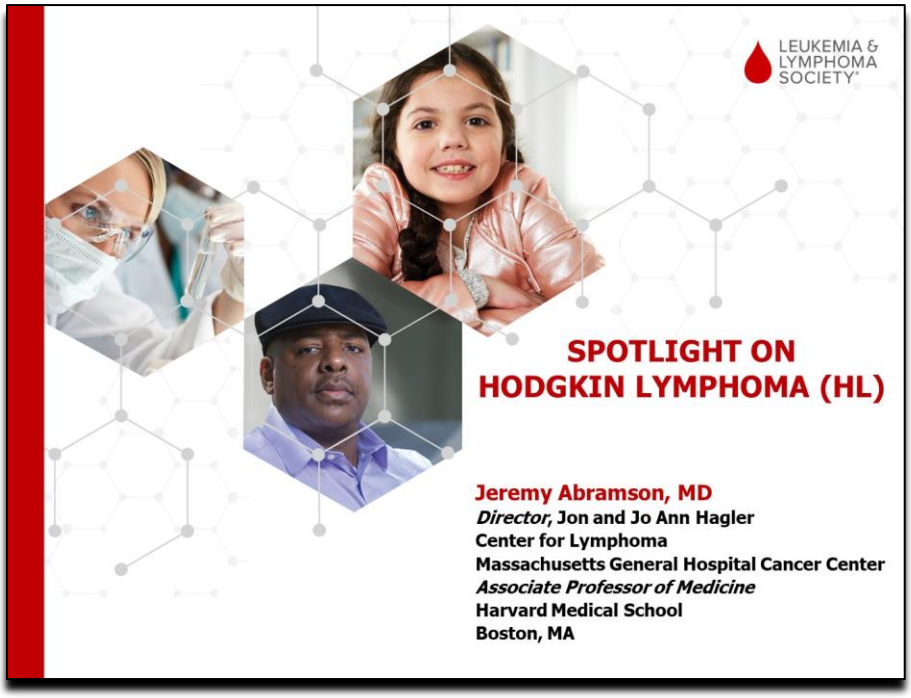


Spotlight on Hodgkin Lymphoma

Operator
Greetings, and welcome to Spotlight on Hodgkin Lymphoma, a live telephone and web education program. At this time, all participants are in a listen-only mode. 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. Jeremy Abramson for volunteering his time and sharing his expertise for this. Now Erin, a Hodgkin lymphoma survivor, will share some opening remarks.

Welcoming Remarks

Erin Cummings
Hello, everyone. I'm Erin Cummings, and I'm delighted to welcome you to today's event. As somebody who has lived through Hodgkin lymphoma for many years, I understand the importance of keeping up with the latest treatment for Hodgkin's and knowing what to expect post-treatment.

I am truly thankful to The Leukemia & Lymphoma Society and Dr. Jeremy Abramson from the Massachusetts General Hospital Cancer Center for making this event possible. I have been a cancer survivor for 52 years now. I was diagnosed with Hodgkin's in 1972 when I was 15 years old. My prognosis at the time was poor. I relapsed twice in the first year. I was getting several rounds of cobalt radiation, followed by MOPP chemotherapy. I was terrified, lonely, and horribly sick from the treatment. I desperately wanted to be a normal teenage kid, and cancer was not a part of the plan.

When I reached the five-year remission point in my recovery, I started to breathe again and allowed myself to believe in the future. And I was lucky. However, being declared cured didn't mean the end of my cancer ordeal. The treatments I received years ago have led to various health issues like subsequent cancers, heart disease, and pulmonary fibrosis, among others.

