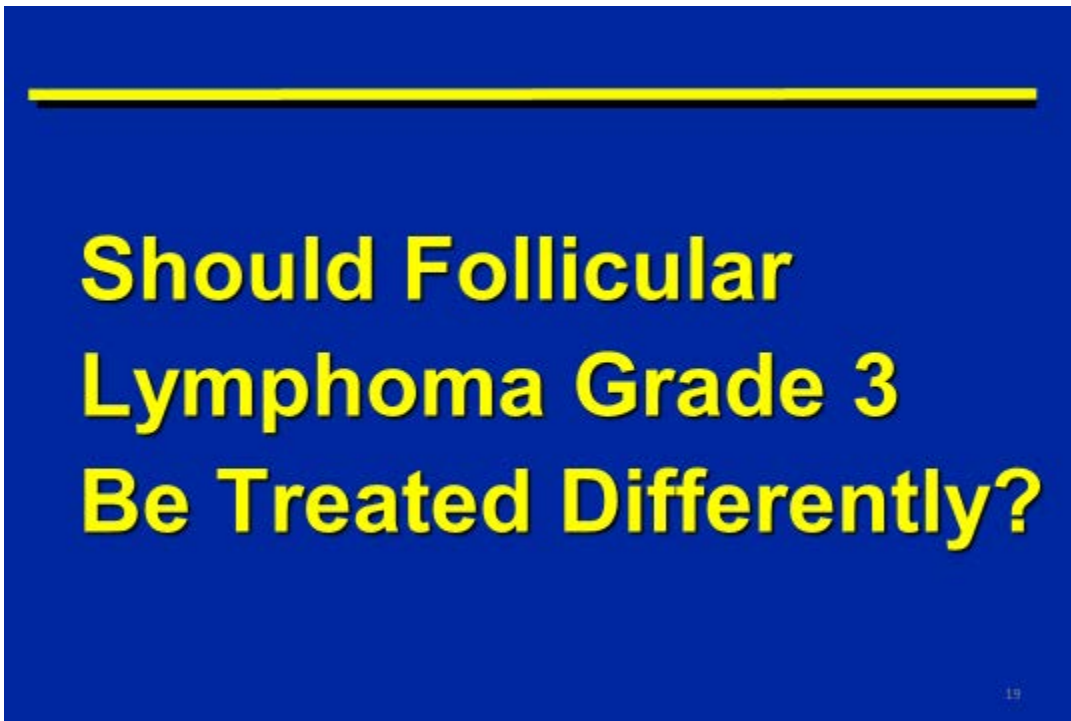
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Follicular small cleaved or grade 1 follicular lymphoma has a very few large cells, grade 2 has some large and some small cells and grade 3 has lots of large cells. The number on the right here, that percent is when we tested this with expert pathologists to show that it is kind of hard making these distinctions among the different subgroups of follicular lymphoma. And the pathologists don't do it nearly as accurately as they make some other diagnoses.

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

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And it's a general principle, partly reflecting that I suppose, patients with follicular lymphoma tend to be treated in the same way with the one exception. We know that some patients with follicular grade 3 have a disease that behaves like diffuse large B-cell lymphoma. And if they're treated in the same way as diffuse large B-cell lymphoma patients, they have a good chance to be cured. But that's the subset of patients. And how to tell those from other follicular lymphomas that behave in a more indolent or low-grade fashion is kind of a challenge. Some of us would treat everybody that gets called grade 3 aggressively so we don't miss treating with a large B-cell lymphoma regimen one of these patients who has a chance to be cured relatively easily. But this is a point physicians argue about.



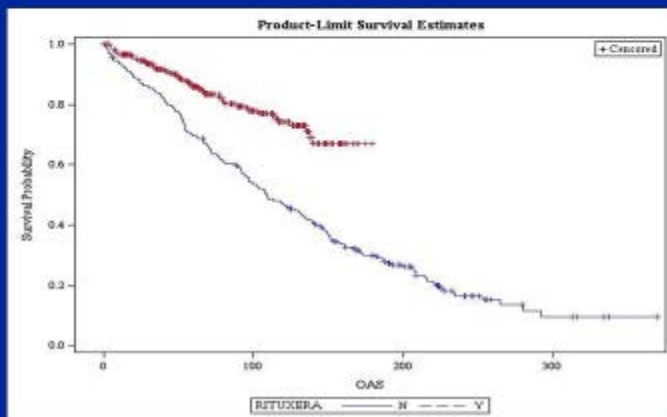
This just makes the same point, that I believe and I think most oncologists in the United States believe, that we should try to identify those patients with follicular lymphoma that have a more aggressive disease and treat them like they have diffuse large B-cell lymphoma.



# Is Survival Improving for Low Grade Follicular Lymphoma?

Now what about the majority of patients with follicular lymphoma, the ones that might get called low-grade follicular lymphoma? Some people would say that we just don't do much, that this is one of the diseases that it's perfectly acceptable to not treat at diagnosis, to do so-called watch and wait. And for some patients, the disease won't cause any trouble for a very long time. And since we've known about this group of patients, it looks like the median survival for patients with low-grade follicular lymphoma, that is the time the middle patients survive, half the people would live longer than this and half less long, is about ten years. Well, have new drugs made any difference in this? And the answer is yes.

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



This is data from the Nebraska Lymphoma Study Group showing two curves. You can see that the percent surviving is on the left-hand side, and across the bottom are the number of months patients are surviving. Then the curves themselves show you the proportion still alive at that particular point. So 100 months is about, what, eight years. You go a little bit past that, you have ten years. And then if you went between the 200 and 300, you'd have 20 years. You can see that in the days before rituximab was available, the median survival, that half-life, hits just right at ten years. But since rituximab, the brighter-colored line on the top, is a much improved survival; and that has not even come close to reaching the median survival yet when it's out around 15 years. And our statisticians think if you try to estimate this, this is going to be closer to a 20-year median or average survival. And, of course, some of these patients are going to be cured; but some patients who have recurrent disease still live a much longer time since we've had available these new treatments.



