Resilience Through Progress: Slow Growing Non-Hodgkin Lymphoma (NHL)

Operator
Greetings, and welcome to Resilience Through Progress: Slow Growing Non-Hodgkin Lymphoma, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

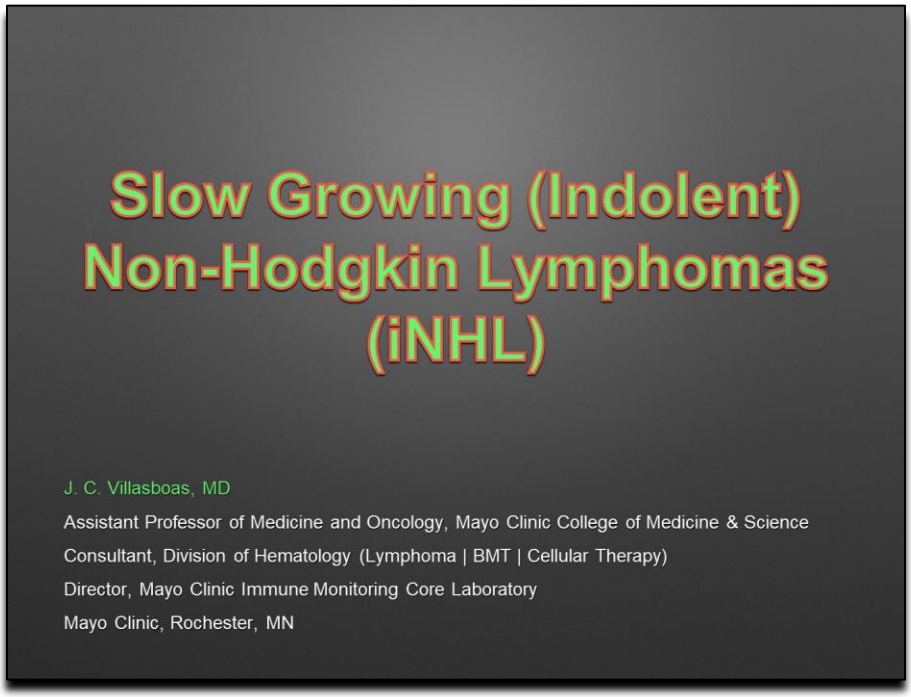
Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. J.C. Villasboas for volunteering his time and sharing his expertise with us today. For this program, we would like to acknowledge and thank our supporters, Genentech, Inc. and Biogen and Kite, a Gilead Company.

Advances in the treatment of NHL are resulting in improved remission and cure rates. New treatment approaches are being studied in clinical trials for patients of all ages and for all stages of the disease. LLS's investment in lymphoma research has led to many treatment advances and innovative immunotherapies, such as the first chimeric antigen receptor, CAR T-cell therapy approved by the FDA for lymphoma patients. Our current lymphoma research commitment exceeds $73 million, so we can continue to bring promising new treatments to patients.

Research will help us achieve an end to cancer. In the meantime, patients need help before, during, and after their diagnosis and treatment. LLS is the leading non-profit that does just that, by helping patients navigate their cancer treatment, to ensure they have access to quality, affordable, and coordinated care.

Speaker Disclosure

I am now pleased to introduce our speaker, Dr. J.C. Villasboas, Assistant Professor of Medicine and Oncology at the Mayo Clinic College of Medicine and Science; Consultant, Division of Hematology; Director, Mayo Clinic Immune Monitoring Core Laboratory in Mayo Clinic in Rochester, Minnesota.

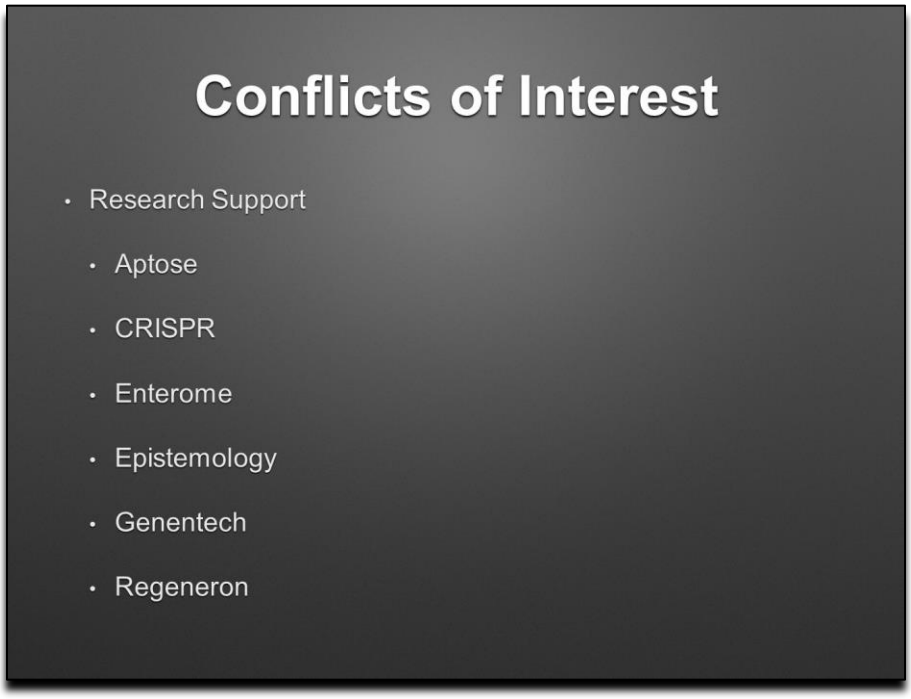


Slow Growing (Indolent) Non-Hodgkin Lymphomas (iNHL)

Dr. Villasboas, I am privileged to turn the program over to you.

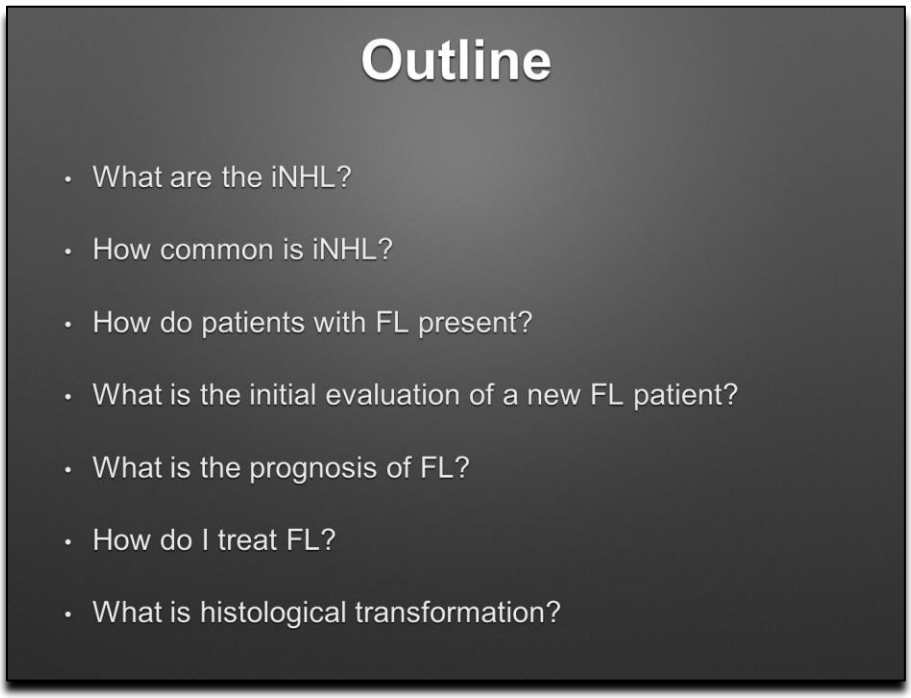
J.C. Villasboas, M.D.
Thank you, very much, Lizette. Good morning, and afternoon to some of you. Thank you for attending this webinar, which will focus on slow growing, often known as indolent, non-Hodgkin lymphomas. As you have heard, my name is J.C. Villasboas. I'm a physician scientist here at the Mayo Clinic in Rochester, Minnesota. I'm a Consultant for the Division of Hematology. And my clinical practice is focused on treating patients with lymphomas, including stem cell transplantation and cellular therapy.

Our laboratory studies the interaction between the immune system and lymphoma cells, with the goal of improving current therapies and discovering new ways to harness the power of the immune system against lymphoma. Lastly, I direct the immune monitoring core here at the Mayo Clinic, which is a Mayo Clinic-wide laboratory that helps researchers interested in studying the immune system, in the context of cancer and other diseases. So, without further ado, let's get the program started.



Conflicts of Interest

This slide summarizes my potential conflicts of interest. Mayo Clinic receives research support from the following companies, as listed on this slide.



Outline

With this page, I just want to go over the outline of the discussion we'll have over the next several minutes. We will, as you've heard, focus on slow growing, or indolent non-Hodgkin lymphoma. So, the first thing that we'll do is to put this group of diseases into the bigger context of lymphoma, as a disease category.

Next, we'll look at the epidemiology of these slow growing lymphomas, to discuss how rare or common they are and how much they represent, in terms of the total burden of cancer diagnoses in the United States. I will take out of this group, then, one particular disease, which is follicular lymphoma, which is a prototype for slow growing, B-cell, non-Hodgkin lymphomas. And using that disease, I'll walk you over the typical things I see in clinics, such as the initial presentation, the initial evaluation of patients with follicular lymphoma, and I will use a few, real-life examples of patients that I have treated in my clinic to illustrate how we manage patients with follicular lymphoma in 2023.

Lastly, we'll talk about a very specific and important topic in indolent non-Hodgkin lymphoma, which is the concept of histological transformation. At the end, we'll have time for questions.

What are the iNHL?

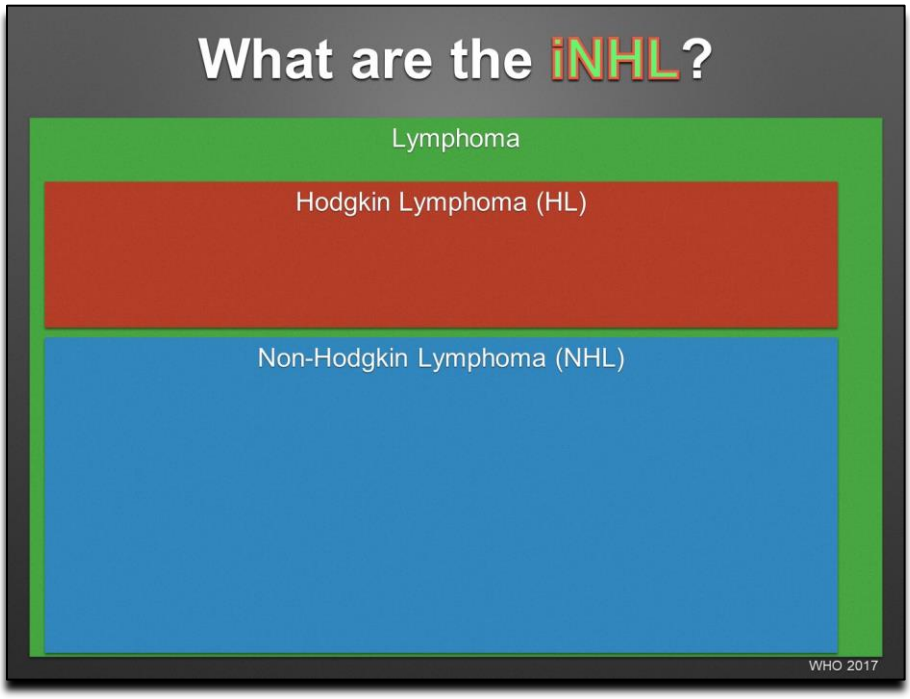
So let's start by discussing what are we calling indolent, or slow growing, non-Hodgkin lymphomas. And as I typically do in clinic, when I see a patient who has been newly diagnosed with lymphoma

What are the iNHL?

I like to start with a bigger picture of what is lymphoma, in general, and what are the different subtypes of lymphoma. After all, it is truly not fair to call this one disease, because there are nearly 100 different

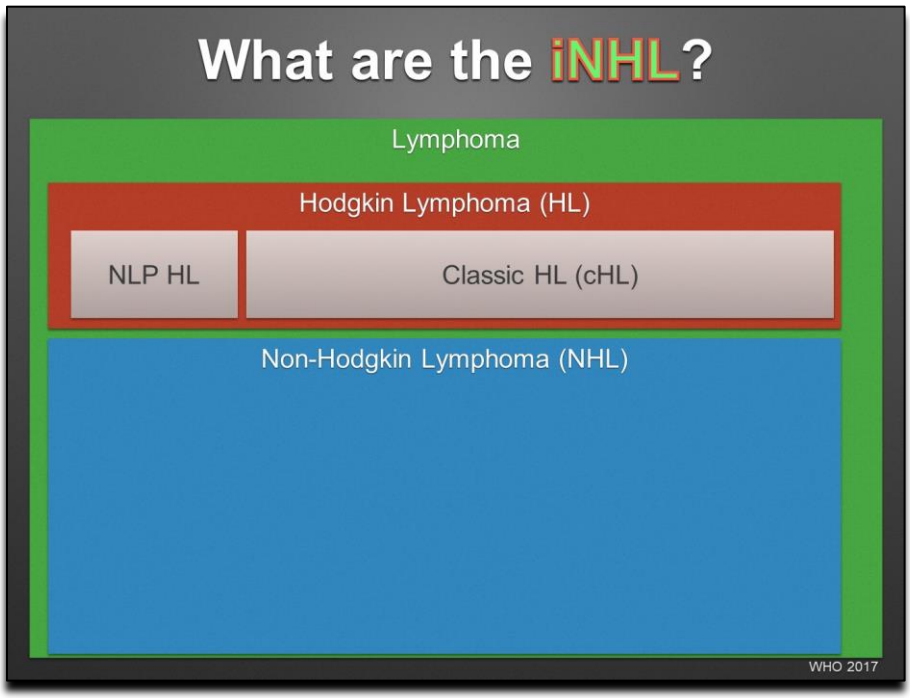
sub types of lymphoma, depending on which classification system you're using. So, for the purposes of this discussion here, we're going to be using the 2017 World Health Organization classification for lymphomas. As you know by now, I'm sure, lymphomas are cancers of lymphocytes. And lymphocytes are one particular type of white blood cells.

White blood cells are cells of the immune system, whose [one of] primary reasons for existence is to fight infections. Any cells in our body can become cancerous. And when cancer occurs in lymphocytes, it typically receives the name of lymphoma. But there are multiple different types of lymphoma, with very different biological and clinical behavior. So, it does make sense to stop for a moment and put this into context, about what are the different, broad categories of lymphoma, and then discriminate inside this bigger group, which are the slow growing, non-Hodgkin lymphomas that we'll be focusing on today.



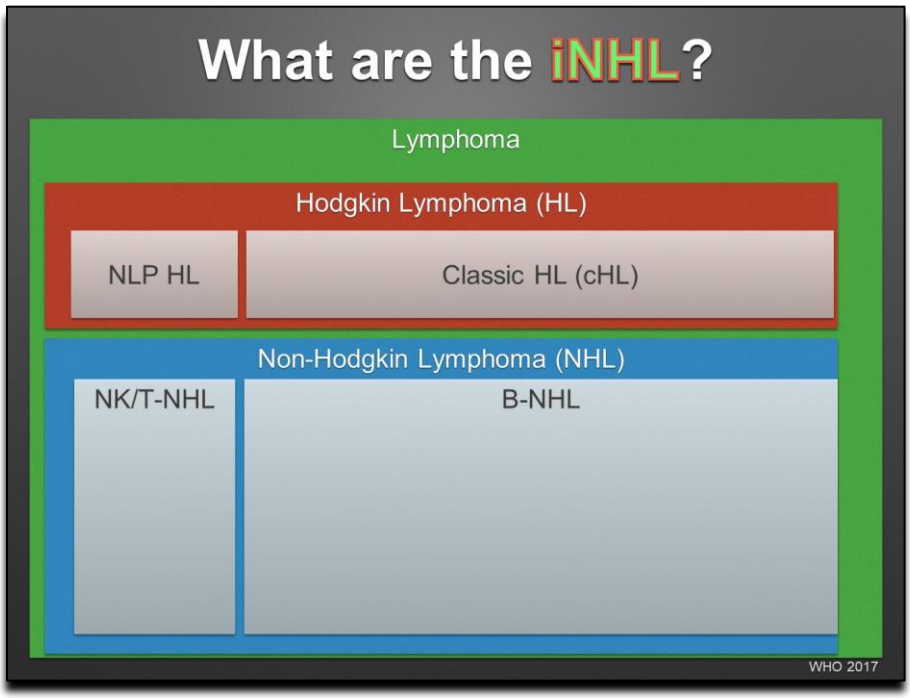
What are the iNHL?

Inside the group of lymphoma, I typically divide between the two, bigger groups. On top, you see Hodgkin lymphomas, and on the bottom, non-Hodgkin lymphomas.



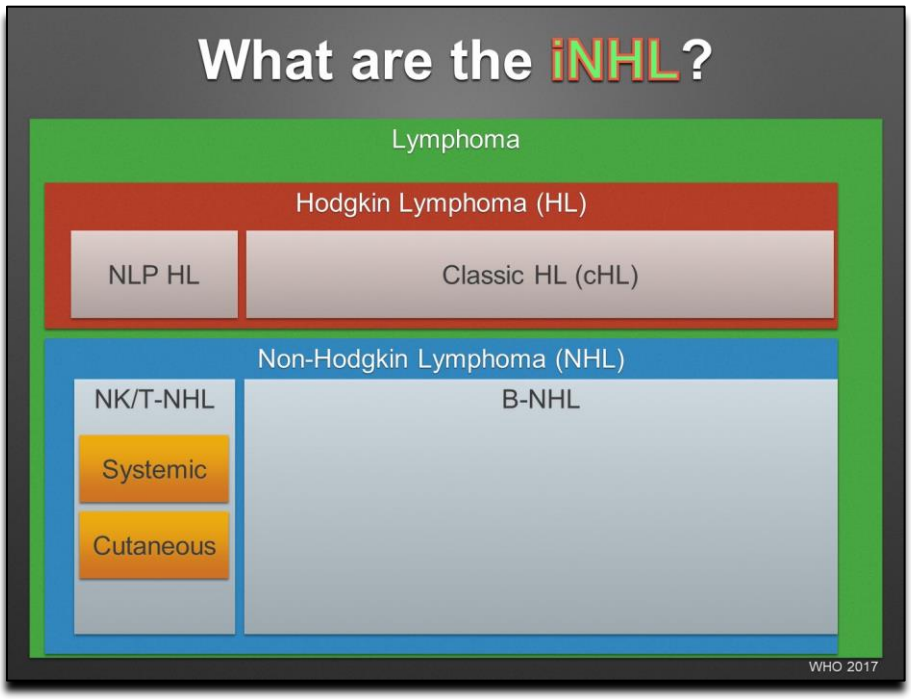
What are the iNHL?

Inside the Hodgkin lymphoma group, I will normally divide between something called nodular lymphocyte-predominant Hodgkin lymphoma, or NLP HL, and classic Hodgkin lymphoma, or cHL.



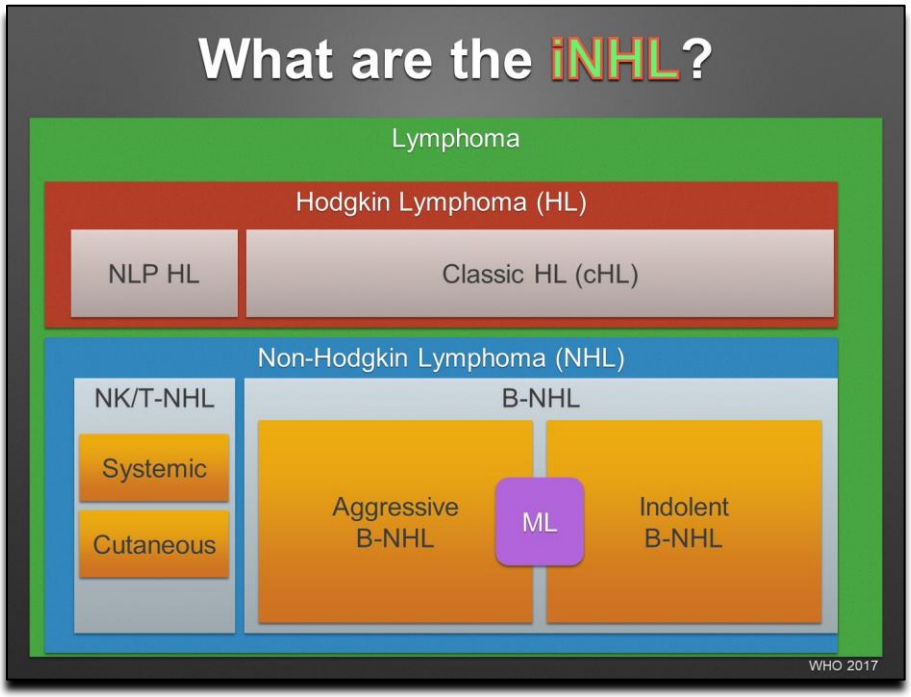
What are the iNHL?

Inside the non-Hodgkin lymphoma group, I like to divide between those that arise from natural killer cells, or T-cells, which we'll term NK or T cell, non-Hodgkin lymphoma, and those that arise from B-cell -- from B lymphocytes, which we'll term B-cell, non-Hodgkin lymphomas.



What are the iNHL?

Inside the NK/T-cell NHL group, I find useful to divide diseases based on their clinical presentation. So those cases that present with involvement of lymph nodes, spleen, or internal organs, we'll call those systemic, natural killer, or T-cell non-Hodgkin lymphomas. But there is a specific group of diseases in this category that tends to be isolated to the skin, to the cutaneous compartment. And we can term those as primary, cutaneous, T Cell, non-Hodgkin lymphomas.



What are the iNHL?

Inside the B-cell group, the most useful division, in my mind, is according to clinical and biological behavior. As you can see here, we can divide B-cell non-Hodgkin lymphomas in aggressive and indolent.

With aggressive, as the word implies, meaning those cases of lymphomas that tend to present with symptoms that tend to grow fast. In other words, I like to say, in clinic, that these are the lymphomas that find the patient. So patient is fine one day and the next day, they have new symptoms that lead them to seek medical attention and end up with a diagnosis of lymphoma.

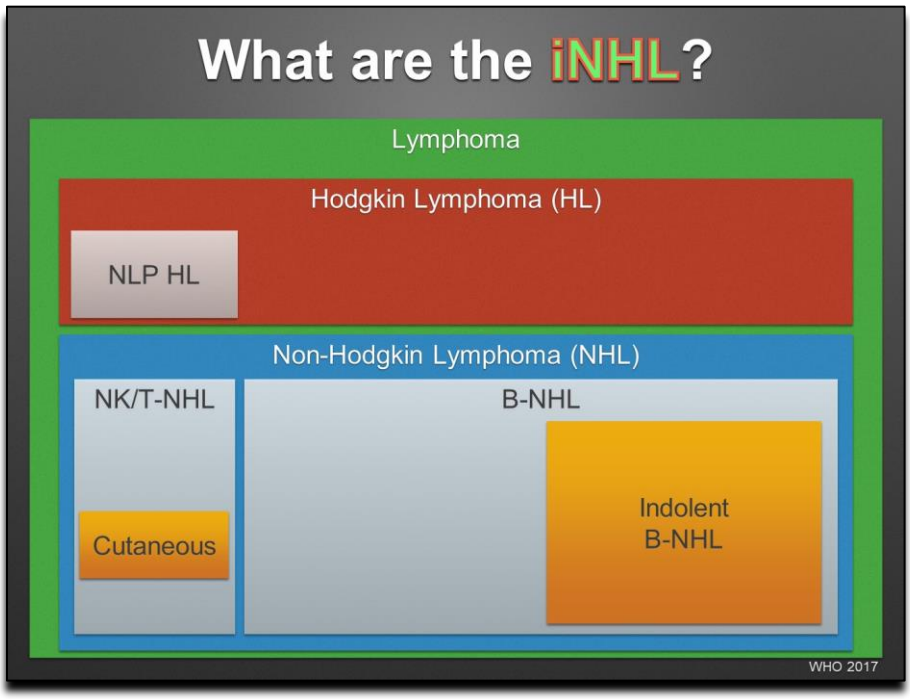
On the other hand, slow growing, or indolent lymphomas, sometimes are found by the patient or by the doctors taking care of those patients, sometimes incidentally or by accident. And this is because, due to its slow growth pattern, the organs and systems of the patient can accommodate that growth, leading to the absence or very mild symptoms. Another important distinction, which is a generalizable distinction, however, is that aggressive lymphomas tend to be treated with an intention of curing the patient.