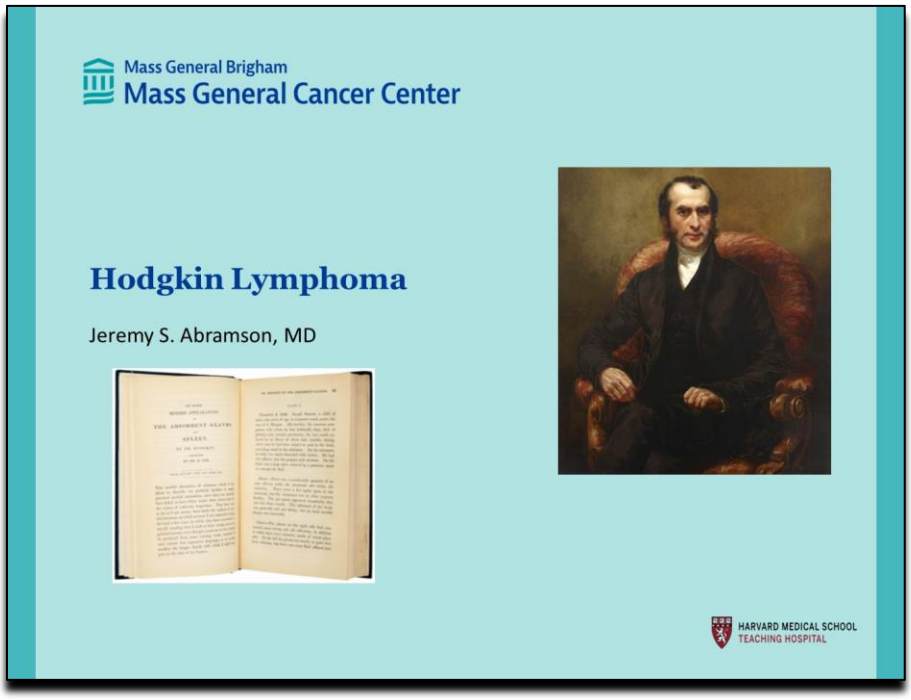
These are some of those late effects of past cancer treatments. As challenging as they have been for me, however, they have not been insurmountable, not by a long shot. Twenty years ago today, I had open heart surgery at Massachusetts General Hospital to replace my aortic valve. Eighteen months later, I completed my sixth marathon. Again, I was lucky, lucky to have the best medical care possible.

For the past two years, I've been advocating for my fellow Hodgkin's survivors, ensuring that they understand the risks of late effects, empowering them to take charge of their health, and offering reassurance that they are not alone. I co-founded Hodgkin's International, a nonprofit organization dedicated to this cause. You may find us at http://www.hodgkinsinternational.org/.

When I participated in my first *Light the Night* Walk many years ago, my aim was simply to kick back to a new situation that played a vital role in advancing Hodgkin's research. I had no idea that LLS would continue to light the way for me and for so many others. I hope that my story is a message of hope to you. With everything that I've been through, I am still here. I am living proof that miracles do happen. Believe, and thank you.

Disclosures

Lizette Figueroa-Rivera
Thank you so much, Erin, and thank you to your organization on shedding light into long-term and late effects of Hodgkin lymphoma.

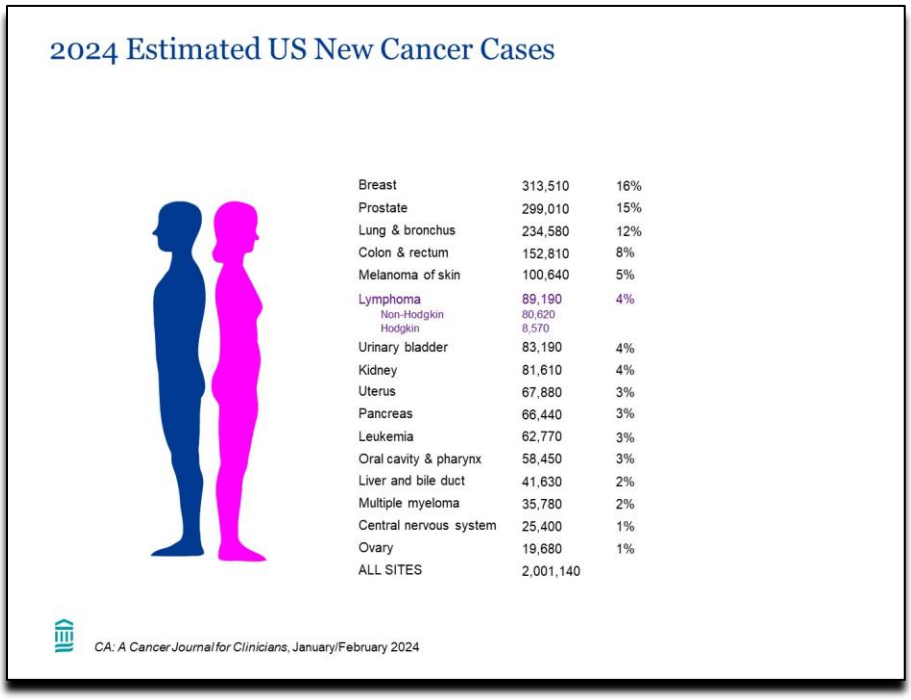


Hodgkin Lymphoma

I am now pleased to introduce our speaker, Jeremy Abramson, Director, Jon and Jo Ann Hagler Center for Lymphoma at Massachusetts General Hospital Cancer Center, an Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts. Dr. Abramson, I am now privileged to turn the program over to you.