# Mantle Cell Lymphoma

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Mantle cell lymphoma (MCL) is an interesting and relatively new disease. You can see on the next slide the history of this disease.

## 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

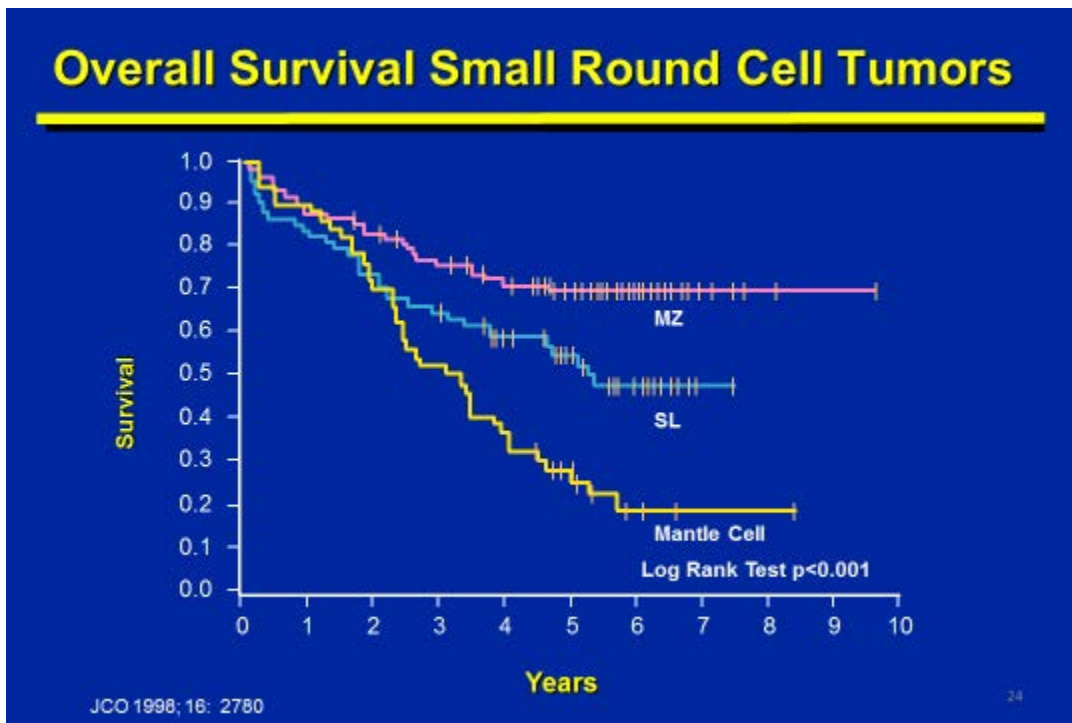
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In 1974 in the United States, a pathologist named Cos Berard described in these little small cell lymphomas one he called lymphocytic lymphoma of intermediate differentiation. In the same year, a

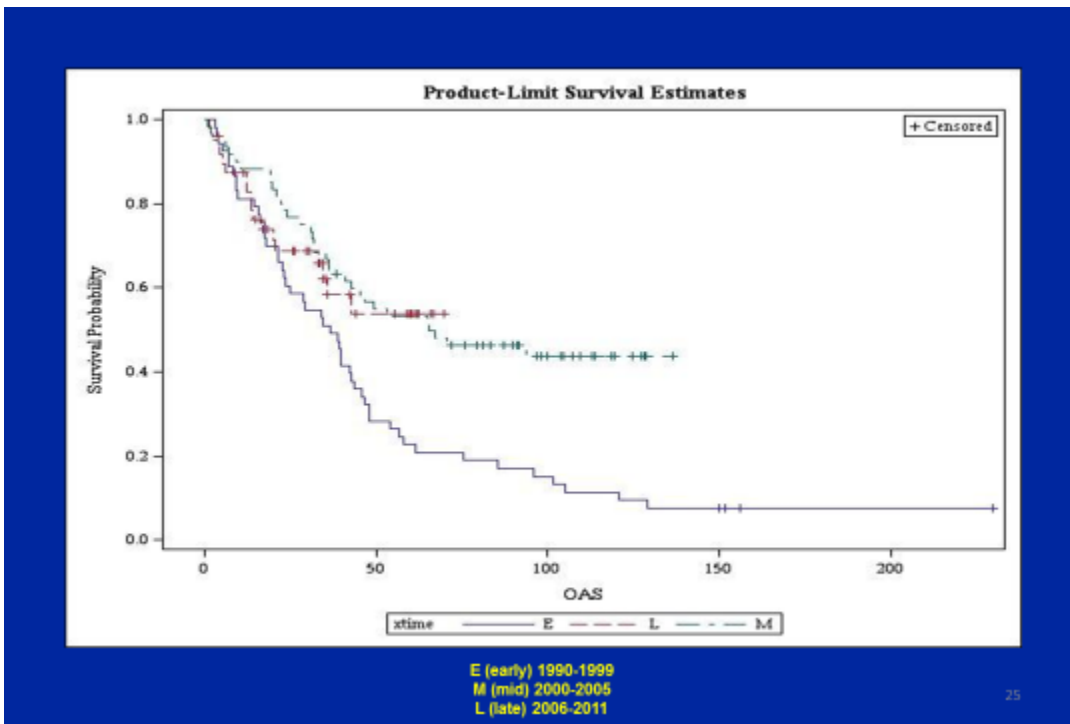
TRANSCRIPT

man named Karl Lennert in Germany described what he called centrocytic lymphoma. And both of them felt they were seeing something new that wasn't being recognized. In 1982, two pathologists, Danny Weisenburger and Henry Rappaport, described what they called mantle-zone lymphoma, which was the same thing but grew with a pattern that wasn't just a diffuse growth pattern. It grew like in follicles.