And what I mean by that is, there is an indication for treatment. And that treatment is usually given with the goal of eradicating any visible amount of lymphoma, and the potential expectation that, if that treatment is successful, the lymphoma will not return. On the other hand, indolent, slow growing, non-Hodgkin lymphomas are treated with the goal of disease control. And by that, I mean that my goal, as a doctor of a patient with indolent, non-Hodgkin lymphoma, is to maximize their quantity and quality of life with the minimum amount of symptoms from either the disease or the treatments that we choose.

However, with indolent B-cell non-Hodgkin lymphoma, there is an expectation that, if enough time is given, the disease is very likely to recur or relapse, and we may need to do treatments in another phase of the treatments. Notice that I put in the middle of the aggressive and the indolent, B-cell, non-Hodgkin lymphoma, a category in and of itself, where we fit the mantle cell lymphoma patients.

I believe mantle cell lymphoma deserves a category in and of itself, because it shares features of both aggressive lymphomas, in terms of presentation, symptoms, as well as indolent lymphomas, due to its tendency to recur, despite aggressive behavior. And that's why I don't think it fits squarely, neither on the aggressive, nor the indolent lymphoma category, and I typically put it outside of both those two groups.

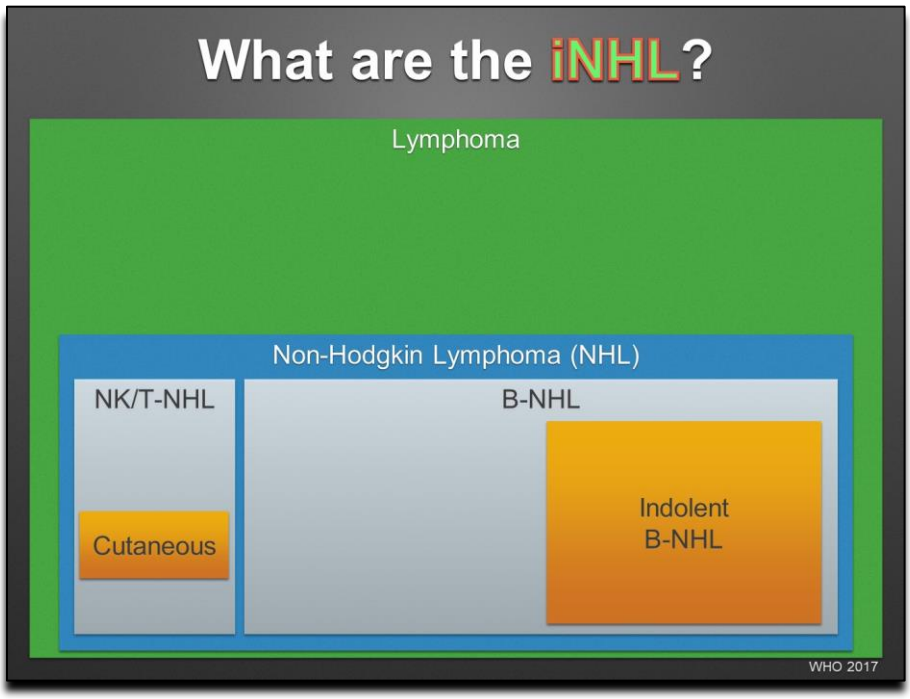
So, knowing the overview of the lymphoma classification, I just wanted to highlight which are the slow growing types of non-Hodgkin lymphoma that we will be discussing today.



What are the iNHL?

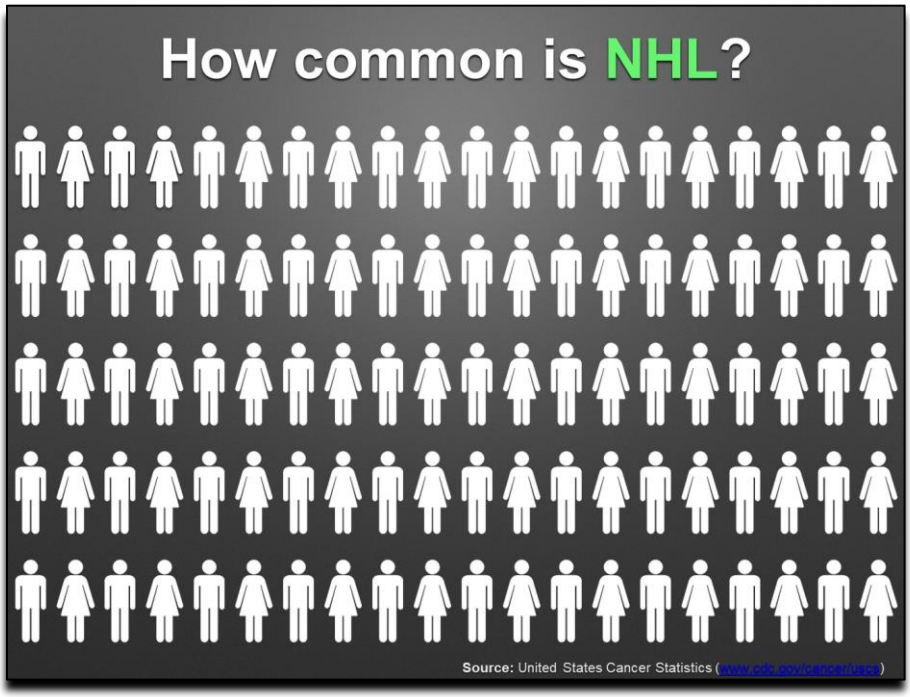
So, in terms of clinical behavior, I left on the screen here the types of lymphoma that tend to have a slow growing pattern, or an indolent pattern. So, inside the Hodgkin lymphoma group, we see that type of behavior in the nodular lymphocyte-predominant Hodgkin lymphoma patients. Inside the T-cell and

NK-cell non-Hodgkin lymphoma, we may see a similar behavior of slow growth in the primary, cutaneous, T-cell non-Hodgkin lymphoma, with the prototype disease, in this particular case, being mycosis fungoides. And then, to the right, you see that we left the indolent B-cell non-Hodgkin lymphomas inside the B-NHL category, as the prototype disease -- prototype group for this slow growing behavior.



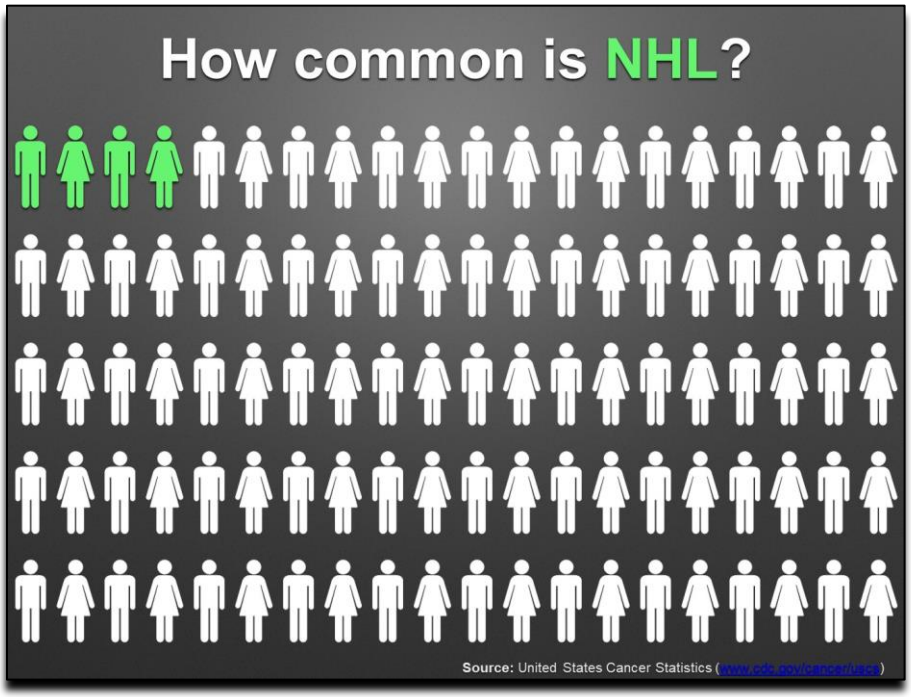
What are the iNHL?

So, for the purpose of today, we are really going to concentrate, simply by its higher incidence, in the indolent B-cell non-Hodgkin lymphoma, but I'm happy to take questions about the other slow growing lymphoma subtypes at the end.



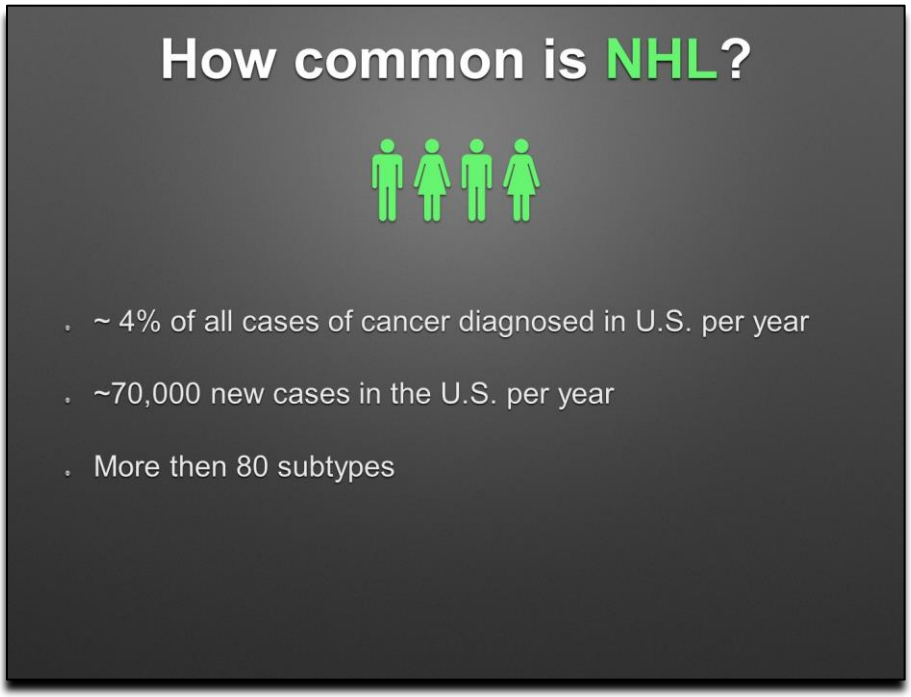
How common is NHL?

So, moving on to our discussion. And we're going to take a look now, in the next few slides, on the epidemiology of these indolent non-Hodgkin lymphomas. But once again, we'll start with a broader scope. According to the CDC, in 2020, out of 100 patients diagnosed with cancer in the United States,



How common is NHL?

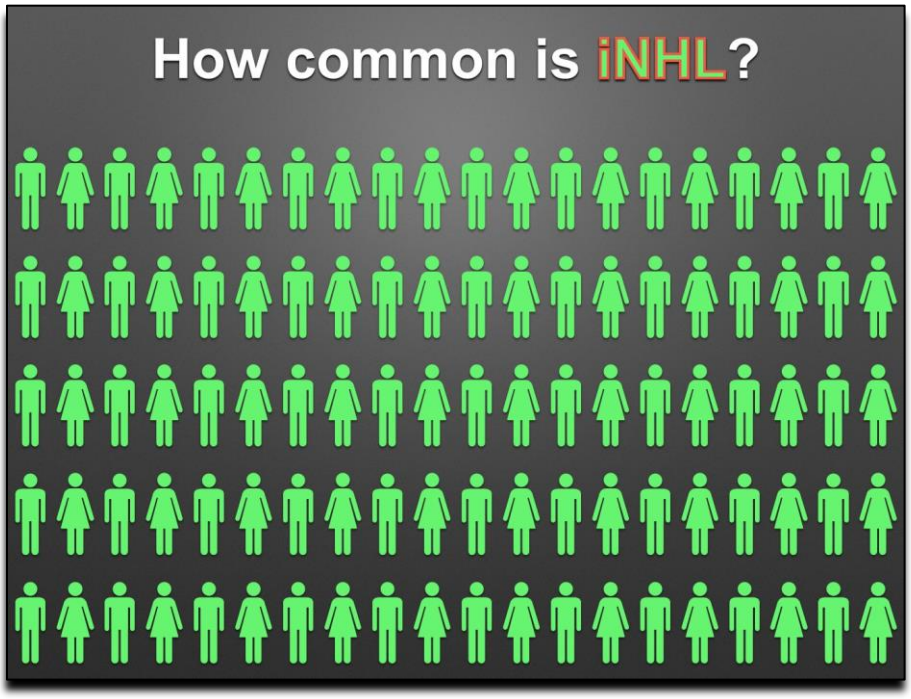
about four of them were cancers of lymphocytes, or lymphomas.



How common is NHL?

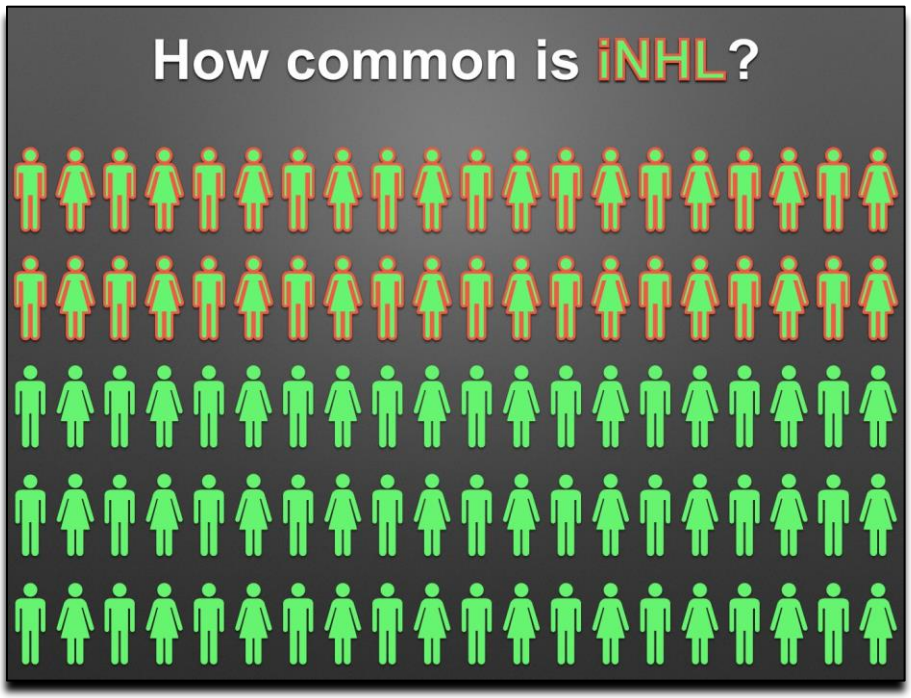
This corresponds, therefore, to approximately 4% of all cases of cancer diagnosed in the United States per year, are patients with non Hodgkin lymphoma, which leads you to conclude that lymphomas, in general, are relatively rare diseases, compared to other cancers, such as breast cancer, colon cancer, and lung cancer, for example.

Approximately 4% of cases of cancer in the United States corresponds to approximately 70,000 new patients with lymphoma diagnosed in this country, per year. And as you have just heard, depending on the classification category that we use, there are different subtypes -- between 80 to 100 different subtypes, depending on what system you're using. And, by the way, the systems are being revised as we speak, with two, newer classifications coming out in 2023.



How common is iNHL?

So now that we know how lymphoma represents 4% of total cancers in the U.S., let's just look inside that group and ask the question, okay, how common, inside lymphoma cases, is the slow growing type? So how common is indolent non-Hodgkin lymphoma?

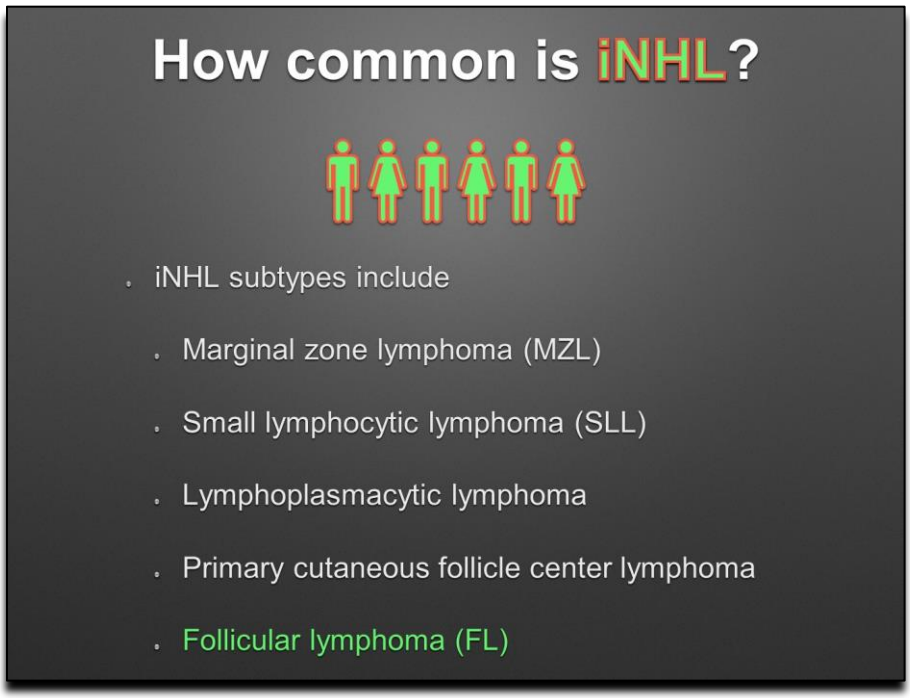


How common is iNHL?

So, if I see 100 patients in clinic, with lymphoma, I could expect that approximately 40 of those are going to have a slow growing behavior.

How common is iNHL?

Therefore, indolent non-Hodgkin lymphomas represent about 40% of all cases of non-Hodgkin lymphoma diagnosed in this country per year.

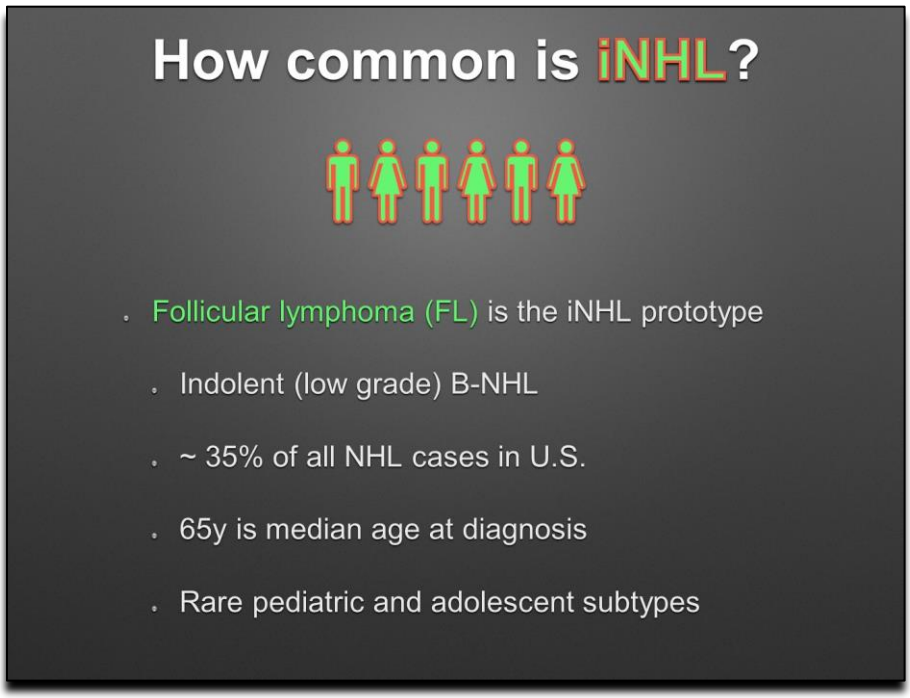


How common is iNHL?

Inside this group, we have different diseases. So, it's still a generalizable category, which speaks to their biological behavior and clinical behavior, but they are different diseases, with very special characteristics inside that broader group. These include marginal zone lymphoma, or MZL, which in and of itself, may have different presentations, such as systemic or nodal marginal zone lymphoma, splenic marginal zone lymphoma, and extranodal marginal zone lymphoma.

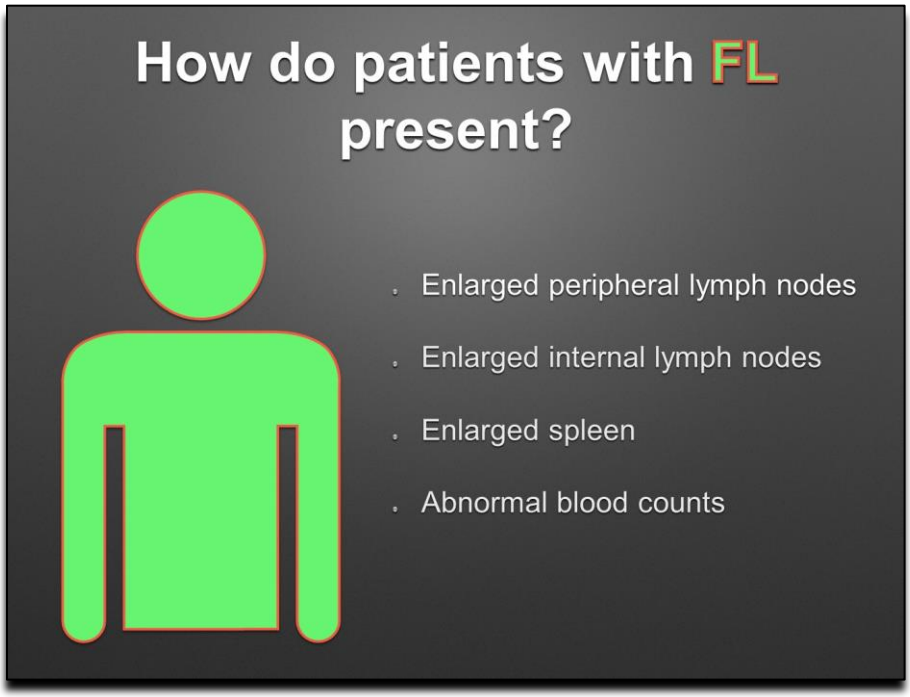
We also have, for example, small lymphocytic lymphoma, which is a lymph node presentation of chronic lymphocytic leukemia, or CLL. We may have in this group, also patients with lymphoplasmacytic lymphoma, which tends to be associated with the production of abnormal proteins in the blood. We may also have in this group of indolent B-cell non-Hodgkin lymphomas, lymphomas that are isolated to the skin compartment. So, one of the examples is primary cutaneous follicle center lymphoma, which is very much a follicular lymphoma, isolated to the skin compartment.

And then, lastly, we have follicular lymphoma in this group, amongst others.