In 1987, somebody described a specific genetic mistake that involves transfer of genetic material between chromosomes 11 and 14. And in 1990, it was shown that part of that translocation involved a gene called Bcl-1 or cyclin D1 protein that it makes. And all of this information led to finally in 1992 people deciding that there was a thing called mantle cell lymphoma. It was a special disease. It was specifically associated with that translocation I mentioned, and pathologists could recognize it reproducibly. So we've only known that there was a thing called mantle cell lymphoma for about 25 years.



You can see that at the time it was described, in a study we did, we looked at the survival of patients with these are three different kinds of small cell lymphoma that could be conceivably confused with one another. The top or marginal zone lymphomas that we'll come back and talk about in a minute, the next small lymphocytic lymphoma that we'll talk about in a minute and the bottom yellow line are mantle cell lymphoma patients. And you can see that half the patients died by three to four years. It was a very much worse disease. Now this is before we knew it existed, most of these patients were treated.



What's happened is once we knew it was there, we've tried to improve therapies specific for this disease. For example, CHOP, a regimen that was used for most lymphomas, isn't a very good treatment for mantle cell lymphoma. But when we began treating the patients in different ways, you can see that the treatment results quickly improved. The top lines are patients treated, again, in the Nebraska Lymphoma Study Group after 2000. And by ten years, where with the old treatment only about one in ten patients were still alive, now between 40 and 50% of the patients are still alive. So once we know a subgroup exists and can study it and try to find the vulnerabilities of that particular kind of lymphoma to the treatments we have available, we generally improve the outcome.

## Mantle Cell Histological Appearance

- Diffuse
- Nodular
- Blastic

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Mantle cell lymphoma can have a variety of different appearances under the microscope. It can be diffuse, that is no apparent pattern; it can be nodular, that's what I showed you earlier that was described back in the '80s, and that's if you want to think about it in a simple-minded way, a follicular variant of mantle cell lymphoma; and then blastic means the cells look much more immature. So there are three different names that could be attached to a diagnosis of mantle cell lymphoma.

## Mantle Cell Lymphoma Presenting as “CLL”

- 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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And mantle cell lymphoma is one of those lymphomas that sometimes presents mimicking chronic lymphocytic leukemia or CLL. As we'll talk about in a minute, there's other lymphomas that can do that too.

It's interesting that that particular translocation between chromosomes 11 and 14, when it was originally described, was described as something that was seen in a subtype of CLL, even though we know now it goes with mantle cell lymphoma.

There's a group of patients in those that present like CLL that have enlarged spleen. They don't have any enlarged lymph nodes. They aren't ill. And even before we had better treatments, lived a much longer period of time. And some of these patients go a very long time without requiring therapy. I have a patient who currently is much past five years, never been treated. So this can be a little subgroup of patients who have much more indolent disease.

## Conclusion

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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So what have we learned about mantle cell lymphoma? Our treatment results are much better. Rituximab has made a difference here too. But clinical trials have made a big difference, where taking what was, we thought, the standard therapy and comparing it to new treatment approaches, we've steadily improved the results. And there's every reason to believe this is going to continue to be the case as several new drugs seem to be particularly useful in mantle cell lymphoma.



# Marginal Zone Lymphoma

Marginal zone lymphoma, so the hardest subtype for most people to think about, these are lymphomas that originate in lymph nodes outside the follicle and outside what's referred to as the mantle zone, which is where mantle cell lymphomas come from. And marginal zone lymphomas are less easy to diagnose. A little bit fuzzier topic.

But there are three recognized kinds. Let's just talk for just a moment about these.

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

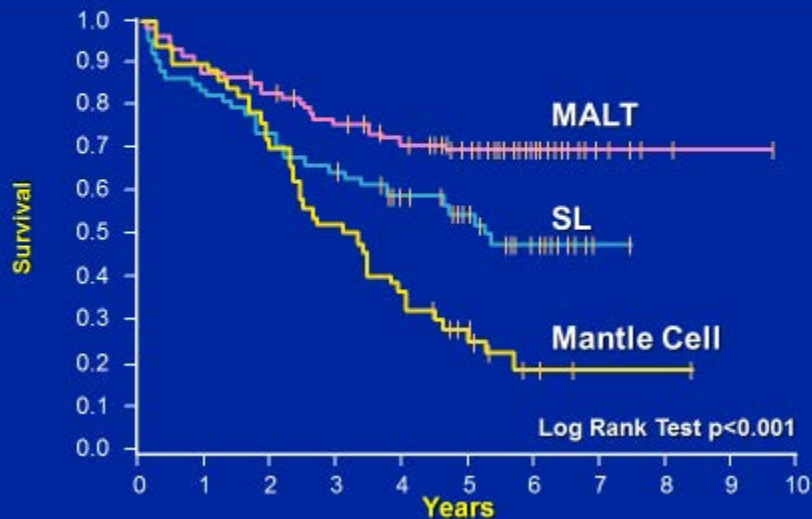
<u>Type</u>	<u>Percent</u>
MALT	7.6%
Nodal	1.8%
Splenic	<1%

MALT lymphomas are the most common by far. And MALT stands for mucosa-associated lymphoid tissue and then lymphoma. So MALT lymphoma. These are lymphocytes that are living in association with epithelial cells. So, rather than calling it MALT, it might be better to call it EALT. MALT lymphomas can appear anywhere you have epithelial cells. So they can appear in the stomach, that's the most common place. They can be in the skin. They can be in the dura lining your brain. They can be pretty much anywhere, any organ that has lymphocytes in it. And these lymphomas, as we'll see in a minute, tend to be localized more than other kinds of lymphomas. It's one of the few kinds of lymphomas where frequently surgery would be a reasonable therapy.