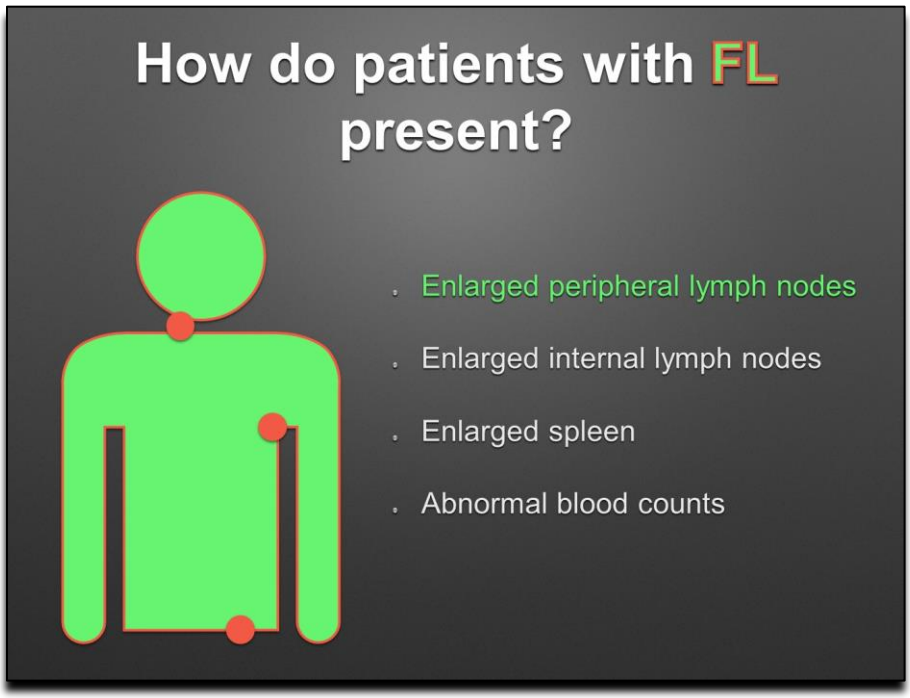
How common is iNHL?

Follicular lymphoma is the indolent non-Hodgkin lymphoma prototype. It accounts for about 35% of all cases of non-Hodgkin lymphoma diagnosed in the U.S. per year. It is a disease that tends to be diagnosed in the fifth or sixth decade of life, with a median age of diagnosis being 65 years. However, there are special types of follicular lymphoma that can happen in pediatric and adolescent populations. And they typically have a very different clinical behavior.



How do patients with FL present?

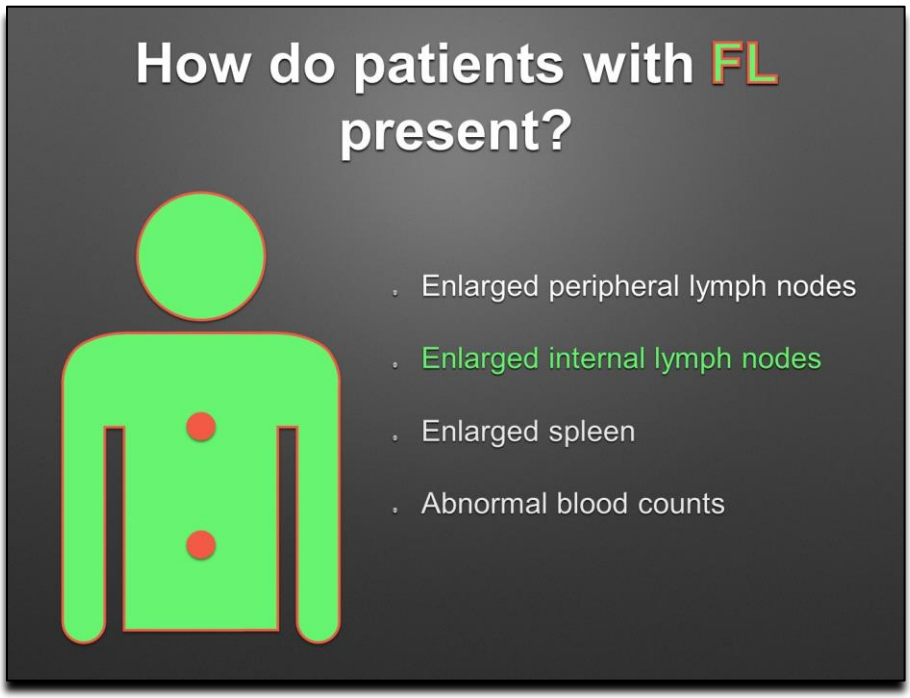
So, moving forward with follicular lymphoma as the representative disease of this group, let's look at some of the typical things that I see in clinic when I'm evaluating and treating these patients. So, let's start by how these patients present to clinic. As you've heard many times, these patients are sent to us with a diagnosis of follicular lymphoma that is found literally by accident.



How do patients with FL present?

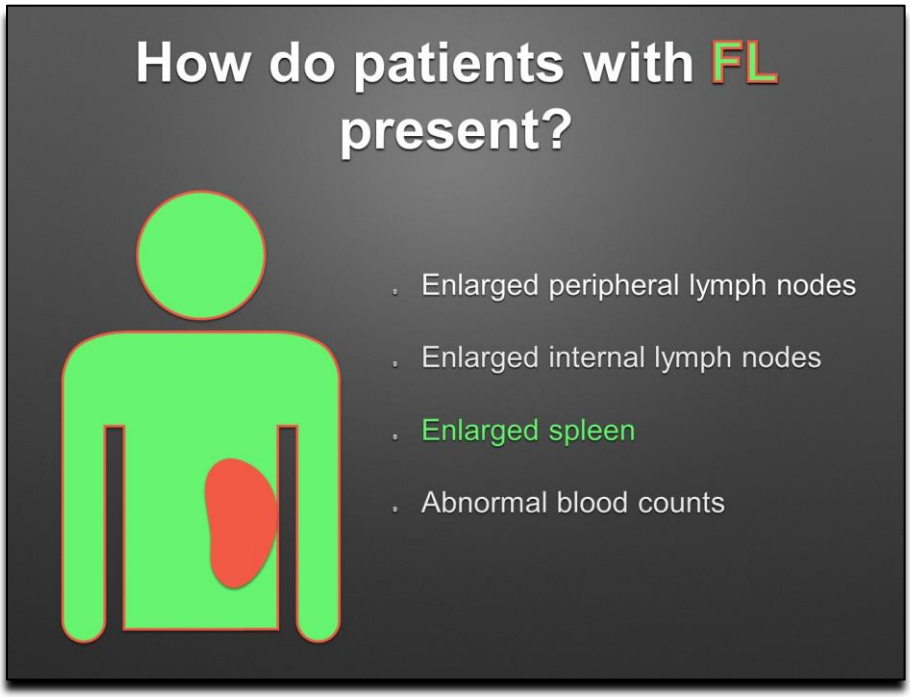
Sometimes, this is because patients felt themselves, enlargements of lymph nodes. While they were shaving or showering or the lymph nodes were felt by a provider, a primary care physician, someone else who was taking care of that patient.

The patient may have the lymph node present, but absolutely no other symptoms.



How do patients with FL present?

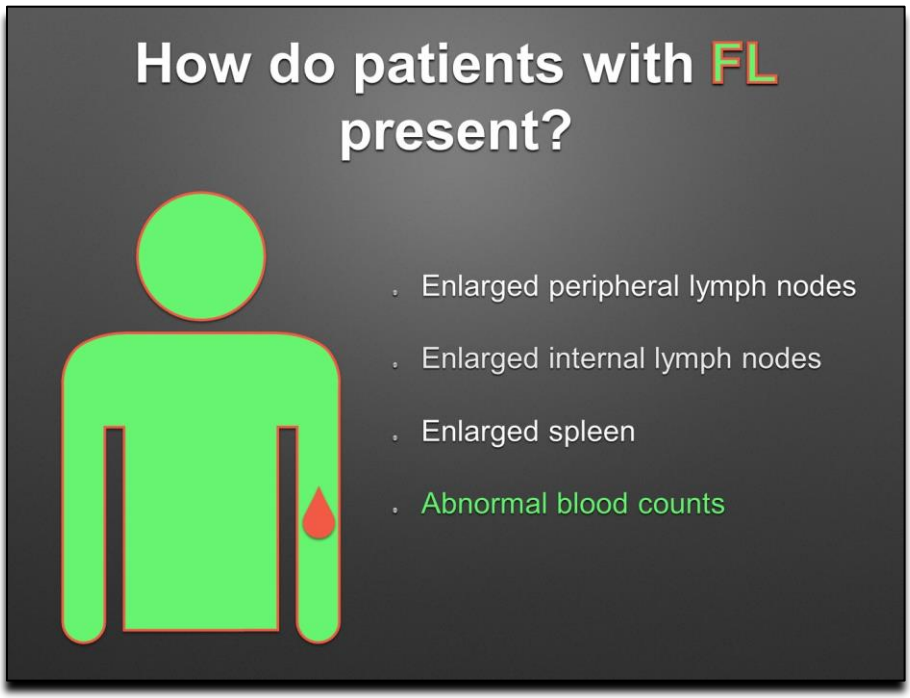
Sometimes, however, the enlargement of these lymph nodes is internal, in lymph nodes that are not accessible, externally, through the physical exam. A very common situation for me to see in clinic is a patient who goes to the emergency room with a kidney stone, and in the process of evaluation for the kidney stone, they have a CT scan of their abdomen, and enlargement of intra-abdominal lymph nodes are noted on that CT scan, having no relationship with the reason that they presented to the emergency room. And this sometimes leads to a diagnosis of incidental follicular lymphoma.



How do patients with FL present?

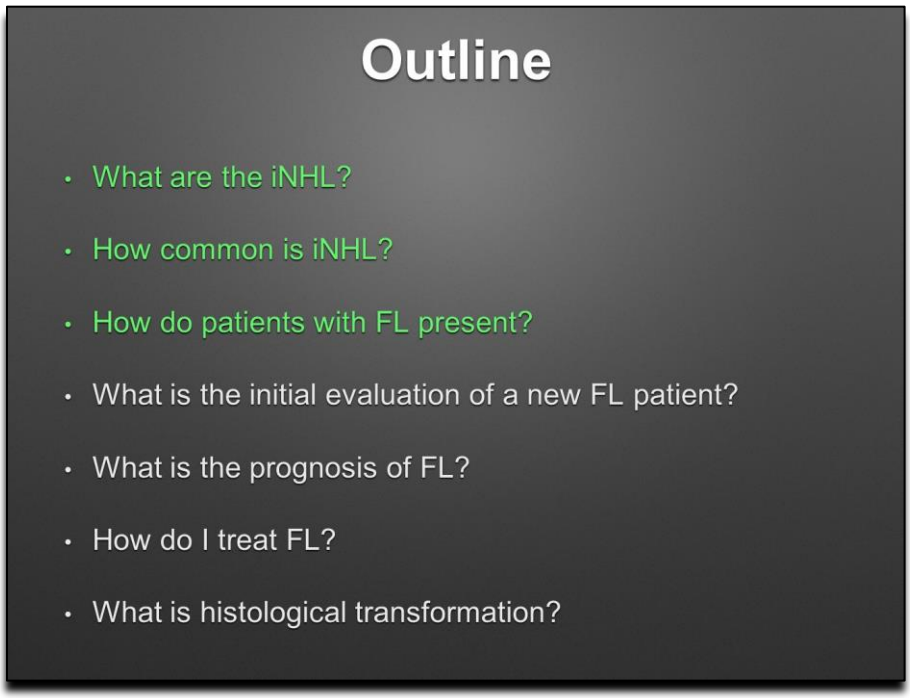
Sometimes indolent non-Hodgkin lymphomas may present with enlargement of the spleen. As you may know, the spleen is a structure -- it's an organ that sits tucked in beneath your left ribcage, and it is about the size of a closed fist. And most people don't even know they have a spleen unless the spleen is enlarged. As the spleen enlarges, it may cause compression on surrounding structures, including the stomach, and this may lead to early satiety, so patients may feel full too early in their meal, they may start to lose weight as a consequence of that.

This may also cause discomfort, pain -- sometimes in the abdomen, but sometimes referred to the left shoulder. And because the blood is filtered through the spleen, as the spleen enlarges, it may act as a big sponge for blood cells. And these may be trapped inside the spleen, leading to consequences on their peripheral blood measurements, with anemia, low platelets, and low white blood cells.



How do patients with FL present?

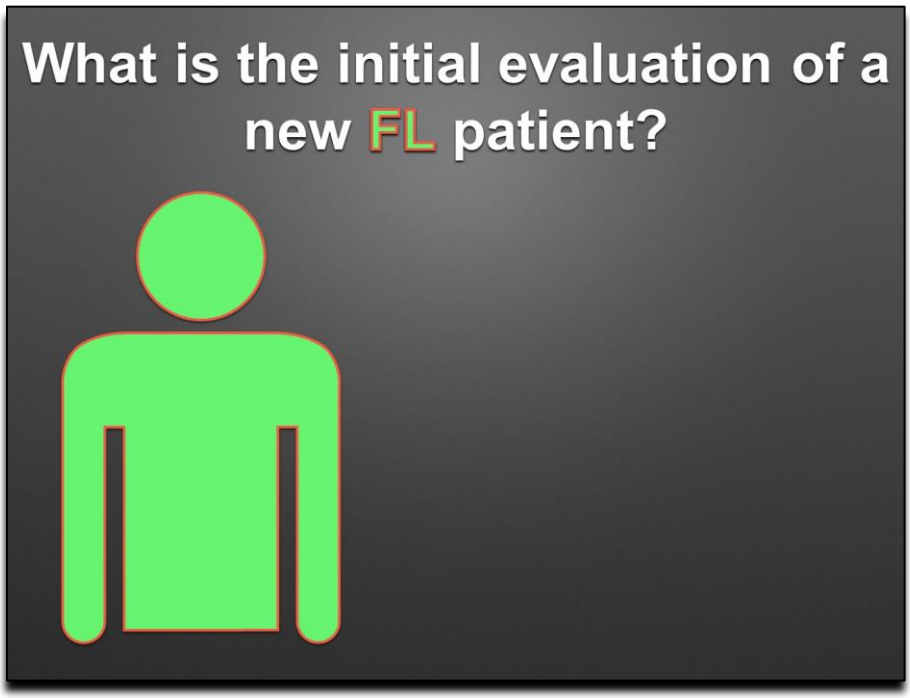
Sometimes, we find patients with indolent non-Hodgkin lymphoma, sometimes accidentally through a blood draw obtained by a primary care physician.



Outline

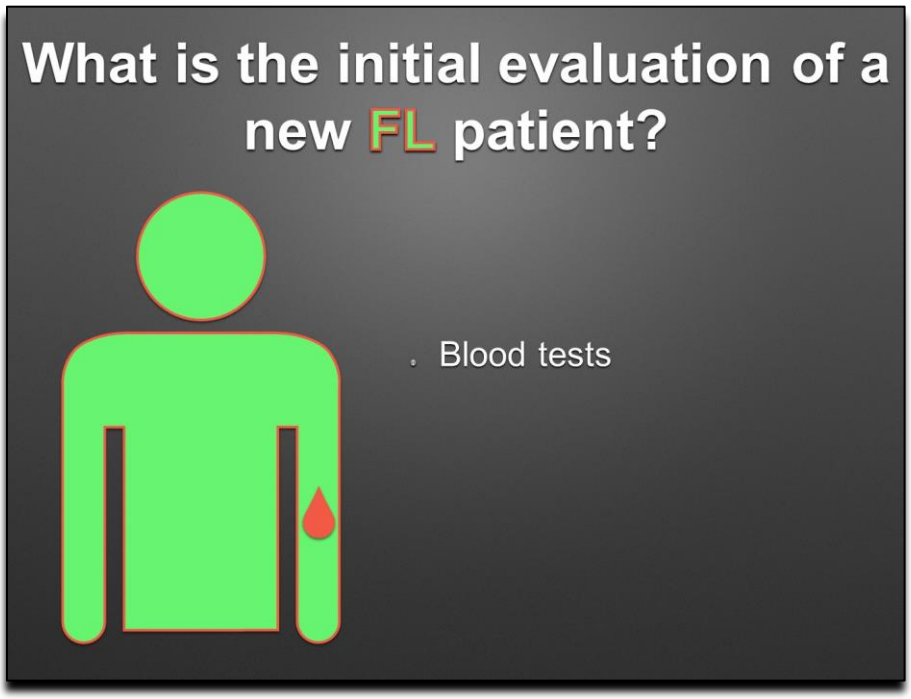
So, once we have a patient with a diagnosis of lymphoma, the next thing we're going to look at, what is the initial evaluation for these patients. But before we proceed in that direction, I just want to take a moment and review what we have discussed so far.

So, I have reviewed with you the definition of a slow growing type of non-Hodgkin lymphoma, in the context of the broader lymphoma categories. We have also reviewed the epidemiology of lymphoma and of slow growing non-Hodgkin lymphomas. And we have taken a look at the typical presentation for a patient with follicular lymphoma, which is the prototype disease for indolent B-cell, non-Hodgkin lymphomas. So, let's move on with the program.



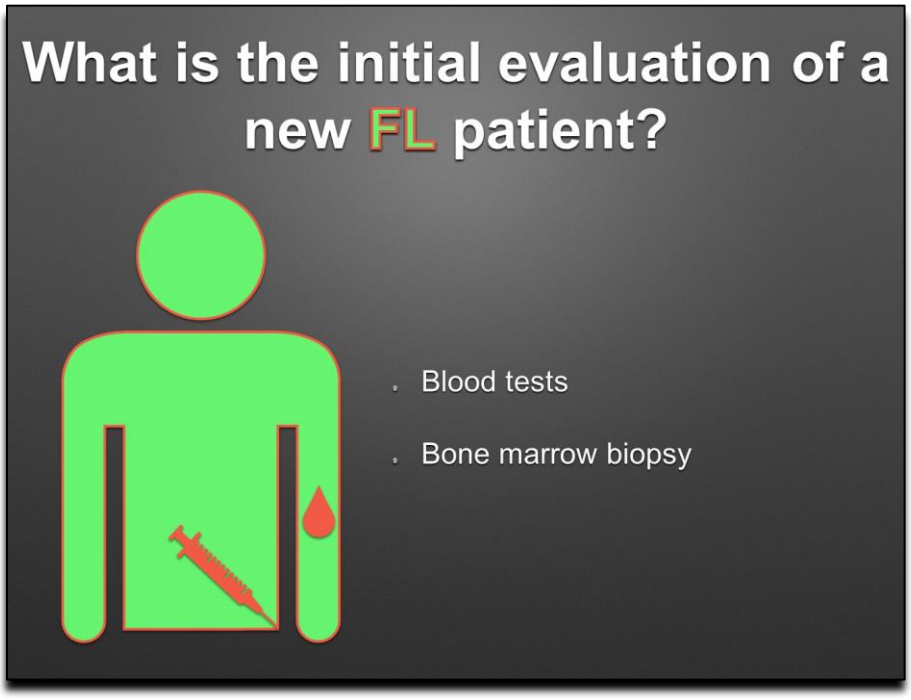
What is the initial evaluation of a new FL patient?

So once a patient presents to clinic with a diagnosis of follicular lymphoma, which by the way, requires pathological examination of abnormal lymph nodes, typically. So that means that the patient must have a biopsy of a tissue, typically a lymph node, analyzed by a pathologist under the microscope, with expertise in this disease. And that's because I want to stress, again, that there are nearly 100 different types of lymphoma, so the expertise of the pathologist may make a good amount of difference in finding the exact type of lymphoma that you have, which consequently leads to very different types of management for the patient.



What is the initial evaluation of a new FL patient?

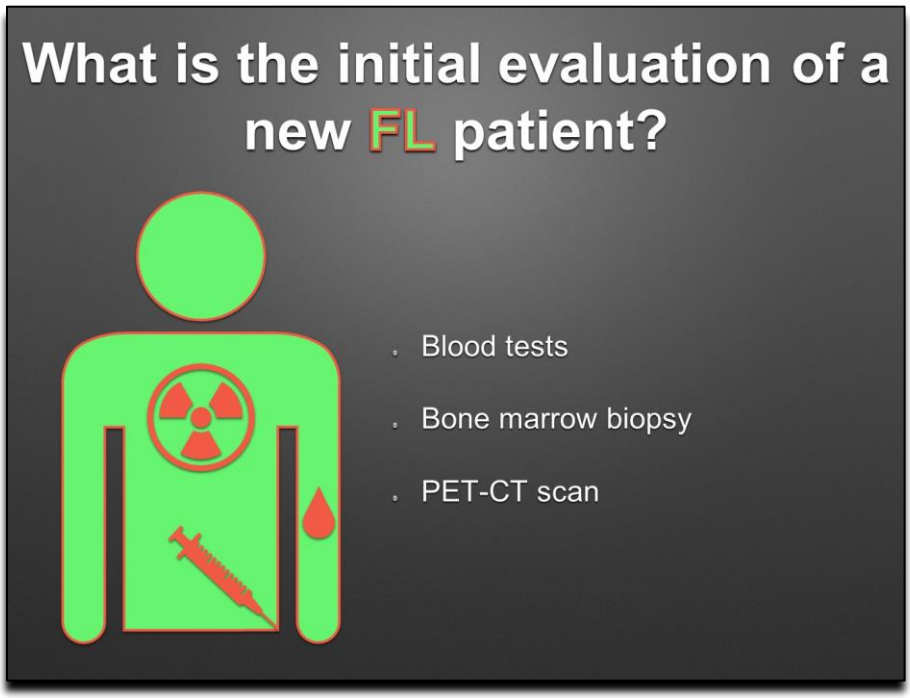
So, once we have a diagnosis and I see the patient in clinic, we'll start by evaluating their blood. What I'm doing there, is trying to find a few things. So I want to find out whether this patient has cells of follicular lymphoma or of their indolent B-cell non-Hodgkin lymphoma circulating in their blood. This has practical and prognostic implications.



What is the initial evaluation of a new FL patient?

We may also need to do an evaluation of the patient's bone marrow. And the bone marrow is the organ that sits inside our bones, that is literally the factory of all the blood cells we have. Lymphoma, I often say to patients, is a liquid disease. It's a liquid cancer, unlike breast cancer, for example, that starts in an organ, the breast, and spreads outward. Lymphoma, many times, may start at multiple locations, simultaneously.

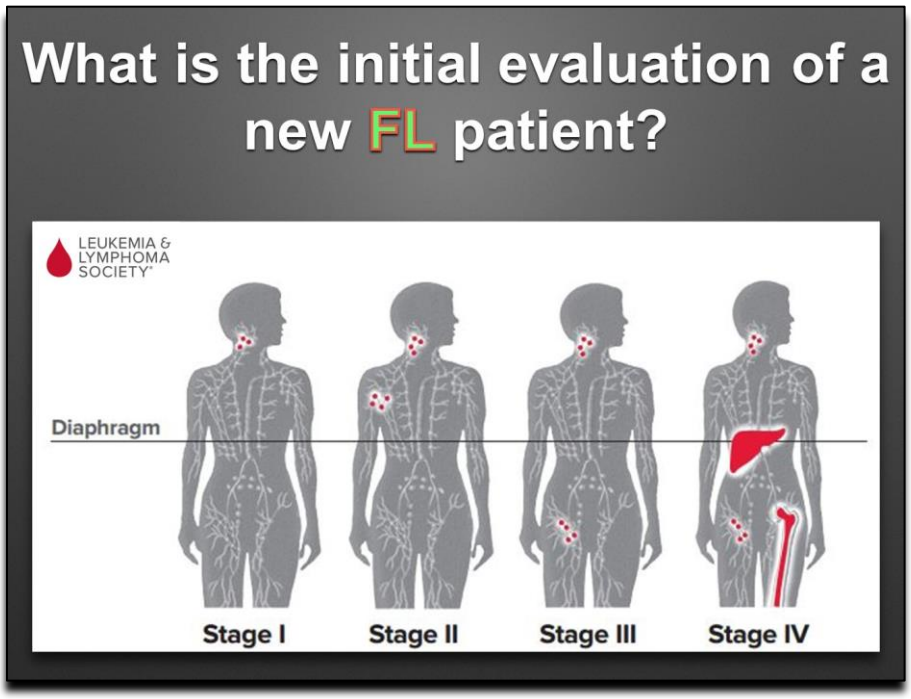
And because it's a cancer of blood cells, it has ready access to the blood and the lymphatic system, so it may be present in multiple areas at the time of presentation. So, in some cases, especially if hinted by abnormal, peripheral blood measurements, I may need to evaluate the patient's bone marrow to determine the accurate stage for that patient with a new diagnosis of follicular lymphoma. And this is done through evaluation of the tissue inside, typically the hip bone, through a bone marrow biopsy.



What is the initial evaluation of a new FL patient?