Nodal marginal zone lymphomas are the fuzziest subgroup. These are lymphomas of the tissues in lymph nodes where the tumor cells mark like marginal zone lymphomas. They have the same immunologic characteristics of other marginal zone lymphomas. But you wouldn't know that they were a marginal zone lymphoma if you didn't do those marking studies. Otherwise, they just look like they could be confused with follicular lymphoma or a variety of other types of lymphomas. They're the hardest ones to diagnose probably. The diagnoses are least reproducible.

And then splenic marginal zone lymphomas are a specific subtype that are here because they, again, mark in the same way. It looks like they originate from cells from that area of the lymph node. But they're completely different. These patients present usually with enlarged spleen and low blood counts without any lymph nodes and can be a diagnostic dilemma. Now the cells are usually in the bone marrow too. And you see these are the least frequent type of marginal zone lymphoma.

## Overall Survival Small Round Cell Tumors



Remember now I showed you this a minute ago, same slide, that way back before we had very sophisticated therapies, the data was generated a long time ago, patients that got called MALT lymphoma, by far the biggest group of marginal zone lymphomas, had a really good outcome. And you can see that this curve seems to flatten out, that the majority of these patients survive a long time, and it looks like maybe they're going to be cured since people aren't any longer falling off the curve there. The curve appears to be flat.



## 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

MALT lymphoma, as we learn more about it, appears to be a process of lymphocytes responding to an antigen. Frequently that antigen is related to a germ, but not always. Immune processes can do this. And the cells keep dividing in response to this antigen. Remember, they're lymphocytes; they're supposed to respond to outside things. And eventually enough genetic mistakes occur that the cells become a lymphoma.


On the second bullet, I want you to notice that many chronic infectious and autoimmune diseases, for example, *Helicobacter pylori* infection in the stomach is thought to be the driving cause to develop gastric or stomach MALT lymphomas. And patients who develop MALT lymphomas in salivary glands or around the eye, might have an infectious process, but sometimes they're people who have Sjögren syndrome, so it might be just an autoimmune-driven process.

And the bottom bullet is the most intriguing one probably. If a germ is doing this, if, for example, *Helicobacter pylori* in your stomach is causing inflammation that eventually leads to the development of a MALT lymphoma, it is extremely interesting that treating those patients with antibiotics that kill the *Helicobacter pylori* will often cause a regression of the lymphoma. Not always. Sometimes the lymphoma's been there long enough it's become independent of stimulation from the bacteria to cause the disease, and it's acting in a more malignant fashion, if you like. But many patients with MALT lymphomas can actually have the tumor regress when they're treated with antibiotics. Also, these are patients—MALT lymphoma patients—where there's no evidence of spread of the lymphoma where surgery, although not usually in the stomach or radiotherapy, both local treatments could have a high cure rate.

# Small Lymphocytic/ Chronic Lymphocytic Leukemia

Small lymphocytic lymphoma, chronic lymphocytic leukemia, two different names for the same disease. Same thing.

## Virchow: Initial Description CLL



**Weißes Blut.**

Meiner sehr wenig color. Blutkörperchen bestand der ungleich größere Theil aus kernlosen farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Protäinmolekülen, größeren, faserigen, festschaltigen, kernlosen Körperchen und granulierten Zellen mit einem runden, kugelförmigen oder fleckförmigen oder mit mehreren kernförmigen, distincten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältnis zwischen den farbigen und farblosen Blutkörperchen stellt sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden scheinen. Wenn ich vorher von weißem Blute sprach, so meine ich in der That ein Blut, in welchem die Proportion zwischen dem color. und farbigen (in Wasser weissen) Blutkörperchen eine umgekehrte ist, ohne daß eine Vermischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

ich würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen Art, wie es mir scheint, nicht unbedeutenden Aufschub beizubringen zu haben. —

Dr. Virchow.

A guy named Virchow, a very famous German pathologist, years ago first described what we think of now as chronic lymphocytic leukemia.

## The Names Can Sometimes Be Confusing

- CLL
- SLL
- Monoclonal B lymphocytosis

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

Now the names here can be confusing. First bullet, chronic lymphocytic leukemia, is somebody who has a bunch of mature lymphocytes who have the particular markings, immunologic markings that I listed at the bottom of this slide. They express CD5; they don't express CD10, a low level of CD20 and so forth. Lymphocytes circulating in your blood have certain specific genetic mistakes. That's CLL. But you have to have more than 5,000 of them, of these abnormal lymphocytes to make the diagnosis.

Small lymphocytic lymphoma is the same cells, but now, rather than presenting in the blood and bone marrow, they present with lymphadenopathy or enlarged spleen or some other way where the cells accumulate in some organ, usually in lymph node. Many of those patients that you would call small lymphocytic lymphoma if you do a bone marrow will still have cells in the bone marrow, abnormal cells. And if you look very carefully, will often have circulating lymphoma cells.

And then to make it all the more confusing, we have a thing called monoclonal B lymphocytosis. And this is a process whereby people have circulating cells that for all the world look like lymphoma cells. The same CD5+, CD10- and so forth. But there aren't very many of them. And this you can think of as a pre-lymphoma condition in the same way that having a monoclonal protein in your blood doesn't necessarily mean you have multiple myeloma. You have plasma cells making one particular antibody, but they're not accumulating and growing and damaging tissues like happens in multiple myeloma.

Well same thing here. You've got these cells that look like lymphoma cells, but they're not continuing to grow or invade organs. And so it's a pre-lymphoma, if you want to think, this monoclonal B lymphocytosis or pre-CLL.