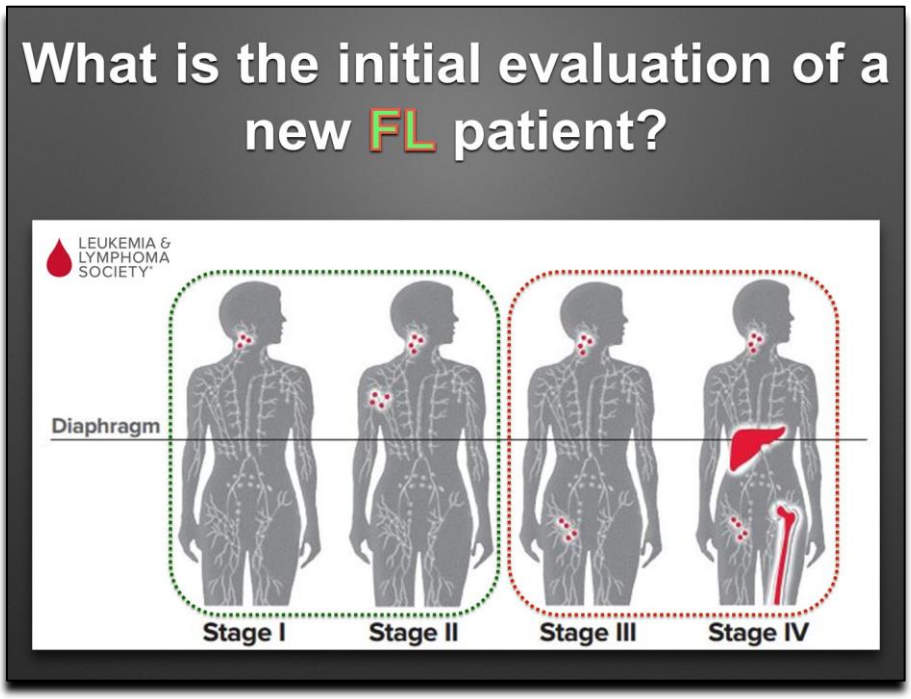
And then, ultimately, almost invariably, in a new patient with follicular lymphoma, I recommend that we have a PET-CT scan, which is an imaging study that combines anatomical description of the internal organs, so the size, locations, and the abnormalities of lymph nodes and the spleen and other internal organs. But it also combines another layer of information, which is the metabolic activity of those organs. And I find it's particularly useful for patients with indolent lymphoma, because in the classic case, we would expect that all the different locations where the lymphoma seems to be happening, they should have relatively similar amount of metabolic activity.

However, if one particular area is more active than the average, or than the others, that particular area may need to be evaluated to rule out the possibility of histological transformation, which is something we'll discuss in a few moments.



What is the initial evaluation of a new FL patient?

So, with this information obtained through blood work, possibly bone marrow biopsy, and PET-CT scan, we can aggregate that information to provide the patient with their stage.

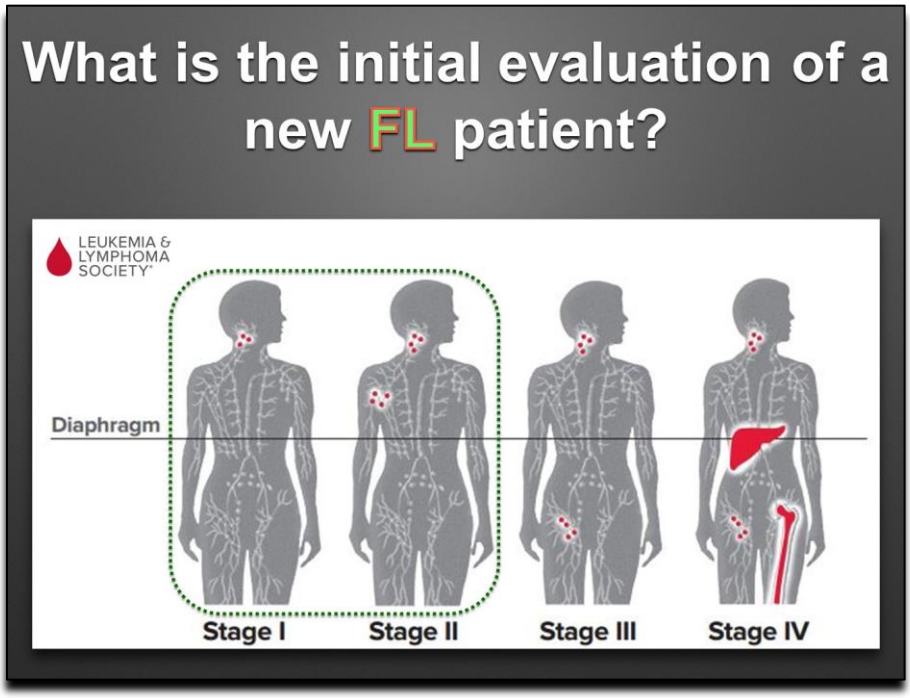


What is the initial evaluation of a new FL patient?

So, this is a picture that comes directly from The Leukemia & Lymphoma Society. And it explains the staging, according to the Ann Arbor classification. Stage I, or those patients who have involvement of lymph nodes, in a single lymph node chain; stage II, are those with involvement of more than one

lymph node chain, however, on the same side of the body, which is defined by the diaphragm. So, as you can see here, on the top side of the body, as opposed to having both sides.

Stage III and IV are defined, in the case of stage III, by two or more lymph node regions, however, on both sides of the diaphragm, as you can see in the middle screen. And finally, if you have involvement of non-lymph node structures, such as the liver, the lung, or the bone marrow, we describe that stage as stage IV.



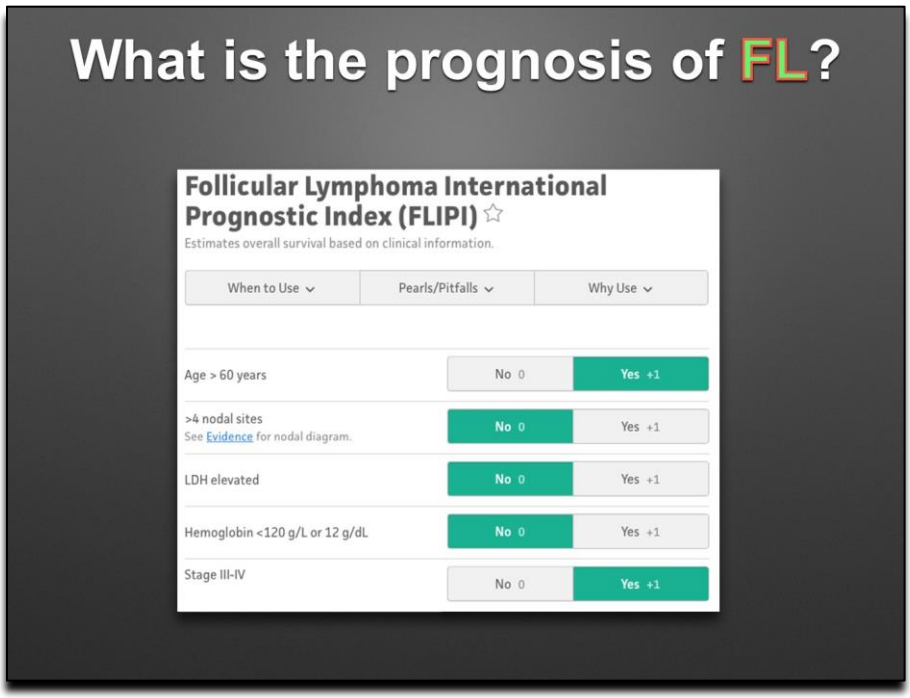
What is the initial evaluation of a new FL patient?

And we typically will aggregate stages I and II and call that limited stage, and stages III and IV, and call that advanced stage.

What is the prognosis of FL?

So, once we have a diagnosis and we have done the initial evaluation and we have the stage, the more common question that follows in clinic is, what's going to happen to me? What can I expect for the future? And truly, it's asking of the doctor to try to predict the future to the best he or she can, which is a very hard thing to do, especially because the information that we have at that time is truly a snapshot in time. It's a static information that we obtain at the time of diagnosis.

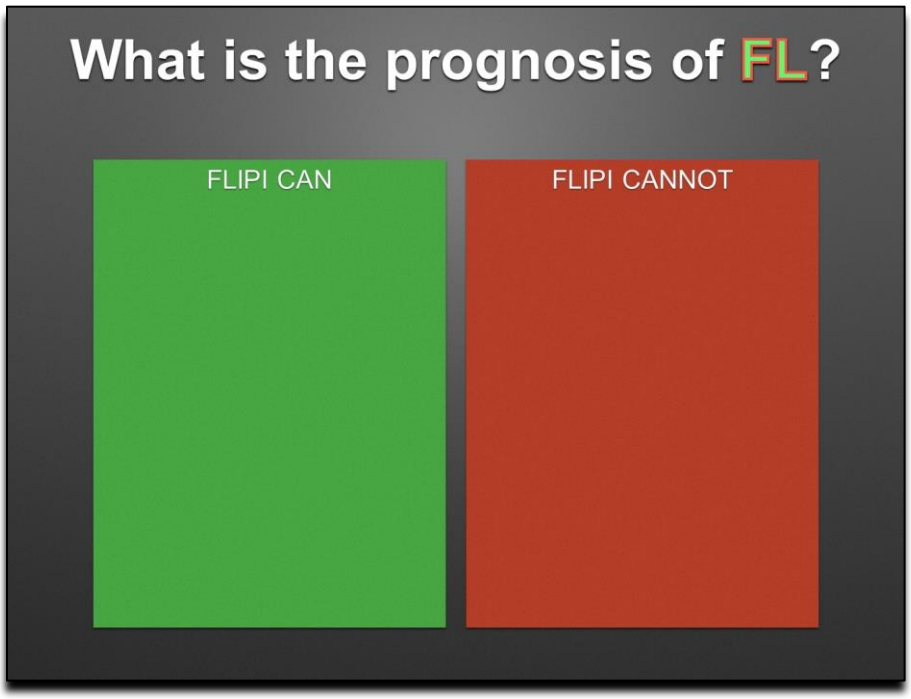
And there are a few things that we can do with that information. But there are other things that we cannot. So, what I'm going to do now is talk about one of these tools and describe it, and help you understand and dissipate some confusion that may happen around the properties of these prognostic tools, so what can they do and what they cannot do, so we're all clear on how they can be best used.



What is the prognosis of FL?

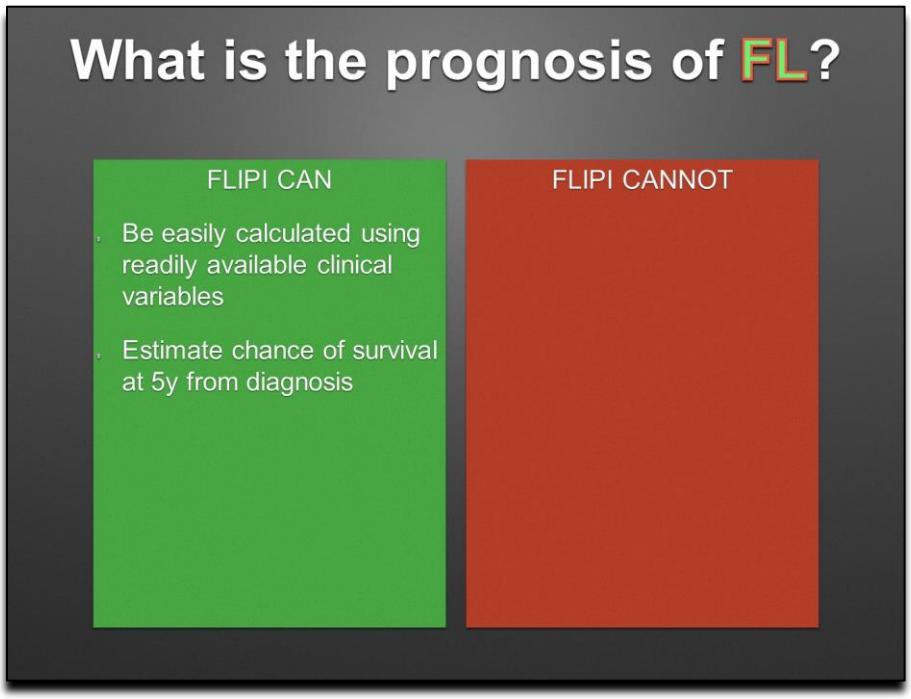
So, one of the most common tools used for prognostication of a patient with follicular lymphoma is called a follicular lymphoma international prognostic index, or FLIPI. This is a very well-studied tool, has been validated in multiple different populations, in different countries. It was initially designed before the common use of rituximab (RITUXAN®) but has been re-validated with the introduction of rituximab in the clinical practice. And it combines, essentially, five different clinical and laboratory values to provide the patient with a score, from 0 to 5. The higher the score, the worse the prognosis, in terms of future likelihood of outcome.

And I will explain what that means. So, these are the factors that we look for to calculate the FLIPI. There are all line calculators that can make these very easy and spit out the prognostic categories for our patients. But while calculating this FLIPI is not complicated at all, there is still a significant degree of confusion about what to do with the information provided by the FLIPI, not only amongst patients, but event amongst hematologists and oncologists who do not see patients with follicular lymphoma commonly in their practice.



What is the prognosis of FL?

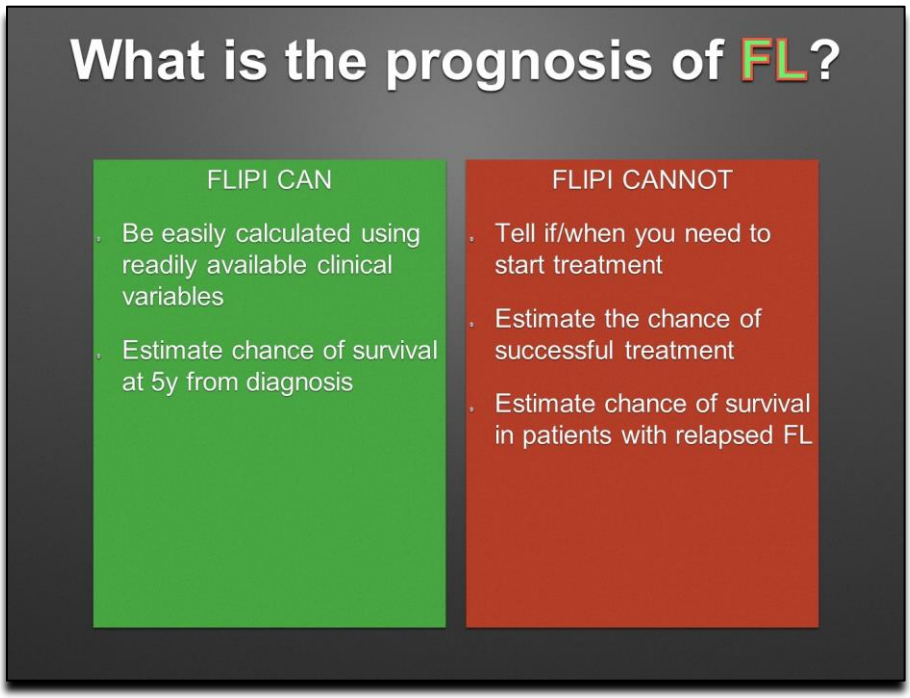
So, on this slide here, I'm going to walk you over what the FLIPI can and what the FLIPI cannot do, so that we are all on the same page about how to use this tool.



What is the prognosis of FL?

First of all, the FLIPI can be calculated using readily available clinical variables. So, it's not anything that requires special, sophisticated genomics evaluation. It is something that can be calculated fairly easily by any provider taking care of a patient with follicular lymphoma.

What it can do, and the way it was designed, was to estimate the chance of the patient being alive five years from the moment of diagnosis. So, what the FLIPI can see is, five years into the future, according to these risk categories, what is the likelihood that a patient sitting in front of me will be alive and doing well five years from now?



What is the prognosis of FL?

However, what the FLIPI cannot do, is the FLIPI cannot tell me or anyone when or if to start treatment for a patient with follicular lymphoma.

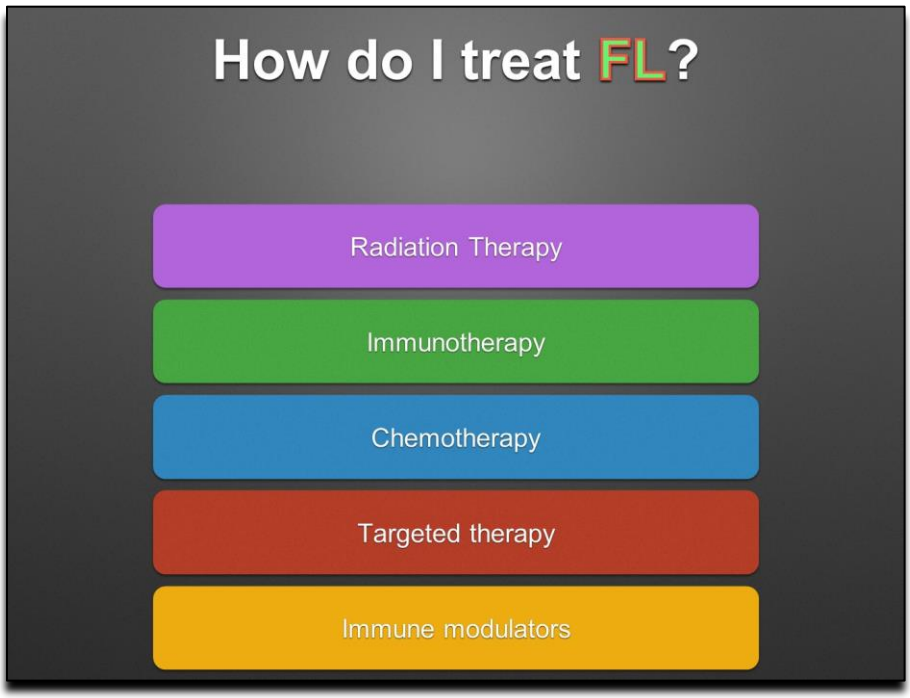
Let me be clear, I have plenty of patients with a high FLIPI score that have not been treated and have not required therapy since the diagnosis and is doing well. Conversely, I have patients with a low FLIPI score that needed to initiate therapy right away, right after diagnosis. So, the FLIPI cannot tell us when and if a patient needs to start therapy. As you will see in a moment, to make that evaluation, there are many more factors that need to be taken into account, and the FLIPI is not one of them.

The second thing that the FLIPI cannot do is to estimate the chance of a successful treatment. What I mean is, a patient with a high FLIPI, compared to a patient with a low FLIPI, does not necessarily have a lower chance of responding well to that treatment, whether it is in terms of efficacy, shrinkage of the tumors, or safety side effects. So, the FLIPI cannot predict that particular outcome.

And lastly, FLIPI was designed as a tool to evaluate patients at the time of diagnosis. So, it's a snapshot in time, at the moment of diagnosis. And in patients who are treated and later on relapse with their lymphoma, follicular in this case, the FLIPI, while it could be re-calculated, the value of the FLIPI, in the relapse setting, is not well defined, as compared to the value of the FLIPI at the time of diagnosis. So FLIPI should be a one-time evaluation that you do with a patient at the moment of their diagnosis.

Once they have started treatment, or once they have started to be followed with you in clinic, there are other factors that are much more useful in determining the long-term outcomes of these patients, such as, for example, how did they respond to their first-line therapy? Are they in remission for 12 or 24 months? Have they achieved a complete remission? Have they relapsed within their first 24 months, after starting chemoimmunotherapy?

So, these are more dynamic factors that we can look at, as we start to walk through with the patient, after their diagnosis of lymphoma. So I wanted to make sure that we are clear on what the FLIPI can do and what the FLIPI cannot do, because as a lymphoma physician, I see a fair amount of misusage of the FLIPI in clinical practice.



How do I treat FL?

So now, we're going to take a moment and, once again, using follicular lymphoma as the prototype disease for this group of lymphomas that we are calling slow growing, non-Hodgkin lymphomas, I'm going to walk you through the management of a few, real-life cases of follicular lymphoma that I have treated in my clinic.

So, all of these are my patients, patients that I have seen in the last 10 years. They are actively under my care. And I have seen some of them, actually, fairly recently, in the last few weeks. What I tell patients with follicular lymphoma is that, in the lymphoma doctor's toolbox, there are different tools. And I have highlighted here some categories of tools that we have at our disposal to manage patients with follicular lymphoma and indolent lymphomas, in general. Okay. I often tell them that these tools, sometimes, are recyclable.

So I can use one tool and put it back in the toolbox. And, if needed later on, I can pick up that tool again and use it one more time, or even more than once. However, there are some tools that we tend to use once and not again, in a more disposable fashion. I also explain that sometimes, as in a real toolbox, we may need to use more than one tool at the same time, so combined therapy is often used, as you will see in a moment.

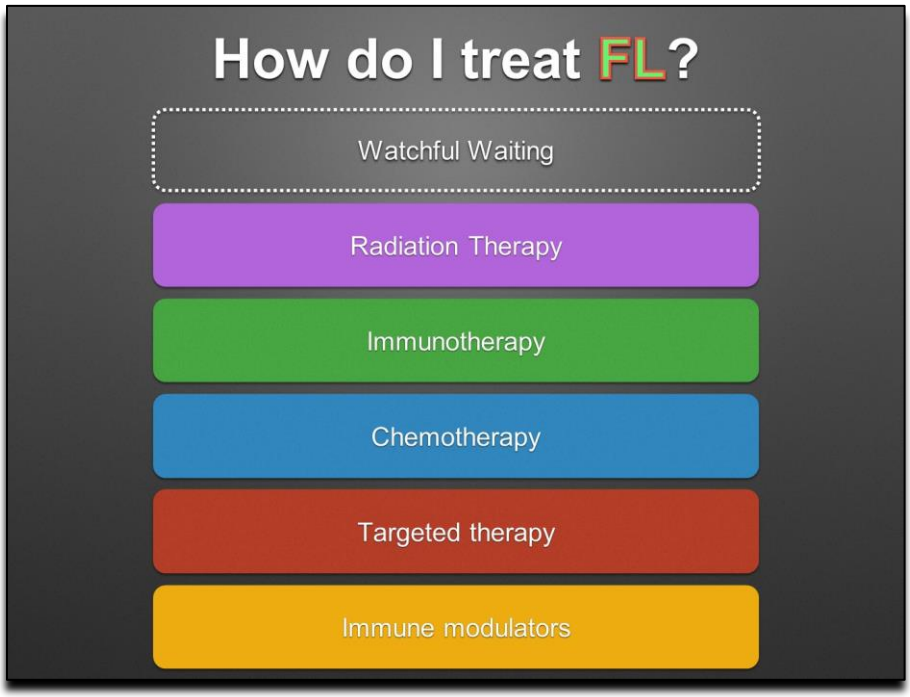
And, again, as you can see in the categories here, we have the ability to treat lymphoma with radiation therapy. We have the ability to treat lymphoma using the immune system, whether it's with monoclonal antibodies, such as CD20 targeting with rituximab, or perhaps, a more novel immunotherapy drug, such as bispecific T-cell engagers, also known as bispecific antibodies. Or, even the more sophisticated chimeric antigen receptor T-cell therapy or CAR T-cell therapy, although in many cases, because it's such a unique form of immunotherapy, CAR T-cell therapy is going to be called cellular therapy, a category in and of itself.

As you can see here, we still use a fair amount. And there is excellent outcomes in many cases, of treating patients with follicular lymphoma with chemotherapy. We sometimes may use targeted therapy to treat these patients. And I would like to define here what I mean by targeted therapy. And I use this name to define drugs that specifically interfere with molecular pathways inside the lymphoma cells.

Good examples of these targeted therapies in lymphoma are BTK inhibitors and EZH2 inhibitors, two kinds of targeted therapy that are now approved to treat patients with indolent non-Hodgkin lymphomas. And then lastly, but not least, we have this other category of drugs that I use the term immunomodulators. So, these are drugs that typically have more than one function. They modulate, meaning that they maximize, they use a particular cell of the immune system to help control the lymphoma.

A good example of an immunomodulator-- sometimes people use the term IMiD, or immunomodulator drugs, is lenalidomide (REVLIMID®).