## Differential Diagnosis

- 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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Now I'd mentioned previously that other lymphomas can present with circulating small lymphocytes, and patients with these diseases are often diagnosed with CLL. And these are some of those things. The top lymphoplasmacytic lymphoma, that's the cell that's associated, the kind of lymphoma that you have if you have Waldenström's macroglobulinemia (WM), 10% looking like CLL. Hairy cell leukemia can be confused as CLL. Different marginal zone lymphomas, all three of those can be confused with CLL. A thing called B-cell prolymphocytic leukemia, I'd already mentioned mantle cell lymphoma. I see probably one or two people a year diagnosed with CLL who really have mantle cell lymphoma. And follicular lymphoma can sometimes present looking like CLL. So you always have to be careful when you make the diagnosis of chronic lymphocytic leukemia that you're not failing to recognize that it's a manifestation of another kind of lymphoma. And because all these diseases wouldn't necessarily benefit from the same treatment, it's kind of important.



# Peripheral T-Cell Lymphoma

The peripheral T-cell lymphomas are an interesting group of diseases. Because the way they're different from B-cells, it's been difficult to diagnose T-cell lymphomas. Peripheral T-cell lymphoma just means mature T-cell lymphoma as opposed to the blastic or immature or progenitor cell lymphomas. These cells don't have the same markers on their surface that allows you to prove that they're clonal, that is, they're all the same. Where in B-cells, it's much, much easier for a pathologist to do that. For that reason and because they're much less frequent, only about one in ten lymphomas are T-cell lymphomas. We haven't learned as much about them as about the B-cell lymphomas, and the results for treatment haven't been as good, and those two things are probably related.

## Indolent PTCLs

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

Like B-cell lymphomas, you can have slow-growing, indolent, less aggressive peripheral T-cell lymphomas and more aggressive ones. Examples of the less aggressive ones are a disease called mycosis fungoides, which is-- Another way to think about it would be kind of like a T-cell MALT lymphoma. It starts in the skin. But it's a more aggressive disease in the long run than MALT lymphomas generally are. But it takes a great period of time often to make the diagnosis, and people live for sometimes decades with the disease, but it's still a very serious condition.

There's a disease called ATL, adult T-cell lymphoma/leukemia, that is related to a virus infection that can have a slow, indolent, nonaggressive course sometimes. Although most often it's an aggressive disease.

## Spectrum of CD30+ Cutaneous Lymphoproliferative Disorders

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

And then there's a group of diseases that are called CD30+ primary cutaneous lymphoproliferative disorders. Long name. And those I want to talk about just for a minute because those can be very confusing. CD30 is a protein that's on some kinds of lymphomas. It's pretty much always on Hodgkin lymphoma, but it's also on these small T-cells that present with skin lesions. The variation here could be from on one extent lymphomatoid papulosis (LyP), which is a disease that comes and goes, patches of skin lesions, doesn't progress as long as it stays lymphomatoid papulosis. But if biopsied looks like an aggressive disease, and these patients are not infrequently treated aggressively, which is not an appropriate thing to do.

I've had more than one patient in my life who had lymphomatoid papulosis who somebody had gotten a biopsy called it an aggressive lymphoma. Got chemotherapy, which makes it go away until you stop the chemotherapy and then it comes back. And so then they had a bone marrow transplant, and that made it go away until a while after the bone marrow transplant and then it comes back. And when I met these people and we got the diagnosis, they often are not very happy to learn that they didn't need any of that treatment, actually. This is a disease you can sometimes just observe or use simple methods to control the skin lesions.

Then you can have a more aggressive variant of one of these CD30+ things called primary cutaneous anaplastic large cell lymphoma (PC-ALCL). And then the third bullet, you can have another disease we'll talk about in a minute that can involve the skin. So these are hard to tell apart sometimes and, in fact, one of the most useful ways is just the history. If the patient had lesions that came and went all by themselves, it helps to make you suspicious they might have lymphomatoid papulosis.

# Aggressive PTCLs

However, most peripheral T-cell lymphomas are aggressive diseases. And I'll talk about some of the subtypes. They're interesting.

## Anaplastic Large Cell Lymphoma

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

Anaplastic large cell lymphoma or large T-cell lymphoma has been around for a long time, but until we had markers to show that these cells were actually tumors of lymphocytes, people with this



disease were sometimes diagnosed as having melanoma, metastatic carcinoma, malignant histiocytosis, a whole variety of different diagnoses until we found a way to show that they marked as T-cells and then found out that they expressed CD30. I mentioned that before.

There is a B-cell variant that's a diffuse large B-cell lymphoma that can have an anaplastic appearance so that can be confused with the anaplastic large T-cell lymphoma. And these tumors are subdivided by whether or not they have a particular genetic mistake that leads to overexpression of a protein called ALK or anaplastic lymphoma kinase. Now this lymphoma is important in other diseases. For example, it's important in lung cancer, but its expression in these anaplastic large T-cell lymphomas tells you that the patient is more likely to respond to therapy and has a higher cure rate, although part of that's because tumors that express ALK are usually younger patients.



And I wanted you to also note that anaplastic large cell lymphoma has another variant that's relatively recently recognized, and that looks like the same disease, but it appears around breast implants. And so a breast implant that swells, becomes tender or red, has a fluid collection around it, sometimes that's because this disease, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) has developed. And that's important to know about because frequently just removing the implant and the capsule where the abnormality was will cure the disease.

# NK/T Cell Lymphomas

## Nasal vs Nasal-type

Now NK (natural killer)/T-cell lymphomas are more complicated and not very nice diseases. They're not very common in the United States. It's quite common in parts of Asia and Latin America. These are sometimes divided into nasal NK/T-cell lymphoma, which is the most common and another one that pathologists used to call nasal NK/T-cell lymphoma, non-nasal type. Don't worry about the names. Most of these present around the face, in the nose or nasal sinuses.

When I was in medical school, we didn't know this was a lymphoma, and it was called lethal midline granuloma. It was a horrible disease, but people knew sometimes it got better with radiotherapy. We now know a lot more about the disease. It's often associated with Epstein-Barr virus infection. It's a very aggressive and unpleasant disease, although the majority of cases have relatively localized disease in the head and neck. And those patients, sometimes the combination of drugs and radiotherapy, but the radiotherapy is probably particularly important, can cure patients with this disease. Patients who have more widespread disease or disease that begins in other parts of the body have a less good outlook.

## Hepatosplenic Gamma/Delta T-cell Lymphoma

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

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Hepatosplenic T-cell lymphoma (HSTCL) – or sometimes called hepatosplenic gamma-delta T-cell lymphoma – is a rare disease, but it's interesting. It usually appears in younger men. It's very difficult to diagnose. Patients have tumor cells in the liver, spleen, and bone marrow, but they don't grow as tumors. They infiltrate throughout the sinuses of these organs and can be overlooked on biopsies. The patients present with low blood counts, fevers, ill and sometimes die without a diagnosis actually ever being made because they look like they have an infection. And even when we do make the diagnosis, we often don't treat these people as well as we would other lymphomas. It's a rare disease, but it's an important one.

## Enteropathy-Type Intestinal T-cell Lymphoma

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

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And enteropathy type intestinal T-cell lymphoma is particularly likely to appear in people who have sprue, usually untreated sprue. If you take the people with the disease, somewhere in at least one study that we were part of, like a third of the people had sprue known when they developed the lymphoma, another third or so appeared to have sprue that hadn't been diagnosed and then some people who don't seem to have sprue get this disease. It's also a very serious kind of disorder. Patients sometimes present with bowel perforation, and the survival rate's been quite low.

# Burkitt Lymphoma

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All right, I'm going to end by talking about another kind of lymphoma that's historically interesting called Burkitt lymphoma.

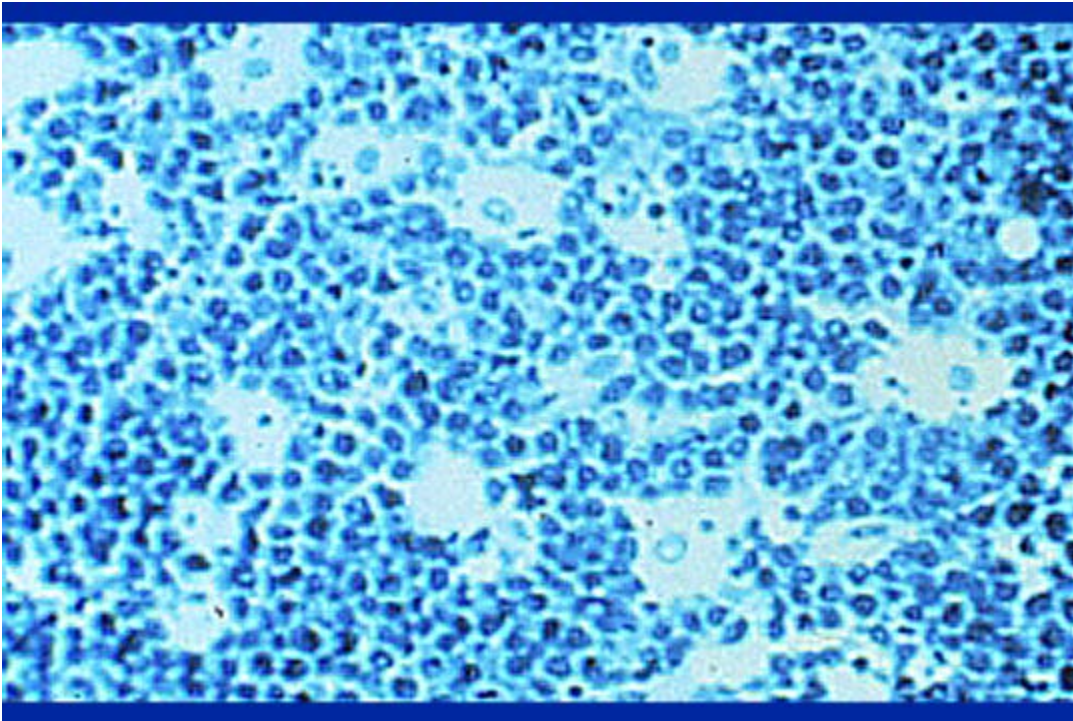


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It's named after this guy. His name is Dennis Burkitt. He was blind in one eye, missionary surgeon in Africa when people told him because of his lack of vision in one eye, he couldn't even be a doctor. He

TRANSCRIPT

worked in East Africa. He'd fly around in his airplane, and he noticed there was a strange disease that African children in certain parts of the country he worked in were developing in the head and neck, and it was a rapidly progressive cancer. And they died. Quickly. Surgery didn't seem to benefit them. It then became apparent this was often associated with the Epstein-Barr virus infection and eventually the disease came to bear his name.



This is the disease I showed you earlier, the starry sky appearance with the histiocytes. They're in dead tumor cells, intermixed among the tumor cells, leading to that starry sky appearance.

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

Burkitt lymphoma was the first malignancy that you could definitely say was cured with chemotherapy. Dennis Burkitt managed to get some cyclophosphamide in East Africa, and he'd give one dose to some of these children. The disease would always regress. Some would get a complete remission with even just one dose, although better if they got more than one, and some of those children were cured. Not nearly all, but some could be cured.

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

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

Today, we're a lot better at treating it than just giving a dose or two of cyclophosphamide. And there are number of regimens, and you can see four of them, four different series listed here. But what I want you to note – now this is adults who don't do as well as children. And the right-hand column, note the event-free survival, that is, these are people in whom the lymphoma went away and never came back, is in the order of 80 to the mid-90s of percent in these studies. So Burkitt lymphoma, this most rapidly growing human cancer, just a horrid disease if you don't have good treatment, is curable in a great majority of patients if the diagnosis is made and the treatment's delivered carefully. There are a whole bunch of things that can cause trouble if you're not good at doing this.