And since we're talking about indolent B-cell non-Hodgkin lymphomas, and follicular lymphoma, in particular, we should not forget that, when treating or perhaps using the word 'managing' patients with follicular lymphoma, we must not forget about the usefulness of a very powerful tool,



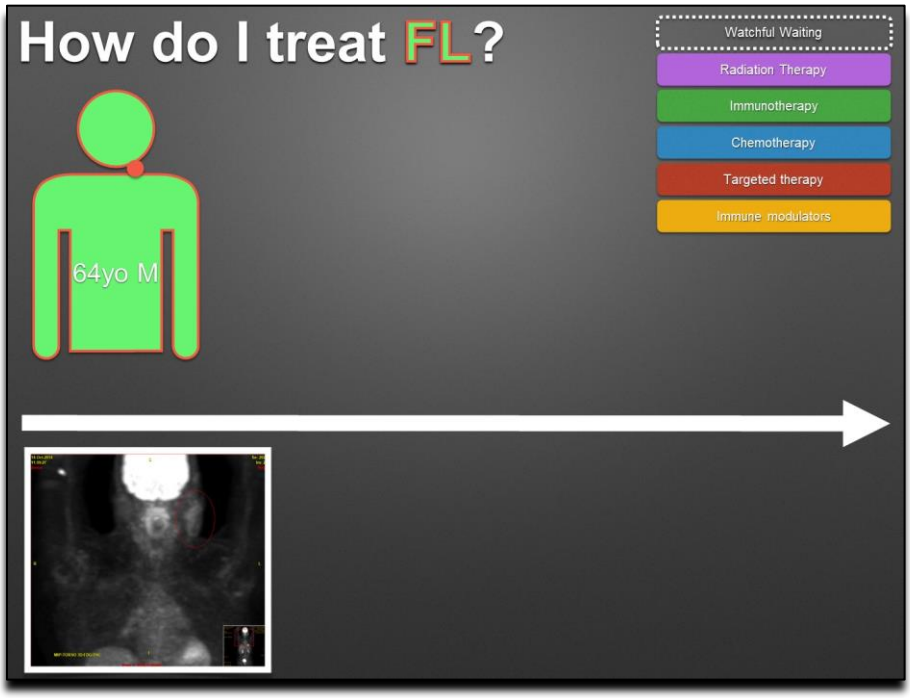
How do I treat FL?

which is to watch and wait. So watchful waiting, in some particular cases, is one of the best things that we can do to maximize the goals of our treatment of our management in these patients, because I must remind you, in follicular lymphoma, in the vast majority of the cases, my goal is not to eradicate the disease to the point that they will never come back again. Unfortunately, as of yet, most patients with follicular lymphoma will experience a relapse.

So my goal as a lymphoma doctor is to maximize the quality of life, minimize any symptoms, whether it's from the lymphoma or the therapies, for the longest amount of time possible, hopefully, to allow that patient to fulfill their life expectancy, without lymphoma interfering with it.

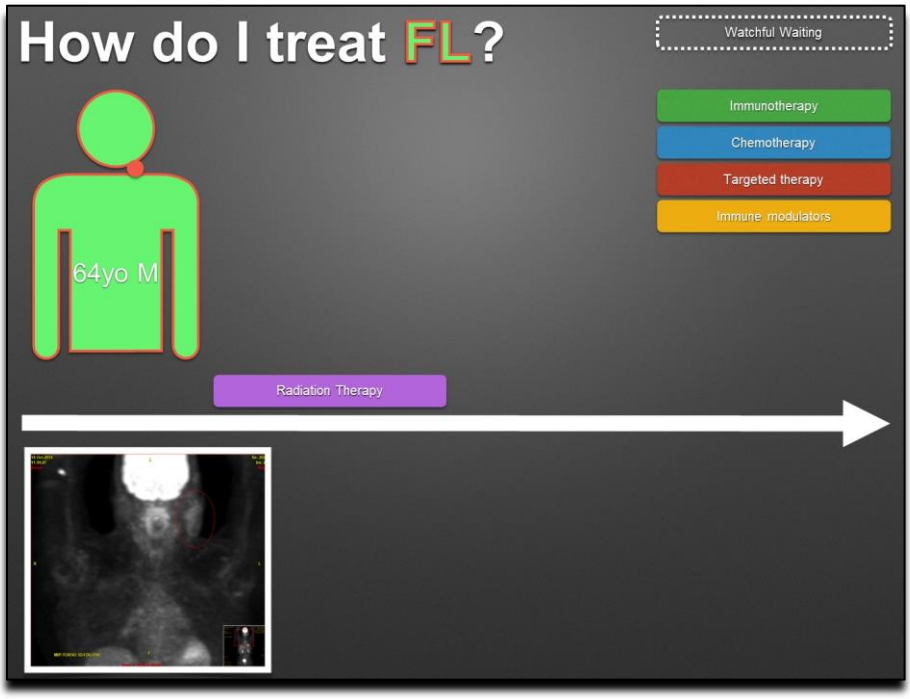
How do I treat FL?

So, with this framework in mind and with this toolbox menu to your right side, I'm going to walk you through a few cases of real-life follicular lymphoma that I have encountered in clinic and managed in the recent past.



How do I treat FL?

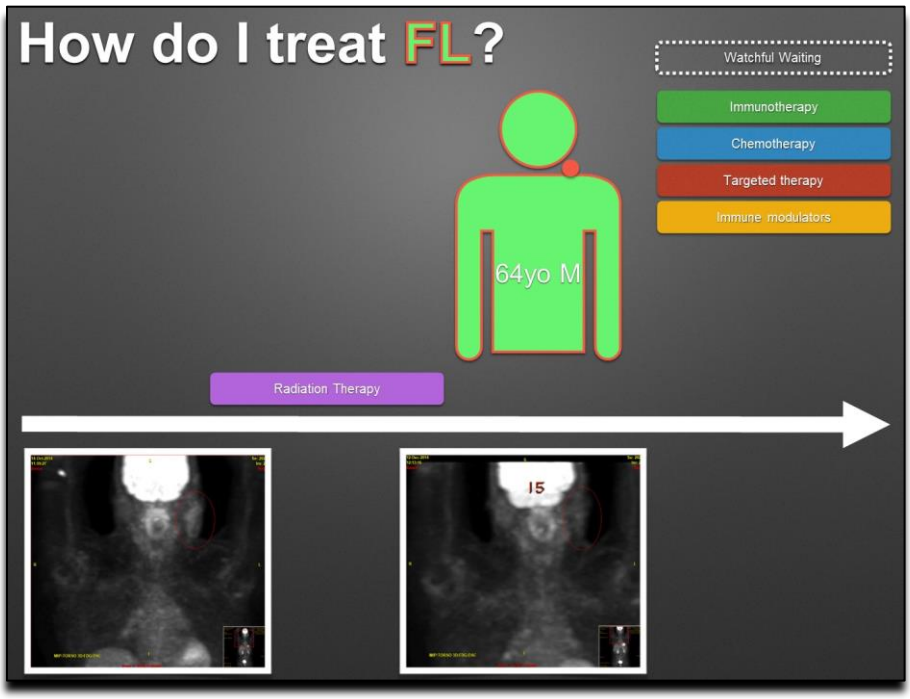
So let's start with this case of a patient, a man, 64-year-old, who identified a lymph node while shaving one morning. He sought attention with a primary care physician. Ultrasound identified enlargement of lymph node, and eventually a biopsy confirmed follicular lymphoma, grade I.



How do I treat FL?

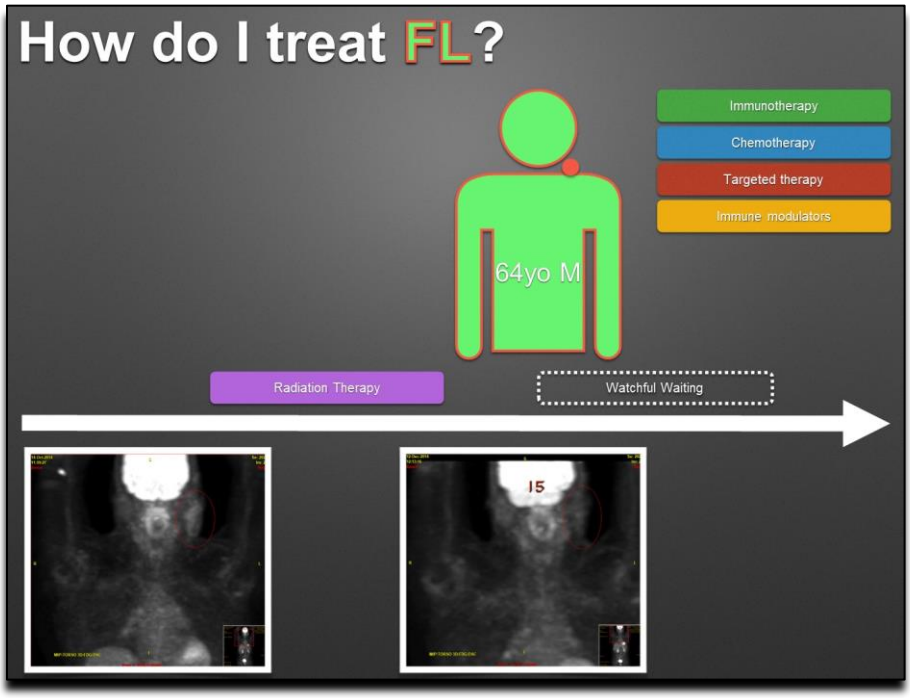
This patient came to me in clinic and I have confirmed that he has stage I disease, with a bone marrow biopsy.

So in this particular case, if I'm going to stage this patient as stage I, limited stage, I must confirm that there is not an obscure occult, or silent involvement of follicular lymphoma in the bone marrow. And having confirmed that, I recommended this patient to be treated with radiation therapy, to that single lymph node chain on the left side of the neck.



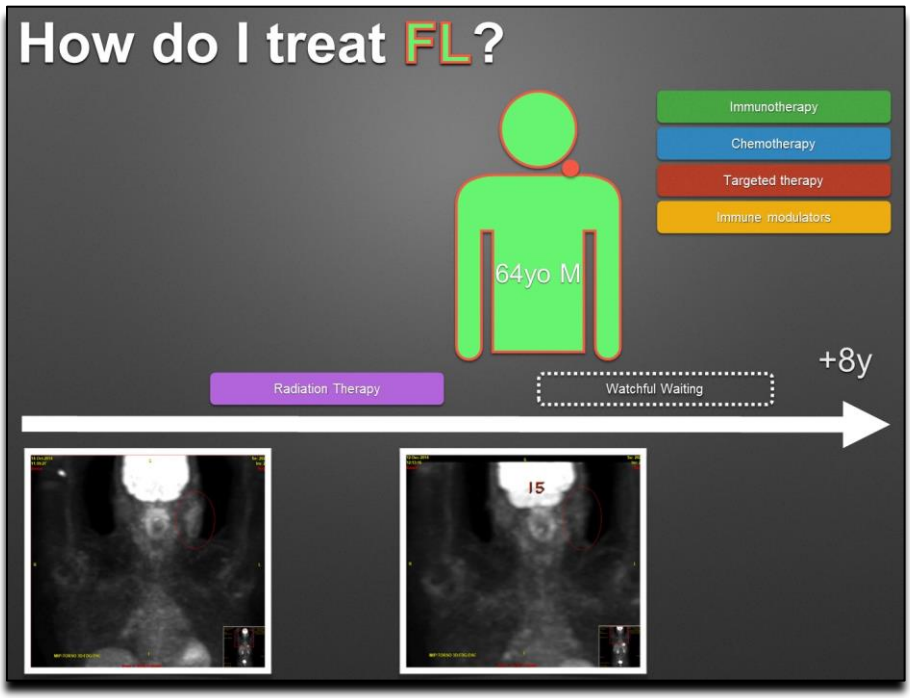
How do I treat FL?

This resulted in complete resolution of the lymphoma to the left side of the neck, as you can see on the follow-up image.



How do I treat FL?

And this patient has been following on watchful waiting since.

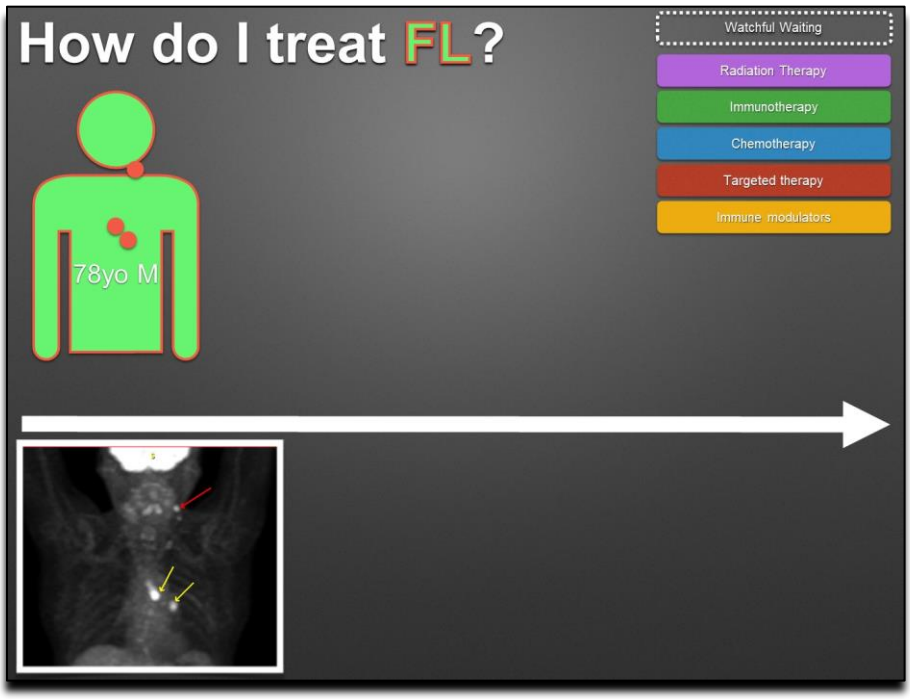


How do I treat FL?

And has been in remission for over eight years now.

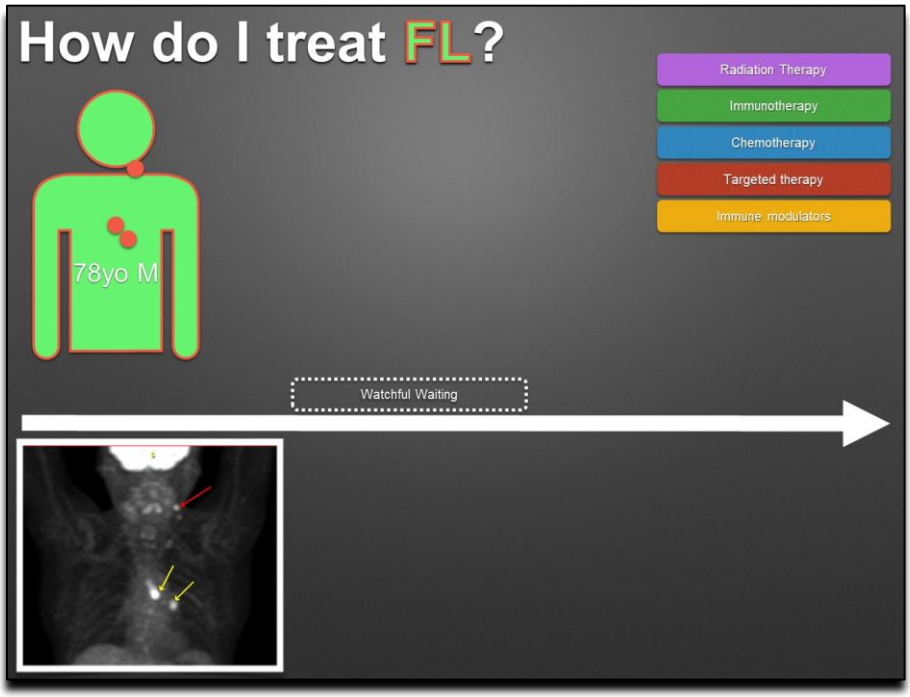
How do I treat FL?

To continue our discussion, let's look at the case of this 78-year-old man



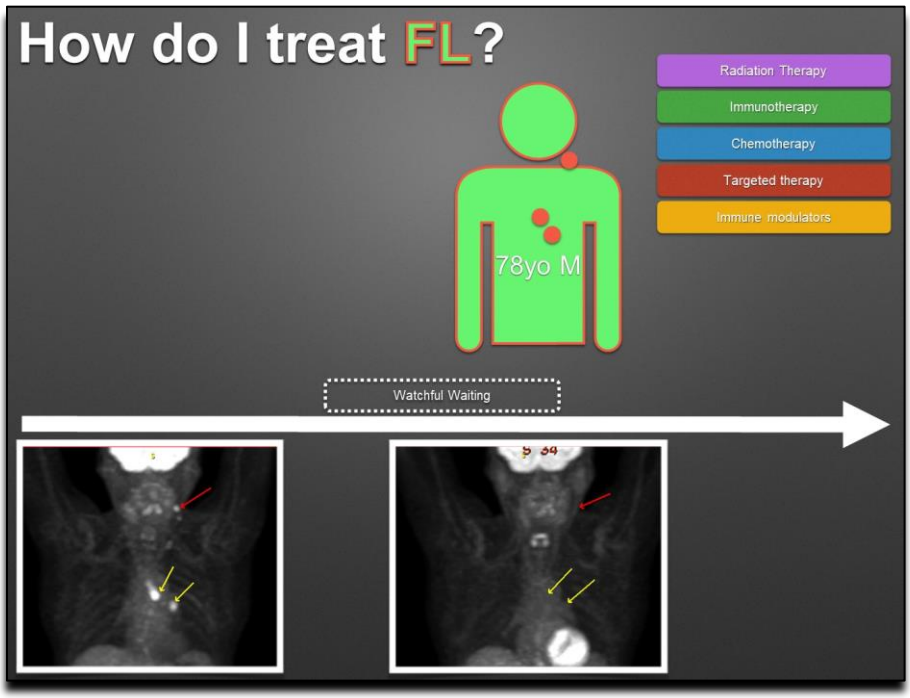
How do I treat FL?
who presented to his primary care physician with a cough. He was diagnosed with influenza. And during the process of evaluation, a CT scan of the chest of was obtained.

This identified enlargement of some lymph nodes in the mediastinal and left cervical area, which was followed by a PET-CT scan. And you're seeing the picture of the PET-CT scan, with the arrows indicating areas of lymph node that were not only enlarged, but metabolically active. Biopsy confirmed follicular lymphoma, a grade I/II.



How do I treat FL?

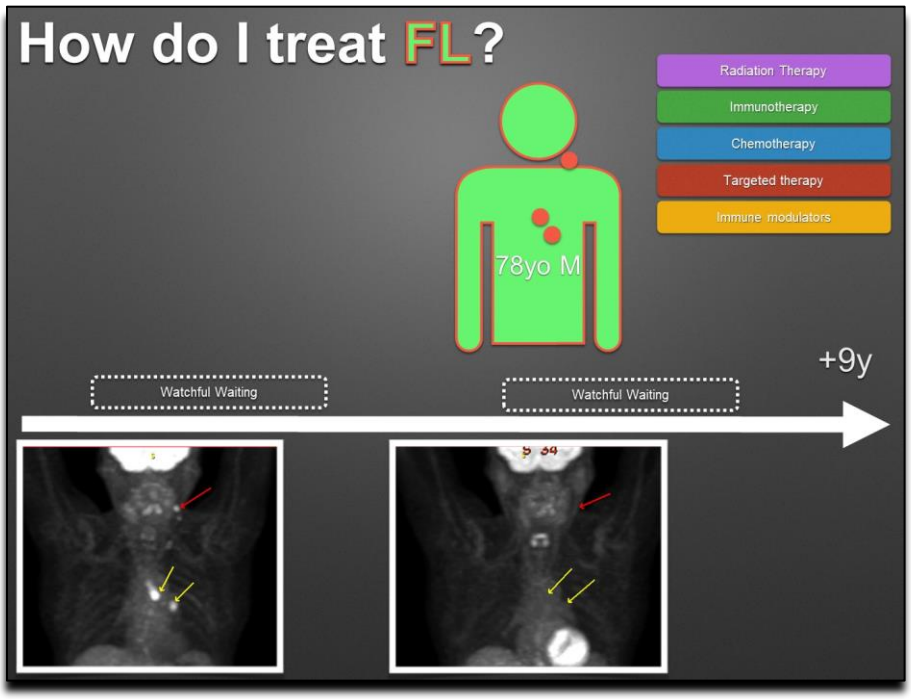
In this particular case, the patient, after resolution of the influenza symptoms, had no symptoms at all from the follicular lymphoma itself. So we could categorize this as incidentally found follicular lymphoma, of low volume, low bulk, and no symptoms. And, therefore, very appropriate for watchful waiting. In this particular case, the patient, later on, went on to develop



How do I treat FL?

a complication of that initial flu infection, and in fact, developed a bacterial pneumonia. After resolution of the bacterial pneumonia with antibiotics, the patient came back to me to clinic, and we had a follow-up of the lymphoma situation, with a repeat PET-CT scan. As you can see on the follow-up image to the right, the areas of lymphoma that were previously seen on the Pet-Scan had resolved. Let me highlight this. This resolved without any treatment and is consistent with a spontaneous resolution of follicular lymphoma. While this is not common, it is still possible that the immune system somehow was activated, perhaps, by that bacterial pneumonia and misfired -- instead of killing the bacteria only, it killed also some of the lymphoma cells, and led this patient to enter a complete remission, without the need for therapy.

I really like to talk about this case, because had I seen, and someone else decided to give this patient, for example, rituximab after their initial diagnosis, they would be crediting rituximab with the resolution of the lymphoma, when in fact, it was probably nothing to do with rituximab. It was truly the patient's own immune system that took care of the lymphoma.

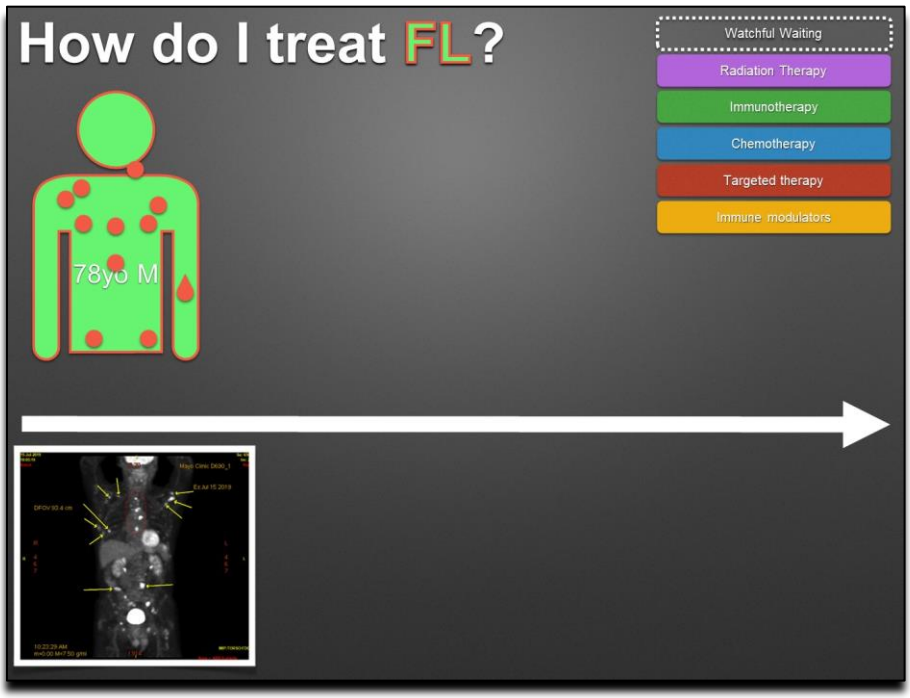


How do I treat FL?

And this particular situation, I have followed this patient now for over nine years. And his follicular lymphoma has never relapsed.

How do I treat FL?