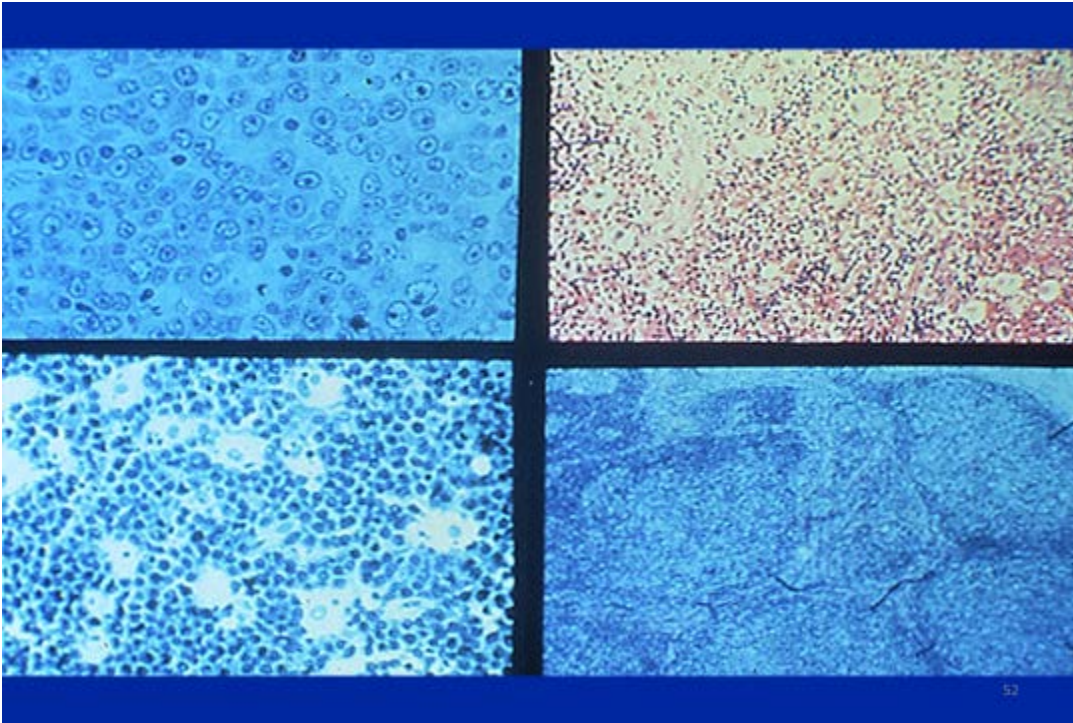
## In Burkitt Lymphoma it is a Tragedy to:

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

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Because of this, I think it is a tragedy to misdiagnose Burkitt lymphoma, so the patient, we don't know they have it, so they don't get treated right or to delay treatment. This is the most rapidly growing cancer, so treatment has to be done properly. And, in fact, our team would look upon a diagnosis of Burkitt lymphoma as an emergency, and we want the patients treated within the next 24 hours if at all possible. And this is the time where it's absolutely vital to give the correct doses. Cutting down on the doses to be nice to the patient will just mean that a patient that might have been cured will die of the disease.





So what I've done for the last about 45 minutes is to review several of the types, but certainly not all the types of non-Hodgkin lymphoma. This is the four different types of lymphoma we started with, including Hodgkin in the upper right-hand corner. You can see that while these are all cancers of lymphocytes, there's really quite a variety of illnesses that need to be diagnosed accurately and treated with the treatment regimen that has been shown to be best for that specific type of lymphoma. Thank you very much for your attention.



The slide features a red background with white and yellow text. At the top left, it reads 'Non-Hodgkin Lymphoma – Know Your Subtype'. At the top right, it includes the Leukemia & Lymphoma Society logo and the 'someday is today' logo. The main heading is 'Q&A Session'. Below this, there are two sections: 'Ask a question by phone:' with a bullet point 'Press star (\*) then the number 1 on your keypad.' and 'Ask a question by web:' with three bullet points: 'Click "Ask a question"', 'Type your question', and 'Click "Submit"'. At the bottom, a note states: '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.'

## QUESTION-AND-ANSWER SESSION

***Lizette Figueroa-Rivera, MA***

Thank you so much, Dr. Armitage, for your very clear and informative presentation. It's now time for the Question and Answer portion of our program. We'll take the first question from our Web audience. Theresa asks, "As a patient, how can we be certain the right diagnosis is made? Why do some lymphomas have bone marrow involvement and others do not, but yet all are blood cancers?"

***James Armitage, MD***

I know we refer to these as blood cancers because they develop from lymphocytes, which are one of the cells that normally circulate in the blood, but lymphocytes are a lot of other places. They live in lymph nodes and they live, as I said, in all your organs where they're doing their job of protecting you. And so not all do involve the bone marrow, but particularly ones that develop in cells that were in the bone marrow then do involve the bone marrow.

And the other question about how you'd be sure you have the right diagnosis, that's a big deal. I personally won't treat a patient for lymphoma where the diagnosis was not made by someone who's an expert in lymphoma pathology. And I don't think you should be treated until somebody who's an expert in lymphoma pathology has looked at the slides, which means that there'd be some places in America where a person like that doesn't work at the hospital – you're in the area where you are – and then those slides should be sent to an expert to be certain you know the subtype. This is not easy to diagnose lymphomas, and making a mistake in the diagnosis could be a tragedy.

***Lizette Figueroa-Rivera, MA***

Thank you, doctor, and we'll take the next question from the phone audience, please.

***Operator***

Thank you. Our first question comes from the line of Ronald from Arizona. Please go ahead.

***Ronald from Arizona***

Hi, doctor, thank you for the presentation NHL. I'm just reintroduced to my lymphoma, came back, and I got a diagnosis locally here at the Prescott Hospital. My first diagnosis was confirmed by Stanford University, and I was diagnosed with non-Hodgkin's lymphoma, grade 1 and 2 originally. I was treated RTV CHOP, a year and a half of Rituxan (rituximab). Just recently, as of Monday, I had a lymph node they noticed during a scan, and I had it biopsied. And the determination locally was that I have the grade 1 and 2 again, but they noticed a real large cell form. So my question is, and I think I will ask to get another opinion on this so I'm treated for the right lymphoma, but I'm wondering just for follow-up, I was under the impression that Rituxan which I was given a year and a half as a maintenance, and I was in remission for three years, is Rituxan still used to follow up on recurrence of grade 1 and 2?

***James Armitage, MD***

Well, you have a follicular lymphoma, low-grade follicular lymphoma it sounds like.

***Ronald from Arizona***

Yes, true.

***James Armitage, MD***

Yes, as long as the CD20, which is the target for rituximab, is still there, you're likely to get it again. Yes, absolutely. The big question is after the disease has recurred, sometimes it doesn't. Some people with low-grade follicular lymphoma don't relapse. They stay well indefinitely. But when it does come back, the big decision is whether or not it would be appropriate to do what's called an autologous bone marrow transplant. So that's the thing you and your doctor probably should talk about. We know that patients who do have an autologous bone marrow transplant, if it's the right thing for you and it matches up with both your desires and your health and a variety of other things, some people are cured by doing that. So it's something that you and your doctor should discuss.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the Web. Doctor, Sandy asks, "What does it mean if your indolent lymphoma starts growing quickly? Should you revisit the original diagnosis?"

***James Armitage, MD***

Well, most low-grade lymphomas, probably true for both B- and T-cells but certainly true for B-cells, can transform to a large cell aggressive lymphoma. And that's a big deal and requires a change in treatment approach. Now, anytime you had disease that had been stable and suddenly grew rapidly, or had been gone and comes back but now grows much more rapidly, the worry is whether or not it could have transformed, changed its nature. And often what would be done, many times a PET (positron emission tomography) scan might be done to see if there's one area where it's gotten way hotter on a PET scan and then that area biopsied. Or if there's only one lymph node growing, biopsy that lymph node. And what you'd be looking for is to be sure it had not changed its nature. It's easier to treat it if it still was an indolent appearing lymphoma under the microscope. But it's a big deal to know. And a sudden change in the way the disease is behaving should always make you concerned about whether or not it could have changed to a different kind of lymphoma, a more aggressive kind.

***Lizette Figueroa-Rivera, MA***

Thank you, doctor. And the next question from our Web audience is from Nora. Nora asks, "Are all lymphomas staged? People would ask me what stage, and my doctor said he didn't have a stage of my Burkitt's extranodal lymphoma. Is this true?"

***James Armitage, MD***

Well, you can stage every lymphoma, and you probably should. This is actually a more complicated topic than you think. Staging generally relates to anatomic sites of involvement where the disease is. Staging was a concept that the surgeons developed because when they try to take out a cancer, they can do it under some circumstances but not others; and stage would let you know that it's more localized and more able to be removed. And, generally, people with less disease involving less places, that is lower stage, have a better outlook than people with higher stage. That's more complicated with lymphomas because the disease isn't as often localized. But we would still stage a patient, but then you also use other characteristics of the disease often to develop a prognostic score. The IPI, International Prognostic Index, is a common example of those.

In Burkitt lymphoma, the honest truth is what your doctor said to you, he's right, that in Burkitt lymphoma the disease is going to be treated the same way wherever it is because Burkitt lymphoma's always treated with chemotherapy, aggressive chemotherapy. Although, still, if there's less of it in less places, that's easier to get rid of it.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the phone audience, please.

***Operator***

Our next question comes from the line of Frieda from Iowa. Please go ahead.

***Frieda from Iowa***

Hello, I was in a year remission from a large B-cell lymphoma of my right kidney. I now have a smaller mass on the same nonfunctioning kidney. It's around my ureter. It's been diagnosed by the pathologist from UNMC as a low-grade large B-cell lymphoma. Do you have any comment on that?

***James Armitage, MD***

Well it can't be low-grade large B-cell lymphoma because there isn't such a thing. If it's a large B-cell lymphoma, that's a high-grade aggressive cancer. And if you had the disease that was, if there was a large B-cell lymphoma before and it recurred, we still have a chance to cure a patient in that situation, but that essentially always would involve a bone marrow transplant of some kind.

Now what does happen, though, is patients with diffuse large B-cell lymphoma sometimes relapse, and the biopsy is a low-grade lymphoma, usually a low-grade follicular lymphoma. And we wonder if those patients originally had a low-grade follicular lymphoma, it transformed to large B-cell lymphoma, then it was diagnosed and you treat it. You'd get rid of the large B-cell lymphoma, but the low-grade lymphoma recurs. That happens sometimes. But I think what you need to do is get a clear answer of what the real diagnosis is. If they said it came back low grade, then it probably actually is a different kind of lymphoma. If it's large B-cell lymphoma still, it needs to be treated promptly and aggressively.

***Lizette Figueroa-Rivera, MA***

Thank you, doctor, and thank you for that question, which is our last question today. Again, thank you so much, Dr. Armitage, for your continued dedication to patients. Your research successes have really made a positive impact on people's lives.

**CLOSING REMARKS**

**Lizette Figueroa-Rivera, MA**

And if we weren't able to get to your question today, I know that we've had a lot of people on the phone lines as well as a lot of people on the Web. Thank you so much for your questions.

**Non-Hodgkin Lymphoma – Know Your Subtype**

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- 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

You can call our Information Specialists here at The Leukemia & Lymphoma Society at 1-800-955-4572. We can provide information about treatment, including clinical trials, or answer other questions you may have about support, including questions about financial assistance or treatment.

And, again, we'd like to acknowledge and thank Bristol-Myers Squibb and Genentech for support of this program. Again, thank you so much, Dr. Armitage, for sharing your knowledge with us today and volunteering your time.

To all the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Good-bye, and we wish you well.