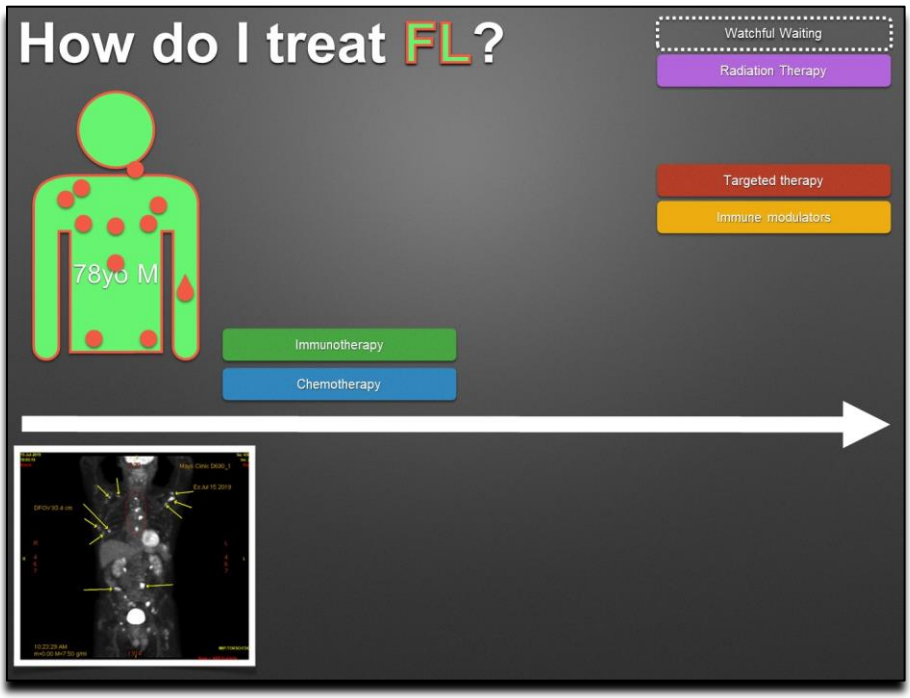
Let's now take a look at another 78-year-old man.



How do I treat FL?

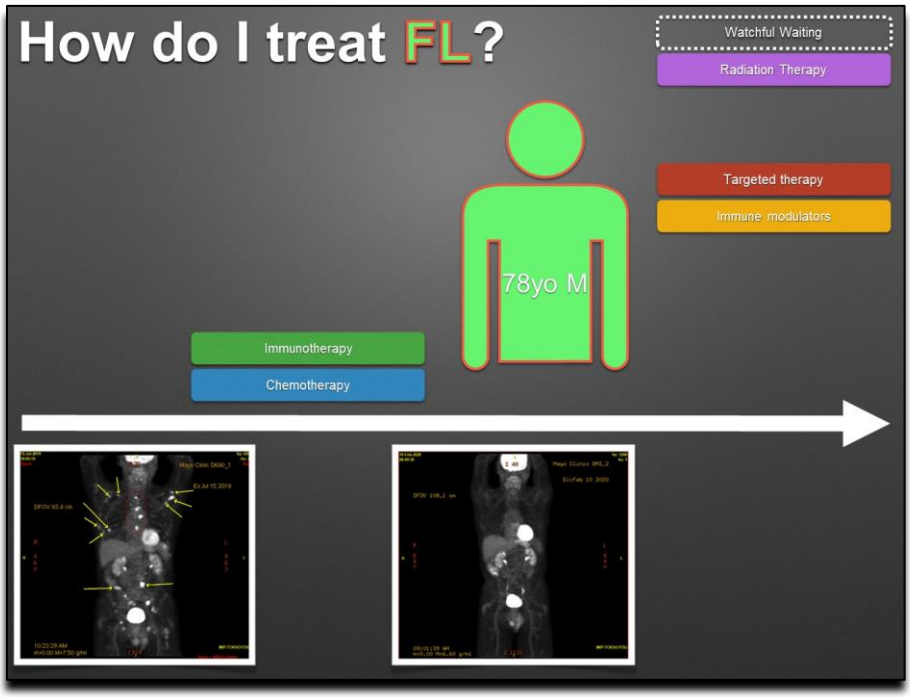
This one, however, presenting with night sweats, weight loss, multiple palpable lymph nodes, and a PET-CT scan demonstrating at least stage III disease by involvement of both sides of the diaphragm, as you can see on the image, as well as involvement of the bone marrow, consistent with stage IV disease.

This patient was not only symptomatic, but he had what we call high-bulk disease, so large volume of cancer in the body, and deserved to be treated with active therapy.



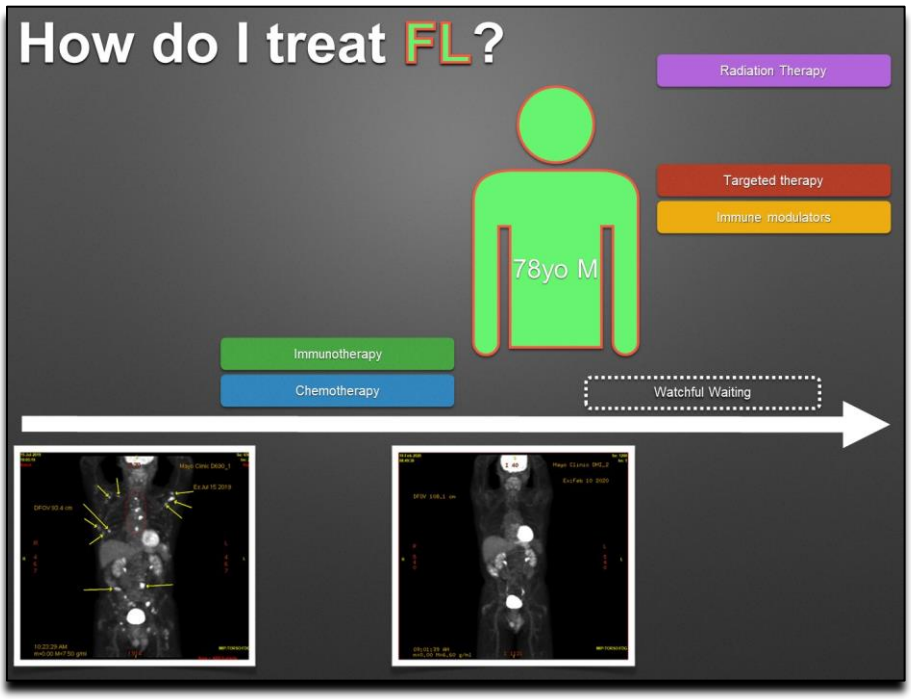
How do I treat FL?

In this case, we combined the chemotherapy drug, bendamustine (BENDEKA®, TREANDA®), with the immunotherapy drug, rituximab, what we are going to call chemoimmunotherapy.



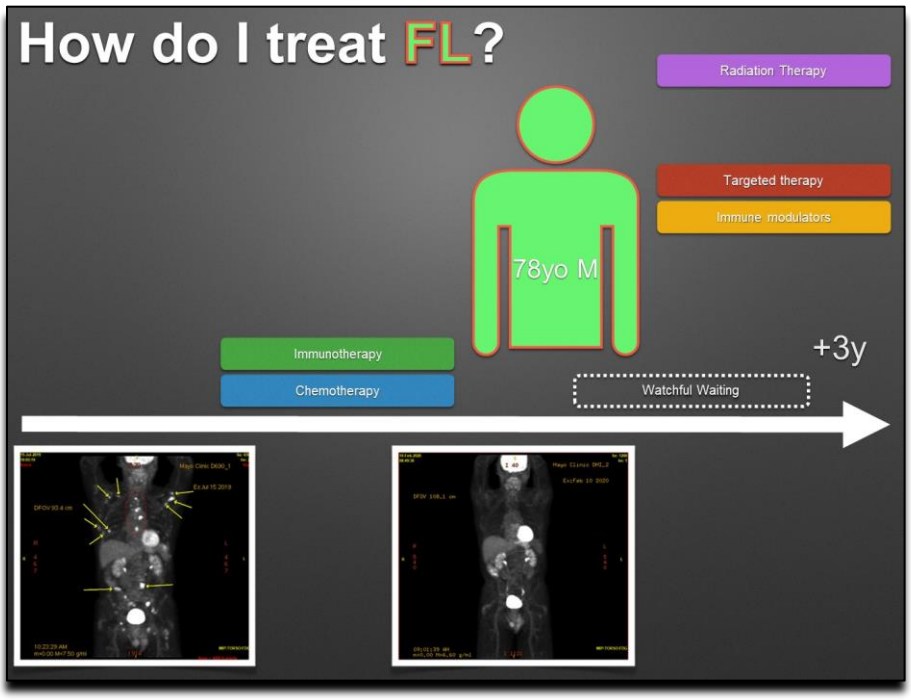
How do I treat FL?

And after six cycles of BR, bendamustine-rituximab, the patient achieved a complete, metabolic response of the follicular lymphoma, as demonstrated by the follow-up PET-CT scan on the right.



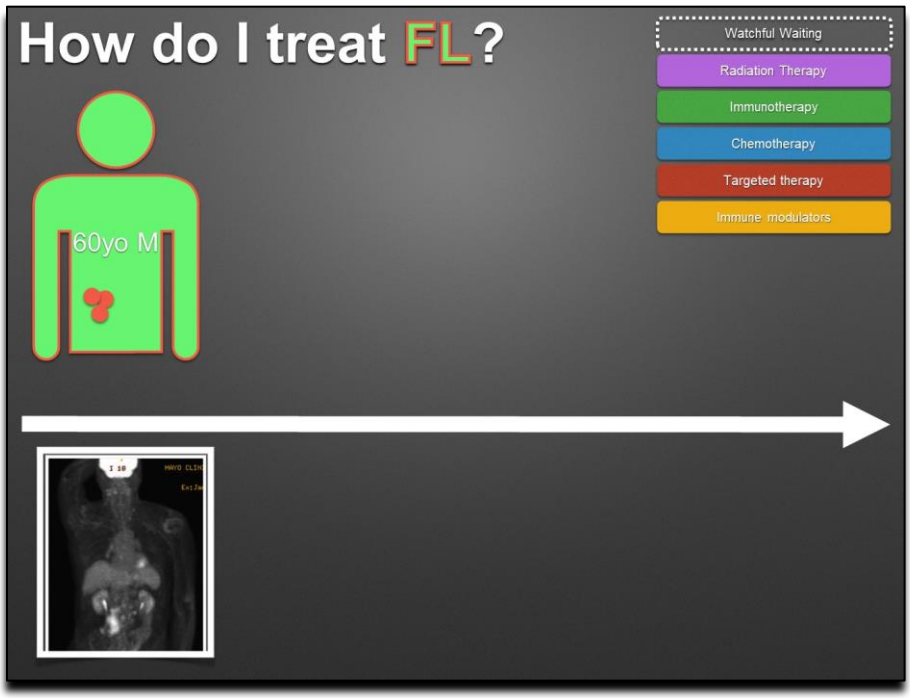
How do I treat FL?

After initial management with bendamustine-rituximab, the patient went on to be watchfully waited.



How do I treat FL?

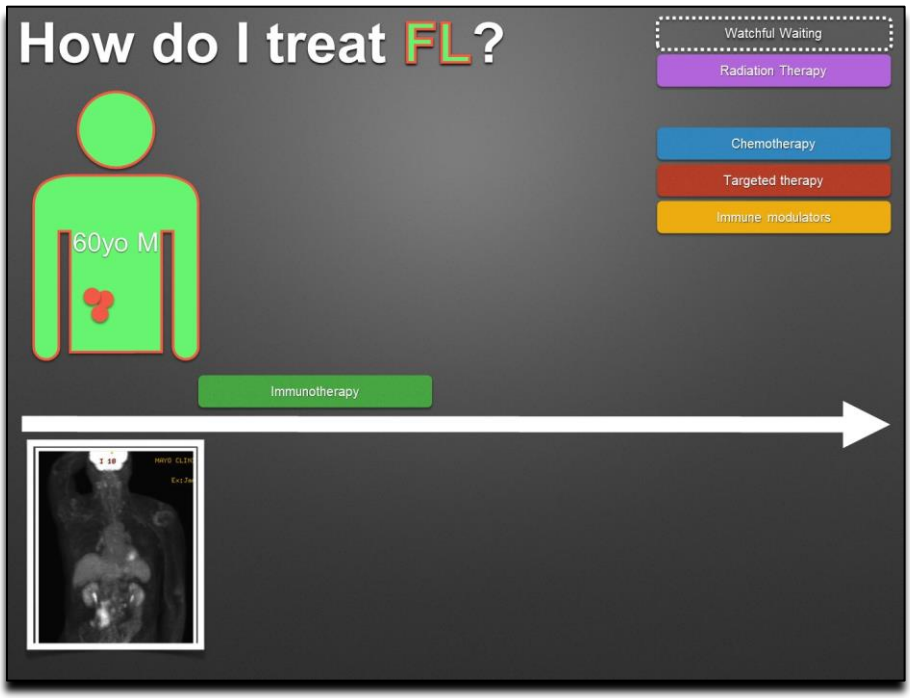
And has been in remission for over three years. This is a good example of a situation where we need to escalate therapy to a combination of two very active drugs, used together in chemoimmunotherapy to manage a patient with follicular lymphoma.



How do I treat FL?

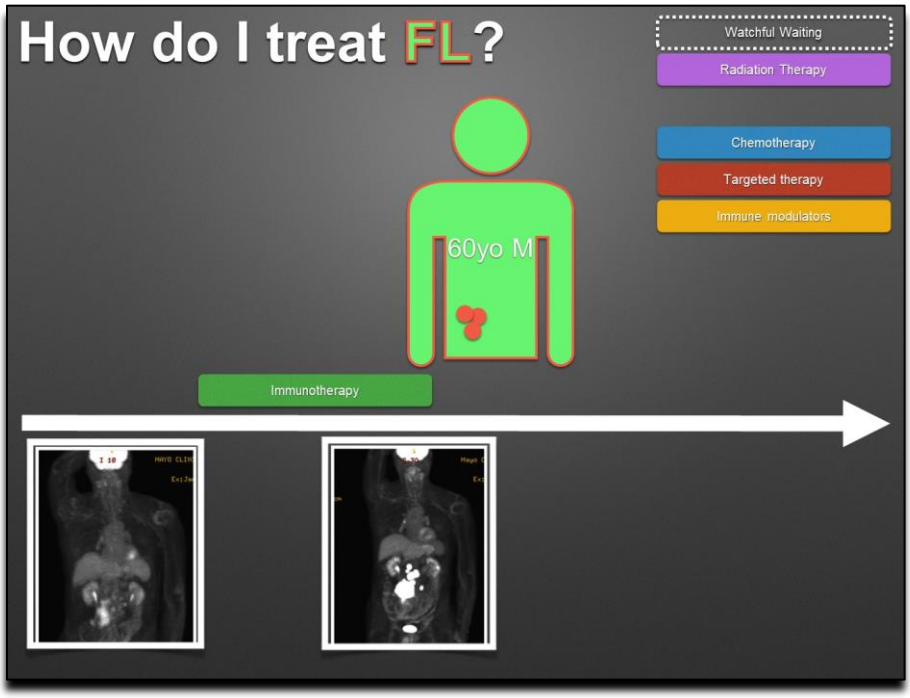
And then lastly, let me talk about the case of this 60-year-old man that I saw in clinic. This was one of the patients diagnosed incidentally. The way we found his lymphoma was literally, he presented to the emergency room with a kidney stone. A CT scan of the abdomen identified enlargement of intra-abdominal lymph nodes and a biopsy was obtained. The biopsy showed follicular lymphoma, grade I.

And the patient was asymptomatic, there was no systemic symptoms, no night sweats, no weight loss. He had no symptoms, abdominally, from the lymphoma. And at this moment, it was felt that the disease was of low bulk, low volume.



How do I treat FL?

And that he was offered watchful waiting for a while, followed by immunotherapy, with rituximab. After four cycles of weekly rituximab, the patient started to develop symptoms -- abdominal pain and fullness.

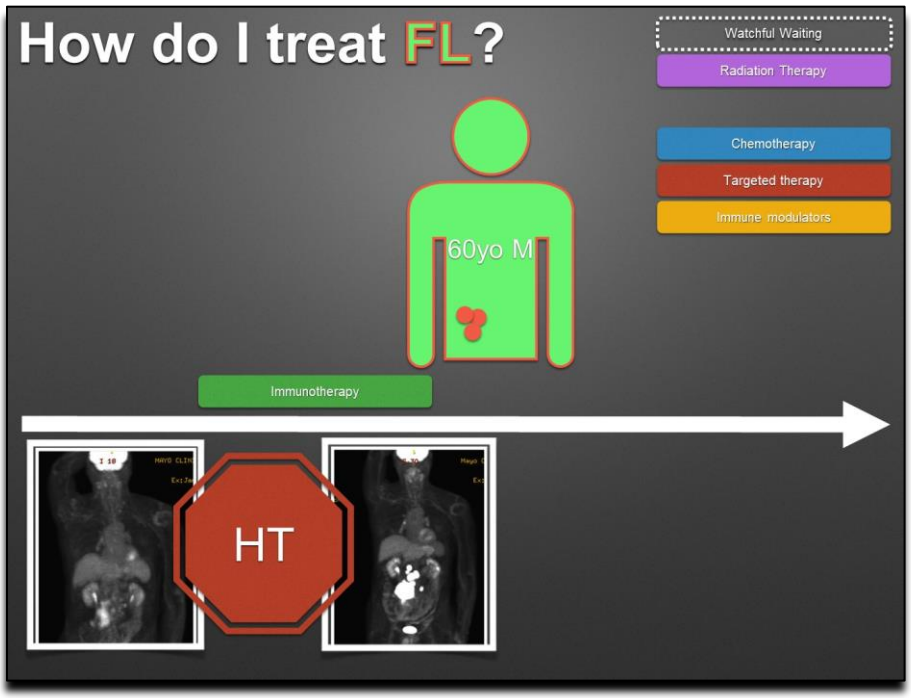


How do I treat FL?

And a follow-up, PET-CT scan identified worsening, not only in terms of size, but metabolic activity of the lymphoma in the abdomen, as you can see by comparing the two images, where we have not only

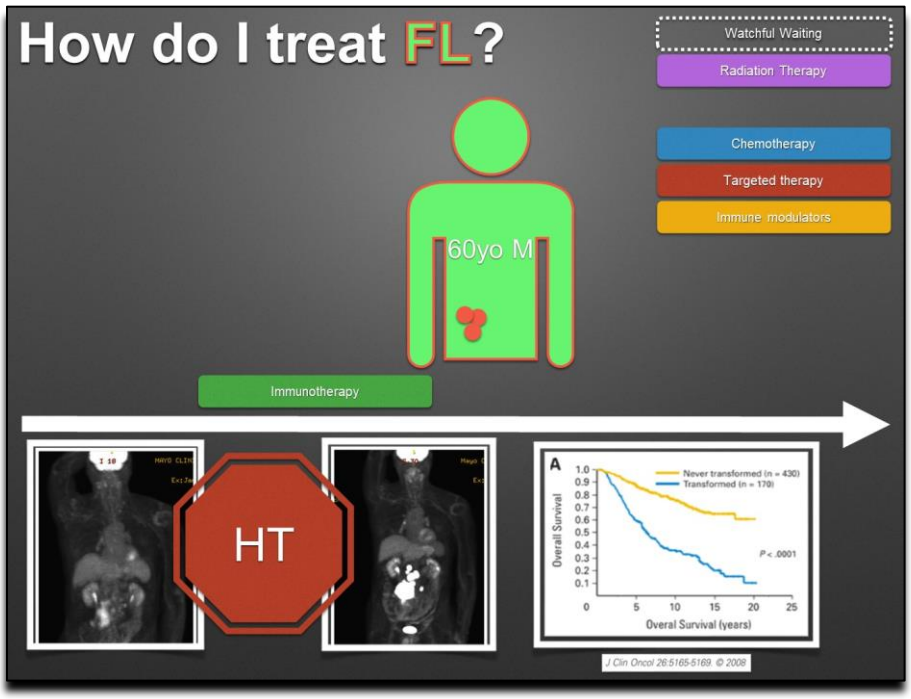
more lymph nodes, but the brightness of the white in the image is much more visible, indicating that this is a more aggressive, more metabolically active malignancy.

When this happens, it is crucial that we obtain a repeat biopsy. And the reason here, is we must exclude the possibility of this process called histological transformation.



How do I treat FL?

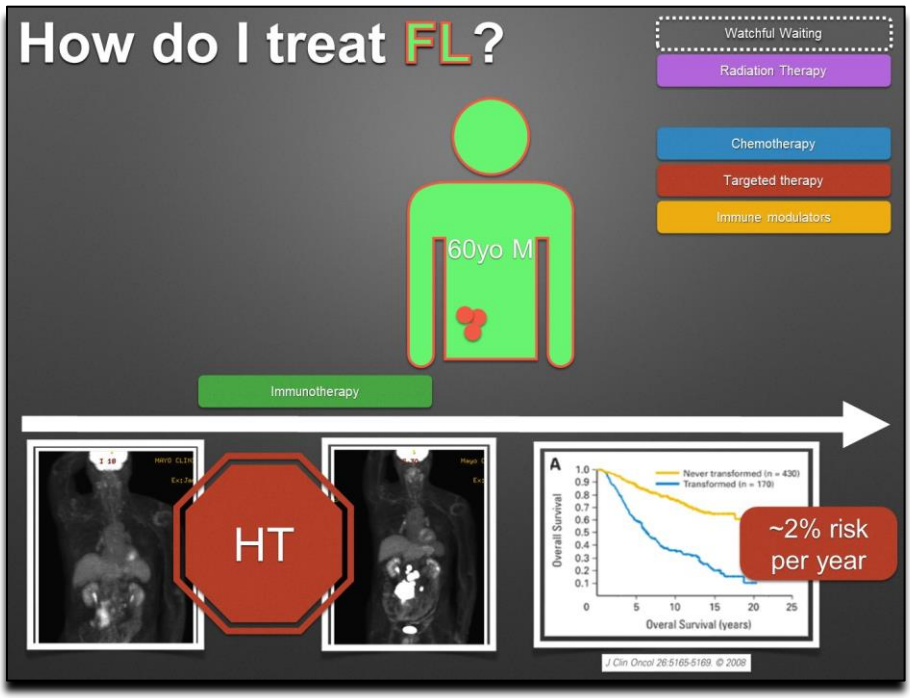
Histological transformation is a term used to define the evolution of a slow growing lymphoma into a fast-growing, more aggressive malignancy. It is truly a catastrophic event in the life of a patient with indolent lymphoma.



How do I treat FL?

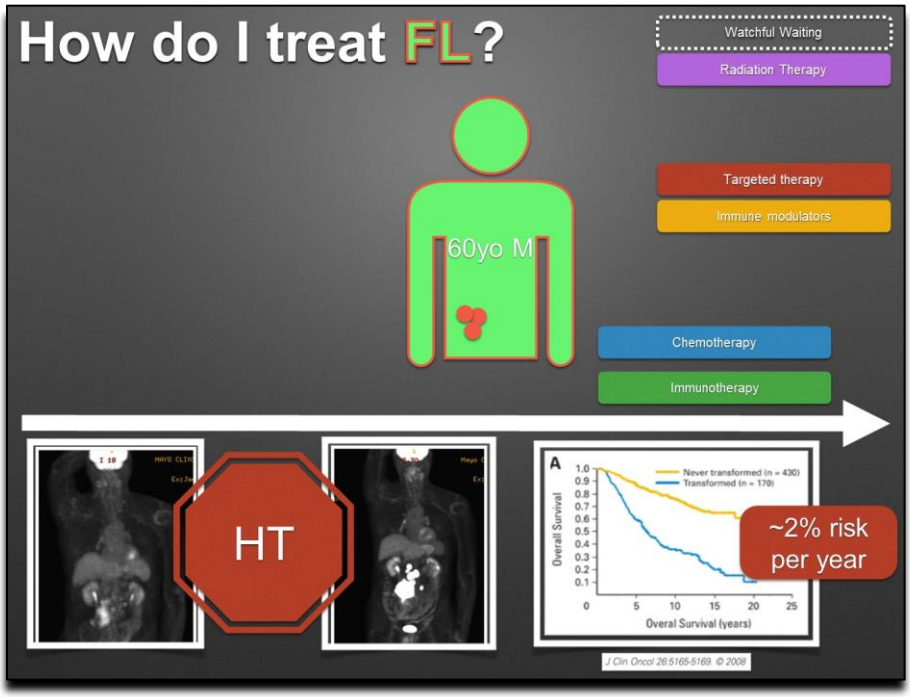
And the reason I say that is, several studies have now demonstrated that, if you look at a cohort of patients with follicular lymphoma or other indolent lymphomas, and you separate them between those that have never experienced a histological transformation event, compared to those that did, the likelihood of survival is much more -- it is much lower, much decreased, in patients who have the transformation event, compared to those who don't.

As you can see here, on a publication from 2008, which included patients treated here at the Mayo Clinic, as well as at the University of Iowa -- and you can see on the blue line, which demonstrates the overall survival, over the years, of patients with follicular lymphoma, those are in the blue line. You can see that their survival decreases drastically, because they have suffered a transformation event, while those that never transformed, they have a slow taper of their survival, indicating that the disease continues on the same slow pace throughout the years.



How do I treat FL?

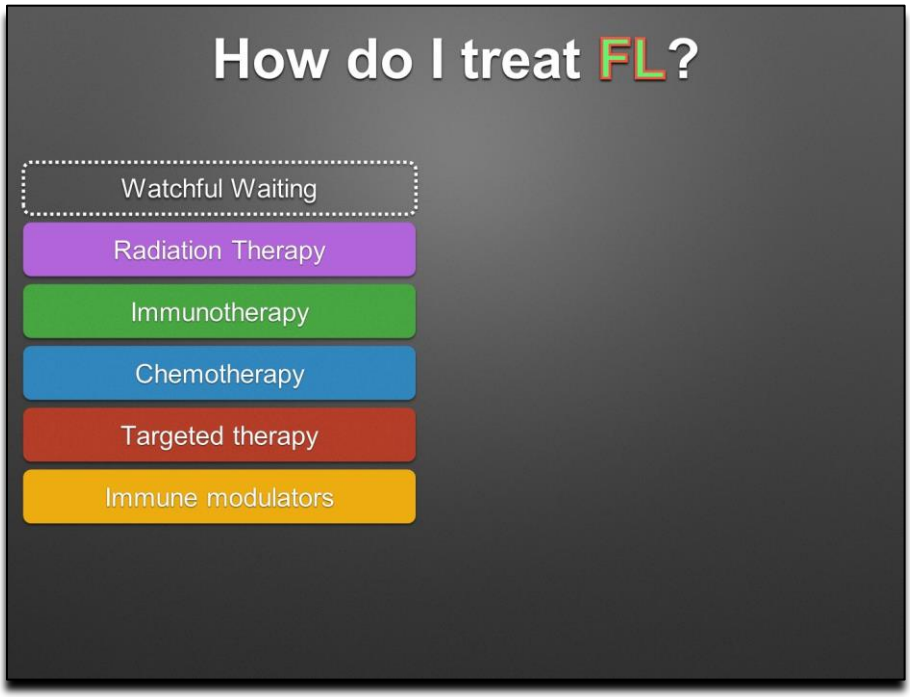
It is estimated that about 2 to 5%, depending on which series you're looking at, the risk of this phenomenon, of histological transformation, happening in patients with follicular lymphoma. And you may ask, why does it happen, how can we prevent it? The truth is, this is an area of active investigation, and our own laboratory is interested in evaluating what are the immunological factors that may contribute or allow this histological transformation event to occur in patients with follicular lymphoma.



How do I treat FL?

In this particular case, and in most cases with transformation of follicular lymphoma to a more aggressive malignancy -- and by the way, the more aggressive malignancy that typically follows is a diffuse large B-cell lymphoma or DLBCL, which is the prototype disease in the aggressive B-cell non-Hodgkin lymphoma category -- so once we have a diagnosis of DLBCL, the goal of therapy is to try to eradicate that aggressive component.

And we typically use chemoimmunotherapy. In this case, the patient was treated with R-CHOP and achieved a complete remission.

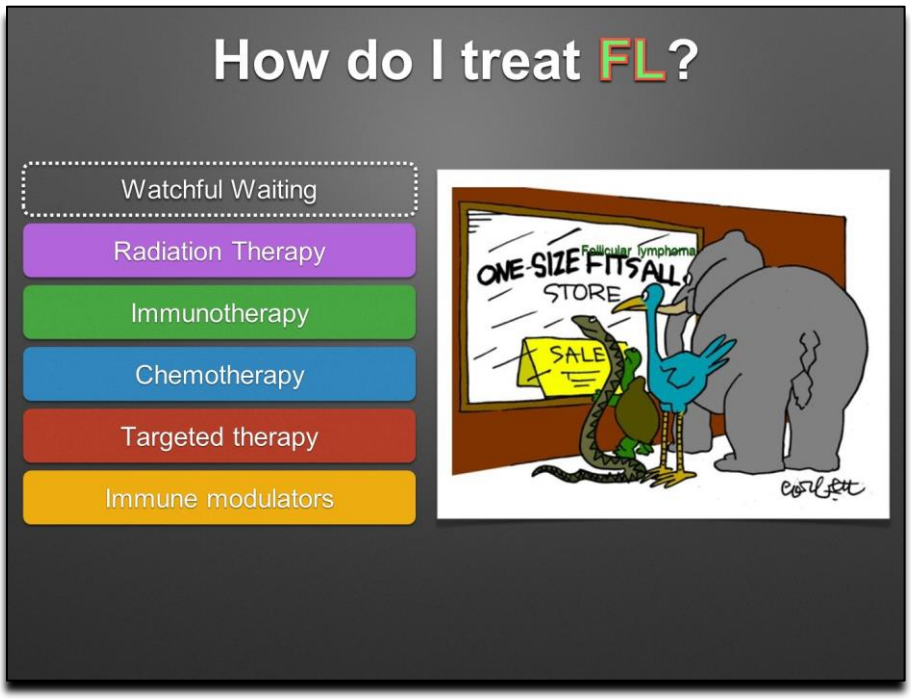


How do I treat FL?

So, as you have just listened, over the last four slides, there is truly not a single way where -- of how to approach a patient with follicular lymphoma. Follicular lymphoma, or indolent lymphomas in general, may present very differently. So if I see five patients in one morning with the same label of follicular lymphoma, it is very likely I will approach these patients differently, not because -- not only because their disease may have very different behaviors, but the patient themselves will have different characteristics.

And when we choose the way to manage these patients, we have to take into account biological factors from their disease, clinical factors regarding their presentation, and also patient preferences and values regarding what do we need to do to maximize the outcome here. Which, as you remember, is a combination of disease control, time, and quality of life.

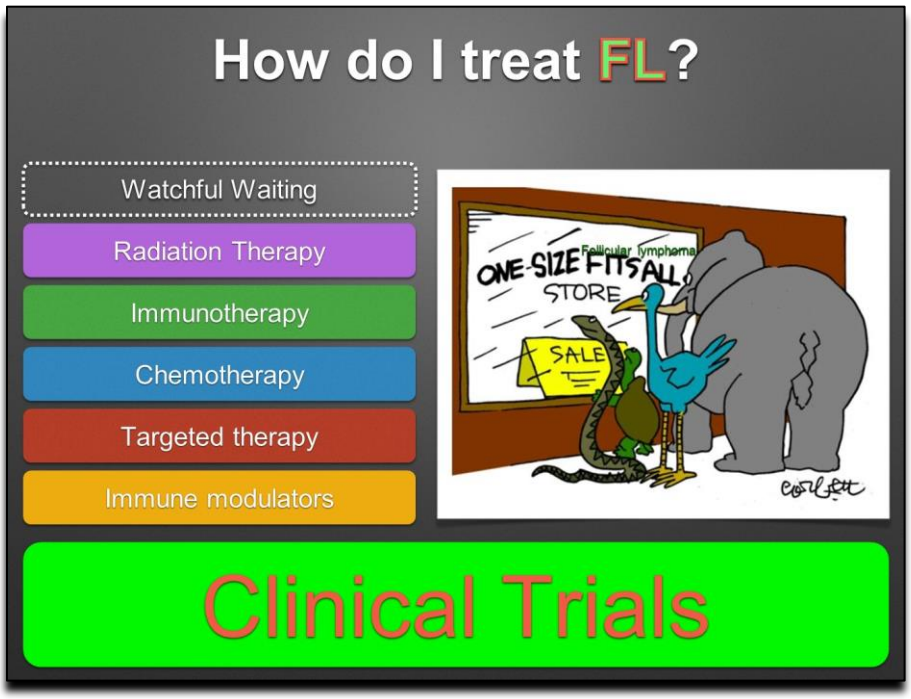
So there is a lot of buzz these days about individualized medicine -- individualized therapy, especially in cancer. And when people use these buzz words, they typically mean some sort of genetic profiling of the tumor, looking for specific mutations that can be targeted by specific drugs, or sometimes using cells to be modified, genetically and sent back to the patient, such as CAR T-cell therapy -- all of those, indeed, represent forms of individualized medicine.



How do I treat FL?

But as a lymphoma physician, to me, there's nothing more individualized than treating patients with indolent non-Hodgkin lymphoma, especially follicular lymphoma. There's truly not a one-size-fits-all type of approach in this disease, and we must look into the details of the case before we can make the best decision about one particular treatment decision -- actually, this is a decision of whether to treat or not to treat at all, and when treating, how to treat.

And this decision may evolve over the life of that patient if they have a relapse. And while we have this toolbox, as you can see on the left here, which has many tools, and thankfully, this toolbox continues to grow, with recent approvals in this space, bringing new hope for patients with follicular lymphoma, this is still not sufficient. I wish to see a day where I can tell a patient with follicular lymphoma that I will guarantee a cure, which is unfortunately not the case for most patients today.

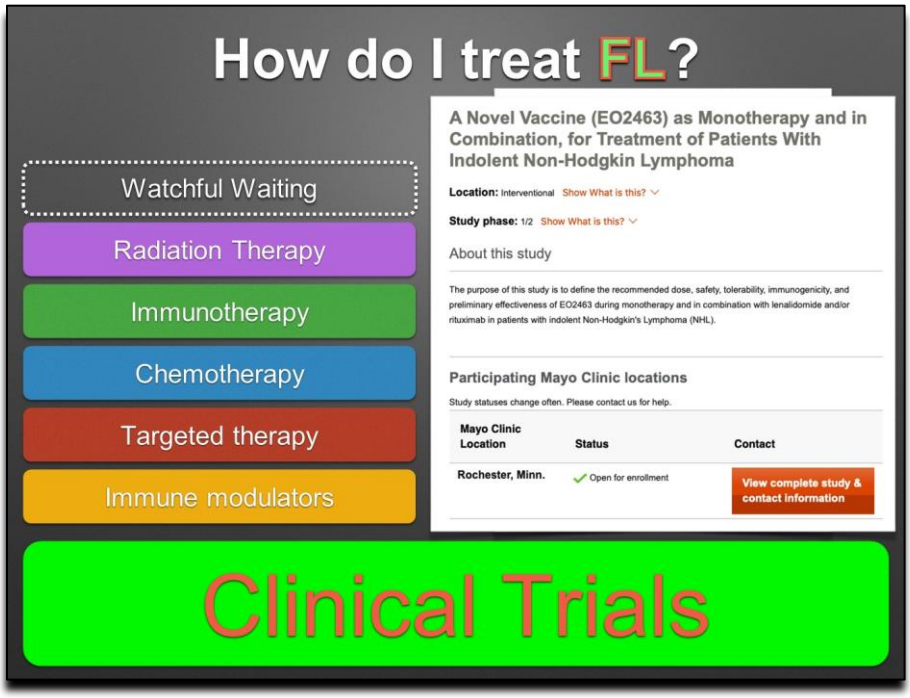


How do I treat FL?

So whenever you have a diagnosis of lymphoma, especially of follicular lymphoma or indolent lymphomas, I think the patient deserves to be considered for clinical trials, because that is the only way that we can guarantee a brighter future for patients with lymphoma and offer patients access to novel therapies for a disease that still needs to be improved. So if you want to learn more about clinical trials in follicular lymphoma or other lymphomas, you may reach out to places such as The Leukemia & Lymphoma Society.

How do I treat FL?

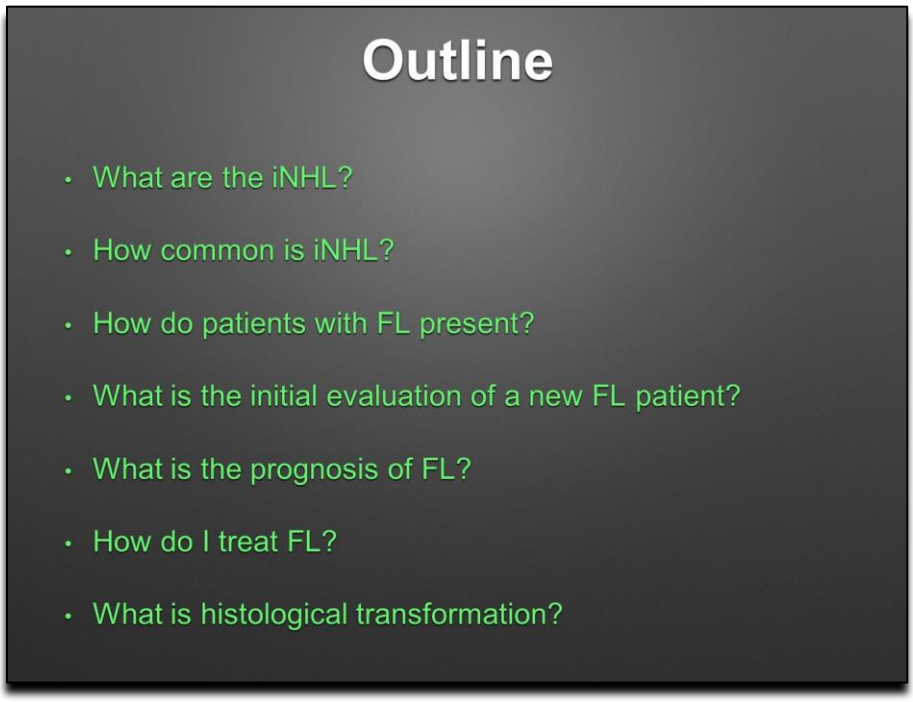
Or you may look into the clinical trials page at the Mayo Clinic. And, for example, if you went today and looked for follicular lymphoma clinical trials,



How do I treat FL?

you will come across one of our studies which is evaluating the use of an anti-lymphoma peptide vaccine for patients with indolent, non-Hodgkin lymphoma. So this study is open to patients who would be, for example, otherwise in watchful waiting. And in this study, we are testing if the use of this lymphoma vaccine can help patients who don't yet need treatment and would otherwise just be observing their lymphoma carefully.

This study is also open for patients who require active therapy. And we're combining the vaccine with active drugs, such as rituximab and lenalidomide. And the study is also open for patients with relapsed disease. So if you want to hear more about this study, I am more than happy to guide you in that direction later.



Outline

So we're coming to a conclusion of our program today. I just wanted to review with you what we have talked about, thus far.

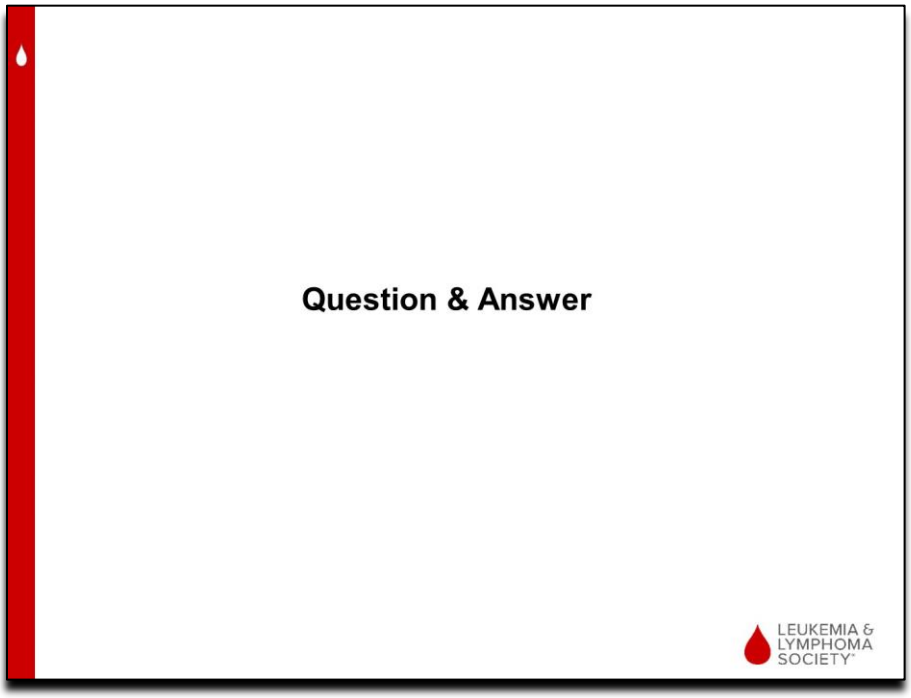
So at the beginning, we looked at this definition. So what are these diseases that we collectively call slow growing, non-Hodgkin lymphomas? And where do they fit into the broader lymphoma classification? Next, we looked at the epidemiology of patients with non-Hodgkin lymphoma, specifically remind you that we saw that non-Hodgkin lymphoma, in general, corresponds to 4% of all cancers diagnosed in the U.S. per year.

Of all non-Hodgkin lymphomas, slow growing types correspond to about 40% of those. And the prototype disease of that group is follicular lymphoma. Using follicular lymphoma, we looked at the general evaluation of a patient with indolent non-Hodgkin lymphoma, how they present to clinic, what are the tests that we require for the evaluation, how do we stage a patient. And then, we discussed, specifically, how to use the available prognostic tools to predict future of a given patient with lymphoma.

And we specifically talked about the FLIPI score and what the FLIPI can do and what the FLIPI cannot do for a patient and the lymphoma doctor. Next, I used a collection of some of my patients in clinic to illustrate to you how we can use different tools in this toolbox to manage patients with follicular lymphoma and with different situations, using patients with low burden that require no therapy, a patient with active symptoms that required treatment, and we then focused, at the very end, on this one, very particular phenomenon, which is the histological transformation, when a slow growing lymphoma becomes a fast-growing, aggressive lymphoma, and how important, how catastrophic that can be for the life of patient with indolent non-Hodgkin lymphoma.

Thank You

So, this brings me to the end of the program today. And I will turn it back to Lizette for managing the Q&A session. I really appreciate you all for joining today. Thank you for your time and I hope this was useful.



Question & Answer

Lizette Figueroa-Rivera

Well, thank you, so much Dr. Villasboas for your very informative presentation. As you mentioned, it is now time for our question-and-answer portion of our program.

And we'll take the first question from our web audience. Doctor, Elizabeth asks, when the slow growing non-Hodgkin lymphoma returns, is it worse than the first time? And how long before it returns?

J.C. Villasboas, M.D.
Thank you for the question. So, as you heard, follicular lymphoma, or these indolent non-Hodgkin lymphomas, may behave very differently. If we're going to try to look at the average, in many cases, it tends to return with a similar biological behavior, so the tendency to grow -- it tends to be similar. However, the response to treatment tends to decrease with additional lines of therapy.

So let me explain that a little bit, to make sure I'm not using too much jargon. So, the likelihood of a patient with follicular lymphoma, for example, to respond to the first treatment we give, is much higher than that same patient to respond to the second treatment we give at the time of the relapse. And that's even without any change in the growth pattern of the lymphoma itself, meaning the speed of growth, which defines the indolent category.

I think that addresses the first part of the question. The second part is, does it tend to come back in the same place? Well, that's truly unpredictable. In patients with follicular lymphoma, or indolent lymphoma for that matter, I will typically tend to do surveillance on the whole body and not just the area where the lymphoma initially presented. I have a fair amount of patients that had lymphoma in the neck and had a recurrence in the abdomen. Soif I only paid attention to the neck, I could have missed that relapse, that is outside the original region. I hope that answers.

Lizette Figueroa-Rivera
Thank you. Now, we'll take the next question from our telephone audience, please.

Cathleen
Yes. I was just wondering -- I've recently been diagnosed with a scleroderma. I'm going to have to spell it. It's S-C-A-R-L-O derma. Would that have anything to do with the follicular lymphoma?

J.C. Villasboas, M.D.
So, scleroderma is an autoimmune disease that typically affects the skin, but can also affect internal organs. While it's different from lymphoma, there is an association between this particular type of autoimmune disease and the occurrence, whether at the same time or in the future, of non-Hodgkin lymphoma. So in the patient who is diagnosed with this disease, most of the time, the doctor will look around to make sure they are not missing a lymphoma.

But if they didn't see it, then you're fine, it doesn't mean that you will have it, for sure, by any means. So, it's not the same, but there is an association between the disease and the future likelihood of developing lymphoma. I hope that answers.

Lizette Figueroa-Rivera
Thank you. And the next question, Alla is asking, being a very rare type of non-Hodgkin lymphoma, how is mantle cell lymphoma benefiting from research conducted on other, more commonly occurring types of non-Hodgkin lymphoma?

J.D. Villasboas, M.D.
Thank you for the question. That's a very important question. As you've heard, mantle cell lymphoma has a behavior very unique, in and of itself. But despite its unique behavior, it is still a B-cell non-Hodgkin lymphoma. And many of the treatments that we use for other B-cell non-Hodgkin lymphomas are also effective in mantle cell lymphoma. Take the example of BTK inhibitors, which were initially

approved for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, that were found to be very active in mantle cell lymphoma.

Another good example is lenalidomide, a drug that we initially started to use in multiple myeloma and is very active mantle in cell lymphoma. And then, maybe last, in the case of CAR T-cell therapy, which were initially approved for diffuse large B-cell lymphoma, has now been approved for mantle cell lymphoma as well and has provided many patients with a long, stable remission.

So despite its rarity, there are common pathways and common targets for these lymphomas, especially because they share many features, coming all from B-cell origin. And, on top of that, despite being rare, there are consortia around the country and around the world, where lymphoma providers like us here, will get together and collect patients with these more rare lymphomas, so that we can design and conduct clinical trials for even the more rare types.

Lizette Figuero-Rivera
Thank you. And also, another type, Waldenstrom's macroglobulinemia -- William is asking, are there any new therapies for Waldenstrom's?

J.C. Villasboas, M.D.
Yeah, Waldenstrom is a very interesting disease. In many places, including us here, it is a disease that is shared by both lymphoma doctors, like myself and myeloma doctors, like other of my colleagues. I don't treat myeloma, but I still see patients with Waldenstrom, because it may present in kind of a halfway disease that has features of both of these categories.

So in terms of newer therapies, I'm very excited about the use of, again, the immune system to control patients with Waldenstrom disease. I am particularly excited about the bispecific antibodies. I'm also excited about the possibility of using CAR T-cell therapy to treat patients with Waldenstrom lymphoma. In fact, I have a patient with Waldenstrom that is currently receiving an in-house, CAR T-cell for Waldenstrom, after having been through, literally, all possible prior lines of therapy. And we hope to see some good outcomes therapy.

So in general, I believe that the future lies on harnessing the power of the immune system to control these diseases, including in the case of Waldenstrom.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our phone audience, please.

Operator
Our phone question comes from Laura, calling from South Dakota. Please state your question.

Laura
I was diagnosed with Waldenstrom's. And then, they did a watch and wait for 16 years. And then, finally in '21, it showed up in some soft tissue in my low back. They did a biopsy and it was the B-cell lymphoma. And so, it obviously, had left my bone marrow. And, I got along fine. The first two therapies went through my port and they did not work.

The third therapy was an oral pill called CALQUENCE® (acalabrutinib). It has worked beautifully, until about six months ago. And now, I have some more soft tissue tumors in my low back and gluteal [muscles that make up the buttock area]. And they're growing. And they've been watching them and they're growing. And the doctor suggested a biopsy. I don't know if the biopsy would be to see if it's transforming to an aggressive state.

I am hesitant about the biopsy, because when they first biopsied that first mass, it spread so fast afterwards. Within two weeks, I had it in both my breasts. So I kind of blamed the biopsy for spreading

it. I might be wrong. But anyway, he's suggesting, now, another biopsy, because the CALQUENCE® evidently is not working as well as it had been. What would you suggest?

J.D. Villasboas, M.D.
Laura, I believe the biopsy is advised. I would agree with that. What I would be looking for, in that biopsy, as you rightfully pointed out, is to make sure we're not dealing with a different disease, an

evolution to a higher grade lymphoma. But at the same time, there are things we can learn from that biopsy regarding why the CALQUENCE® stopped working.

So there are genetic tests that can be done to determine if there's a mutation on the site where the CALQUENCE® acts. And if that's the case, there are CALQUENCE®-like drugs that can be used following. And if we had that information, it may help your doctor decide what's the best next step.

Lizette Figueroa-Rivera
Thank you. And the next question comes from Diane. Diane is asking, does a lymph node biopsy come before a bone marrow biopsy? In other words, does it matter which is done first?

J.C. Villasboas, M.D.
Good question. So, again, hard to generalize. But, I'll say, for the average patient with indolent B-cell non-Hodgkin lymphoma, first, they will have the lymph node biopsied, because that's typically the most visible site of involvement, whether it's because they noticed a lymph node growth, or the CT scan picked up the growth, internally. So, most patients will come to the clinic already with a lymph node biopsy.

And I want to stress a point here, that I may not have made very clear on the presentation, is that if there is a suspicion of lymphoma, fine needle aspiration, which is often done for other cancers, like breast cancer, does not work. It has to be a core needle biopsy. It has to be a good amount of tissue, or even better, a full lymph node excision. But most of the patients are going to come to me with that lymph node biopsy already done, showing the lymphoma.

And then we're going to decide whether a bone marrow biopsy is necessary. There are exceptions, of patients who come already with a bone marrow, either because they were anemic, they had low blood counts, and they went looking into the bone marrow first and saw the lymphoma there. In those cases, if the CT scan indicates a similar pattern everywhere, we may not need a lymph node biopsy to confirm.

However, the definition of many of these lymphomas, as you've heard, there are nearly 100 different types. And their definition typically has to do with which location of the lymph node structure the cancer is. So sometimes we see cells in the bone marrow. They are, for sure, cancerous. But we cannot tell for sure whether it's marginal zone versus some other type because we are not examining the lymph node itself. So, we may need to compliment the diagnostic information that we get from the bone marrow with the lymph node architecture.

Lizette Figueroa-Rivera
Thank you. And the next question coming from Angie. Angie is asking, are there any lifestyle choices that have proven effective for avoiding relapse, for example, diet, exercise, stress management, supplements, or anything to avoid?

J.C. Villasboas, M.D.
Great question. I get asked that all the time. And I counsel patients on it, too. So, I will answer that by highlighting what is known and rooted on the highest rigor of scientific information we have. Okay. So, in terms of supplements, diet, lifestyle, stress -- there's a lot of common sense. Right?

But in the case of lymphoma, there is a clear association between activity levels, exercise, and lymphoma relapse. And I would like to highlight the study done here at the Mayo Clinic and at the University of Iowa, where we evaluated the patients at the time of their diagnosis. And we followed them, longitudinally, that means as they were moving on, after diagnosis and in the many months to years later.

And we evaluated their exercise level. And what was very clear from that study, is that the patients who were either above the exercise level of the average for their age, or those who increased their exercise following the diagnosis of lymphoma -- those two groups of patients -- they did remarkably better, in terms of outcomes, compared to the patients who are not in that group, meaning, compared to the patients who are not exercising at all or the patients who didn't increase their exercise activity following a diagnosis.

You may listen to what I'm saying and reply with commenting, well, that's very expected. Everyone knows that exercise is good, because it prevents heart attacks and strokes and that kills a lot of people. So, what does it have to do with lymphoma, particularly. And the key finding of that study, is that we actually calculated something called the lymphoma-specific mortality. So we counted the patients who had died from lymphoma, not just died, in general, from heart diseases, strokes.

So, when we calculated the lymphoma-specific mortality, that was decreased in patients who were exercising more. So that is the strongest link that I can point to, between a lifestyle intervention and the improvement of lymphoma-specific outcomes. However, this is not an interventional study. So patients were not randomized between going on an exercise routine versus staying on their regular lifestyle, which would be the ultimate way to prove there's a causal association between exercise level and lymphoma outcomes.

But there's plenty of ancillary data in other fields, including the field of immunology, that indicates that exercise activates cells of the immune system that are known to be responsible for lymphoma control, such as natural killer cells. So, even though the link is not direct, there is a hypothesis that, by exercising more, patients may activate the good cells of the immune system that helps keep the lymphoma under control. There are other association studies between other lifestyle factors, such as stress and diet. But the link is, by no means as strong as the one that I pointed out for exercise.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience, please.

Operator
The phone question comes from Cathleen, calling from Virginia. Please state your question.

Cathleen
I've heard that there are testing being done in labs outside of the United States, where they identified the specific gene sequences of different targets, such as cancer. And what these labs do, is take the patient's blood, and it is a very specific test that they do, to come up with a therapy that would be designed to target these cancer cells, based on your genome, I think they call it, or perhaps it's a DNA test.

I don't know if there's anything like that available here. I don't know if that would be something that really doesn't work or be dangerous. I would just like to know what you have heard, as a physician, about these kinds of tests, because they're very expensive, and somewhat complicated to get the blood to the labs. And the one I'm thinking of, it's in Greece. Could you just tell me what you know about that and how you feel about it?

J.C. Villasboas, M.D.
Absolutely. Thank you, Cathleen, for your question. So, just to recap, you're asking what is the value of these individualized medicine tests that are being offered in different places, including places outside the U.S., to help us decide what is the best treatment for patients with lymphoma. So, I would like to go back to that slide, where I had the different animals looking at the store which says one-size-fits-all. And going back to my comment, then, about this concept of personalized or individualized medicine.

To be very simple, I think that, as a point of history that we sit right now, in 2023, if I were a patient with follicular lymphoma, or any lymphoma, for that matter, I would not spend out-of-pocket money looking for these individualized therapies at the time of diagnosis. There is no proven benefit that these will yield any additional information, beyond what we already know, without the tests.

If, however, you are able to participate in a research study that offers such tests, especially if they're not going to be charged to you, because after all, they're going to be used to learn new things for future, I would encourage you to do that. And again, we are working on such a research program here at Mayo, where you -- once you have a diagnosis of lymphoma, we will look at the genes that make up your lymphoma, and also look at the genes that make up your whole DNA, to try to learn from this, what would be, perhaps, the first therapy.

But by all means, this is on the research area. This is not standard, clinical practice. There are no studies that prove that learning about the lymphoma DNA, up front, will change the trajectory of patients with lymphoma. And there are, indeed, studies that tested that, formally. And those studies were negative, meaning that they did not improve patient outcomes.

So the information that the physician needs, is right in front of him or her. These tests are still in evolution. And I would personally not use your personal money to go after these, as of right now. However, a research study is a different situation, and I would highly encourage you to participate if one is available near you.

Lizette Figueroa-Rivera
Thank you. And thank you, Cathleen, for the question. We do have an episode on *The Bloodline with LLS*, our patient podcast that was recently released, discussing genomics. So, you could definitely get more information on Genomics, on *thebloodline.org*.

Doctor, our next question is from Robert. Robert's asking, if there is a relationship between marginal zone lymphoma or treatment with rituximab, with peripheral neuropathy.

J.C. Villasboas, M.D.
Great question, Robert. So, marginal zone lymphoma, amongst the slow growing types of lymphoma, is one that could have, as a clinical characteristic, the production of antibodies. And just as a background, maybe just going back for a moment, marginal zone lymphomas belong to the B-cell non-Hodgkin lymphoma category. B-cells, the normal ones, are the cells of the blood that make antibodies to fight infections, amongst other things.

And when you have a B-cell that becomes cancerous, and if that cell becomes a marginal zone lymphoma, it may retain the ability to produce antibodies, which are proteins. And these antibodies are, let's call them cancerous antibodies. They are not normal, and they are usually of the same type. We call those clonal -- monoclonal proteins. And sometimes, these antibodies can actually stick to nerves and cause damage.

This is a phenomenon that we see with other antibody-producing cancers, such as multiple myeloma and Waldenstrom. And there are specific tests that we can do on the nerve or in the blood to see if the antibody has a tendency to cause damage to the nerve fiber itself. So yes, in some cases, the marginal zone cell will produce an antibody. And the antibody will cause damage to the nerves.

The other question was about whether the rituximab itself may cause damage to the nerves. I will answer it this way -- typically not. That is not a common side effect of rituximab, by all means. But there may be rare cases in which rituximab could lead, either directly or indirectly to nerve damage. But this is exceedingly rare. And in those cases, I usually make sure that we investigate all the other, more likely possibilities before we blame rituximab for it. So, it is very rare, and most of the time, it's not a problem for patients treated with rituximab. What could happen sometimes is, because rituximab is a very active drug in marginal zone lymphoma, if these cells, the marginal zone cells, are attacked by rituximab and they are full of antibodies that are produced, then these antibodies could cause damage to the nerve, the bursting of the cell can lead to an increase of blood levels of these antibodies that may lead to further damage of the nerve.

It wasn't the rituximab, in fact, the rituximab was very effective in killing the cancer. It is the downstream effect of the cancer-killing that may cause nerve damage, at least temporarily.

Lizette Figueroa-Rivera
Thank you. And is there a treatment, doctor, for peripheral neuropathy?

J.C. Villasboas, M.D.
In fact, depending on the cause, rituximab could be used to treat peripheral neuropathy. Unfortunately, peripheral neuropathy remains one of the hardest to treat side effects from the drugs we have. We have good drugs to help with painful neuropathy – gabapentin (Neurontin®), Cymbalta® (duloxetine), for example. But we don't typically have good treatments for the numbness and the paresthesia type -- the sensory, but non-painful type of neuropathy.

Oftentimes, we involve colleagues in our neurology department here, because they may have clinical trials and other options. There are alternatives, complementary medicine treatments that may help, such as acupuncture, nerve stimulation, something called Scrambler Therapy, can also be used. But oftentimes, very unfortunately, this still remains an unmet need for patients with lymphoma.

Lizette Figueroa-Rivera
Thank you. And Margo is asking, after radiation therapy for GI MALT lymphoma, what is the risk of the MALT returning, or a different cancer presenting?

J.C. Villasboas, M.D.
Yeah, so I'll start with the end. The risk of a different cancer, meaning a cancer that is caused directly by the radiation, such as a sarcoma, is very small. And we're talking about way less than 1 in 1,000 cases, especially because, in most cases, the radiation amount is not terribly high.

The risk of MALT returning -- if it's been at least two years from the end of the therapy and the MALT has not returned, as evidenced by surveillance endoscopies, there is still a chance the MALT will return in the long run. And I will quote at least a 40% chance in 10 years. But there are cases of MALT lymphoma that can be completely eradicated with radiation.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Anna. Anna is asking, how does disease management and treatment recommendations differ for younger patients, younger patients under 40?

J.C. Villasboas, M.D.
Great question. So we know, for example, if we just stick with follicular as our exemplar disease, that patients who are diagnosed below the age of 60, even if all the other factors are the same, compared to patients who are over the age 60, their life expectancy tends to be affected by the diagnosis of lymphoma. That is because, obviously, they're going to have more time with that disease and more opportunity for relapse.

At the same time, they also have more opportunity to experience long-term side effects of the treatments that we have. Some of the side effects may be the occurrence of a second malignancy. Unfortunately, some of the chemotherapy drugs we have increase the risk of a second type, usually an aggressive leukemia, later in life, typically 10 to 20 years later. At the same time, the immunotherapy drugs, while very useful and effective, decreases your chance of fighting infections. So these patients are more at risk, especially if exposed at prolonged amount of time, to drugs that affect the immune system. They are at risk of moderate to severe infections.

So, it is a fine balance, because, again, I'm focusing the discussion, once again on slow growing indolent lymphomas, which are diseases that are expected to return, if given enough time. We have to really balance the choice of therapy, the timing of when to start, and what to start against the expectation for life expectancy for that given patient.

So, we really have to individualize the choice of treatment to that patient, knowing that, at least as of right now, I will refrain from telling a patient, with rare exceptions, with follicular lymphoma, that we are going to do a treatment and we don't expect it will ever come back. Those are not words that typically will come out of my mouth in clinic.

Lizette Figueroa-Rivera
Thank you. And Lisa is asking, are treatment options and outcomes the same for men as women? Basically, do different sexes respond the same?

J.D. Villasboas, M.D.
Yeah, interestingly, in lymphoma in general, there tends to be a slight difference in outcomes, when we look at gender/sex. It seems, especially for the aggressive lymphomas, that women do better than men, for reasons that remain unexplained. I personally believe it has something to do with the modulation of the immune system by the sex hormones present in women, estrogen particularly. But this is a general theme scene we see with lymphoma, that women tend to do better than men.

Lizette Figueroa-Rivera
Thank you. Now, I'll take the next question from our telephone audience, please.

Operator
Our phone question comes from Shawn, calling from Pennsylvania. Please state your question.

Shawn
Yes, my question is, I suffer from aggressive, large, B-cell non-Hodgkin lymphoma. And my question is, what's my life expectancy with that? And what are the treatment options do I have for that?

J.D. Villasboas, M.D.
Thank you, Shawn. So just stating back the question to you -- you told me you have a diagnosis of one of the aggressive, B-cell, non-Hodgkin lymphoma, DLBCL or diffuse, large B-cell lymphoma, which is, just to put this in context, again, it's not of the diseases that we have discussed today. But I will be able to answer your question anyway.

So there are different therapies for diffuse large B-cell lymphoma. And these are typically chosen with the goal of cure, of eradicating the disease for the patient. They are often a combination of chemotherapy with immunotherapy drugs. The most common cocktail or combination of drugs is called R-CHOP, R-C-H-O-P. And in terms of prognosis, one of the most useful prognostic tools we have for DLBCL is something called EFS24 or event-free survival at 24 months from diagnosis.

So if you were diagnosed with large cell lymphoma and you were treated with chemoimmunotherapy and you achieved a remission, and you have stayed in remission without any relapse or need for new therapies, for 24 months, counting from the date of your diagnosis, we have demonstrated in studies

done here, validated in international cohorts, that your likelihood of living to 100 years is equal to that of your high school classmates. What that means is, your life expectancy, if you are able to remain in remission for two years after initial treatment for large cell lymphoma, is normalized against gender- and age-matched peers in the United States.

Lizette Figueroa-Rivera
Thank you. And our next question, doctor, Reggie is asking, what does a survivorship care plan look like for an indolent non-Hodgkin lymphoma patient? For example, how many scans or follow-up appointments?

J.C. Villasboas, M.D.
Thank you for that question. So, the question is about how do we follow or surveil patients who have diagnoses of indolent lymphoma. There is a lot, especially according to the age of that patient, how long that patient has stayed in remission, what was the duration of first remission, and the initial sites of involvement. I will tell you what I typically do in clinic.

So let's say I see patient today. It's a new diagnosis of follicular lymphoma. I decide there's no symptom and the disease is small volume and we're going to watch. I would normally bring that patient back in three months. And I will just examine the patient, do some blood work, bring them again, three months later, so six months from diagnosis and repeat the scan.

And what I'm trying to do with that six-month scan is to determine if there's any growth rate between the two scans and try to calculate what the inclination of the curve, in terms of growth. And if it seemed like it's a very flat curve, without any significant change, I would essentially continue to see the patient every three months, for the first two years, but try to scan no more often than every six to 12 months, leaning towards the 12-month, meaning less scans than more scans.

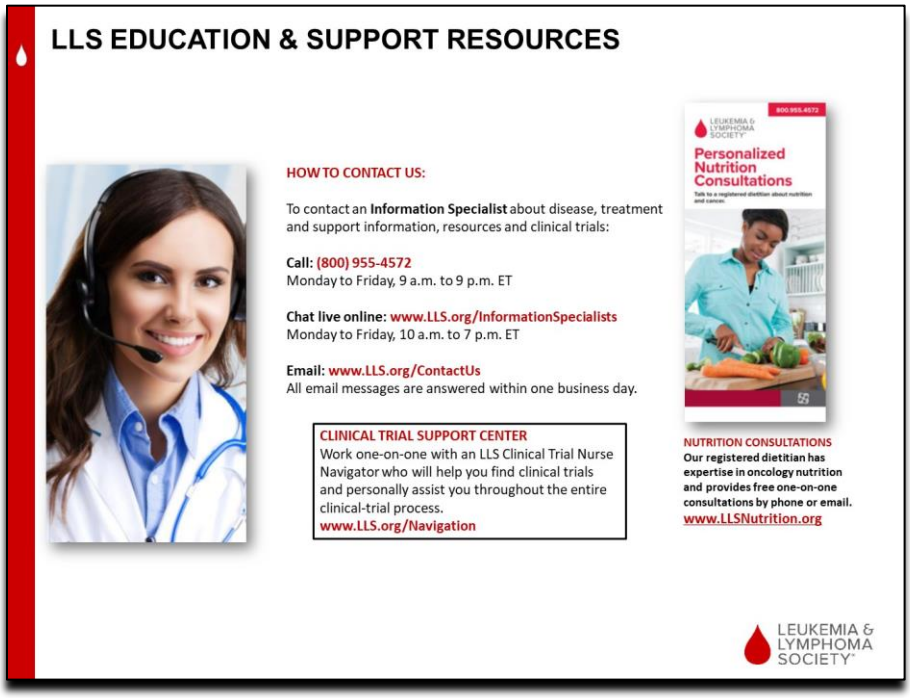
Interestingly, there is a study done in follicular lymphoma, especially those who were already treated once, that looked at the pattern of identification or relapse, so essentially tried to categorize patients between those who were identified to have a relapse, because of symptoms or complaints, versus those who were identified because of a surveillance scan, so a silent relapse with no clinical signs or symptoms. And that study, which is a multi-center study, showed no difference in survival for patients with follicular lymphoma, whether they were found to have a relapse, because they complained about something or because of a CT scan.

And I have that discussion very frankly with my patients. And in many cases, we decide, based on that data, to just continue to surveil the patient with clinical examination, so a visit, history, physical exam, blood work, but no scans. So if I do a scan, I tend to do it once a year, as long as I don't have any suspicion for a change in the rate of growth, or if I have any suspicion for histological transformation to a more aggressive lymphoma.

Lizette Figueroa-Rivera
Thank you, doctor. And Greg and I have the same question for you. Out of all of the new and up-and-coming treatments, what are the ones that you are more excited about?

J.D. Villasboas, M.D.
Great. Thank you for that question. So, what am I most excited about, in the terms of lymphoma treatment, in general, and follicular lymphoma and indolent lymphomas, in particular? I will say it again, I'm very excited about the future of using the immune system to control these diseases. We are seeing remarkable outcomes with therapies such as CAR T-cell therapy. We are seeing patients who are in remission for a good amount of time, we're talking 40 months or plus, after having been treated with everything else under the sun.

We are seeing similar degree of responses, meaning 80-90% response rates with these newer, bispecific antibodies, again, in patients who have been through everything, including stem cell transplantation. In fact, there is already an approval for a drug, which does exactly that in patients with follicular lymphoma. And these are proven -- are shown to be very durable responses, so they not only respond -- causes cancer to shrink, but it seems like the cancer stays shrunk and in remission for a good amount of time.



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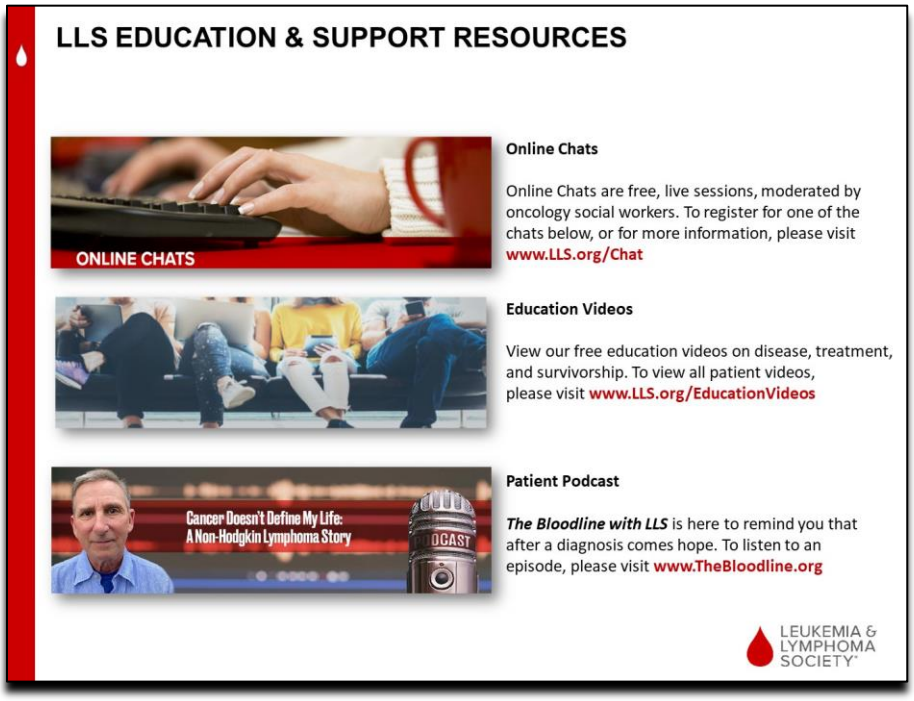
So, I'm very hopeful for the future, where we're going to be evaluating the best sequence for these drugs. But right now, there's not a lot of guidance of how they should be utilized. And I'm also very hopeful to see how we are going to combine these newer immunotherapy drugs with other drugs that work also very well, such as lenalidomide, rituximab, even chemotherapy. So I think the future has a lot of promise, in terms of using the immune system and its multiple ways to control lymphoma.

Lizette Figueroa-Rivera
Great. Thank you so much. And thank you, Greg, for that question, which was our final question today. Again, a special thanks to Dr. Villasboas for sharing your expertise with us and for your continued dedication to our blood cancer patients.

If we weren't able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572, from 9 a.m. to 9 p.m., Eastern Time, or go to lls.org/informationspecialist, to chat online or email us at lls.org/contactus. LLS also has a Clinical Trial Support Center, where clinical trial nurse navigators will personally assist you throughout the entire clinical trial process. You may reach them at lls.org/navigation.



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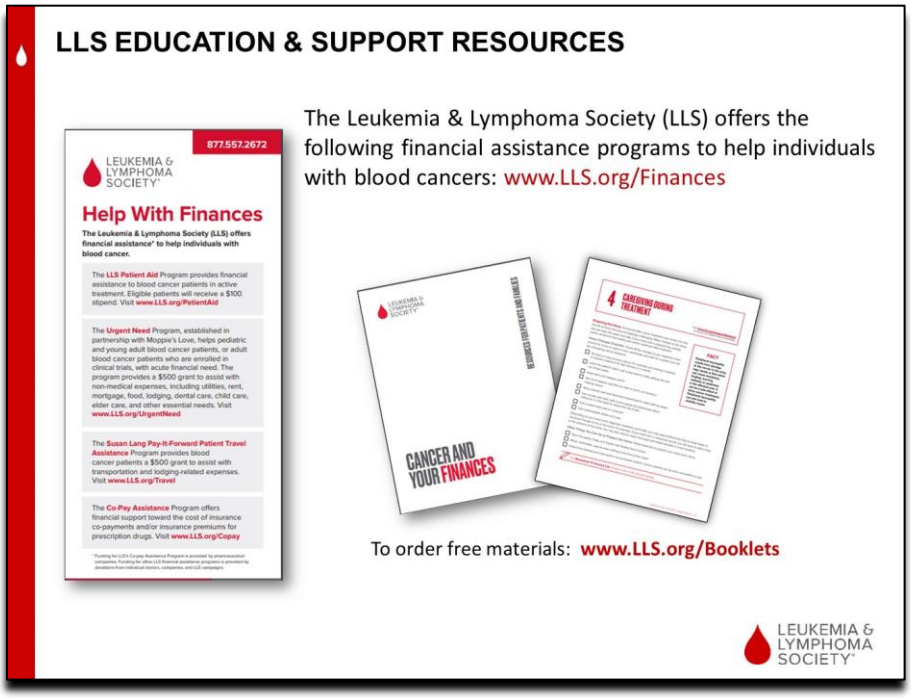
The Leukemia & Lymphoma Society is a proud partner with Dollar For, a national, non-profit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free. Please visit lls.org/dollarfor -- that is lls.org/dollarfor -- for more information.



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Again, we'd like to acknowledge and thank Genentech, Inc., and Biogen and Kite, a Gilead company, for their support.

Thank You

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please consider sharing your story with us. Your words of encouragement can bring hope and confidence to others. You may submit your story at lls.org/voices-of-lls-submission. Again, lls.org/voices-of-lls-submission. Thank you so much and take good care.