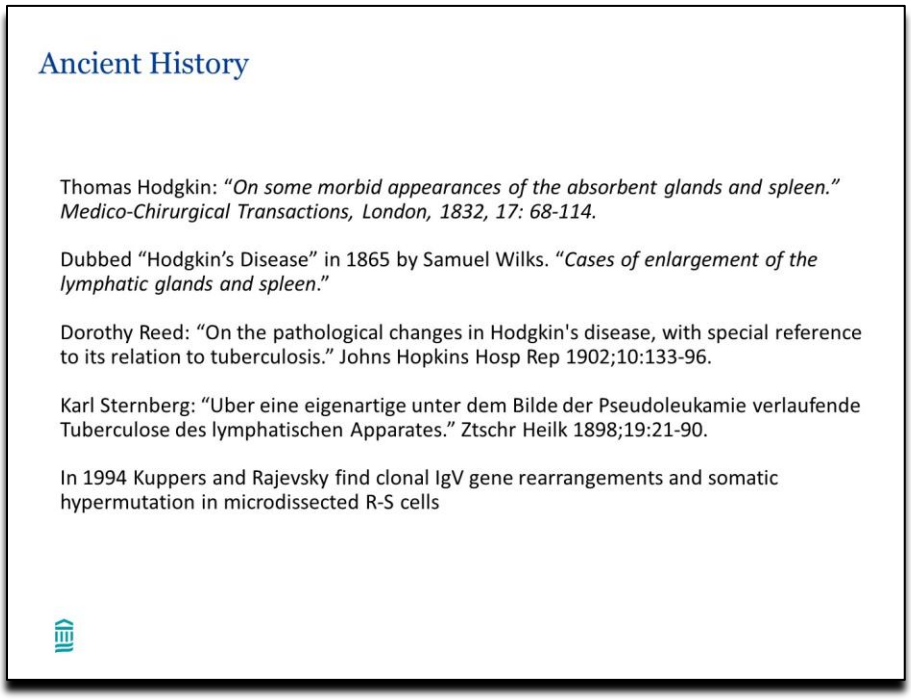
Dr. Jeremy Abramson
Well, thank you very much, Lizette, and I want to also thank Erin for that beautiful story filled with cautionary tales about the potential perils of treatment, but also highlighting the great successes that we've achieved, and highlighting the progress that we have made and still need to make.

So, it will be my great pleasure today to talk with you about the evolving progress and how we manage Hodgkin lymphoma. This handsome devil on the slide right here is none other than Thomas Hodgkin himself, as well as a picture of his original manuscript, which described this disease many, many years ago.



2024 Estimated US New Cancer Cases

Hodgkin lymphoma is not particularly common, though it is not rare. In the United States, there will be just about 8,500 new cases of Hodgkin lymphoma diagnosed every year. And the vast majority of those will be cured with only about 800 deaths related to Hodgkin lymphoma in the United States every year, though obviously that is 800 too many. It dwarfs in comparison to, say, the non-Hodgkin lymphomas, where there are over 80,000 new cases diagnosed every year. And lymphomas in general are, as you can see, the sixth most common cancer in both men and women.



Ancient History

The history of Hodgkin lymphoma is actually quite interesting. Not surprisingly, it begins with Thomas Hodgkin. And in 1832, Thomas Hodgkin described a series of cases that he recognized while working at the Guy's Hospital in London. Thomas Hodgkin was a pathologist. He was not a medical oncologist or internist. And so, he described Hodgkin lymphoma based on what he observed in patients in autopsies that he had conducted at that time. And he had noticed that there were a small number of patients who had developed fairly gradual illnesses that led to weight loss, fevers, enlarged lymph nodes and spleens. And ultimately, patients succumbed to their disease. It was thought at the time that this was probably related to tuberculosis or some other infectious disease. And, of course, TB was quite common at that time.

He didn't know what it was, but he didn't think it was a traditional cancer, as it was considered at the time, or an obvious infectious disease like tuberculosis. And so, he described these cases and called them on some morbid appearances of absorbent glands and spleens and published this in 1832. Absorbent glands are what today we would call lymph nodes.

About 30 years later, another pathologist in London named Samuel Wilks described another series of cases and dubbed these cases Hodgkin's disease, naming it after Thomas Hodgkin, who originally had described the initial cases 30 years earlier. But at that time, it was still unknown whether this represented an infectious disease or a malignancy. And believe it or not, it wasn't until just about the turn of the century, in 1902, when Dorothy Reed, one of the female pioneers in medicine, also a pathologist, took it upon herself to try and determine what made Hodgkin's disease different from other illnesses. And could she identify a particular cause?

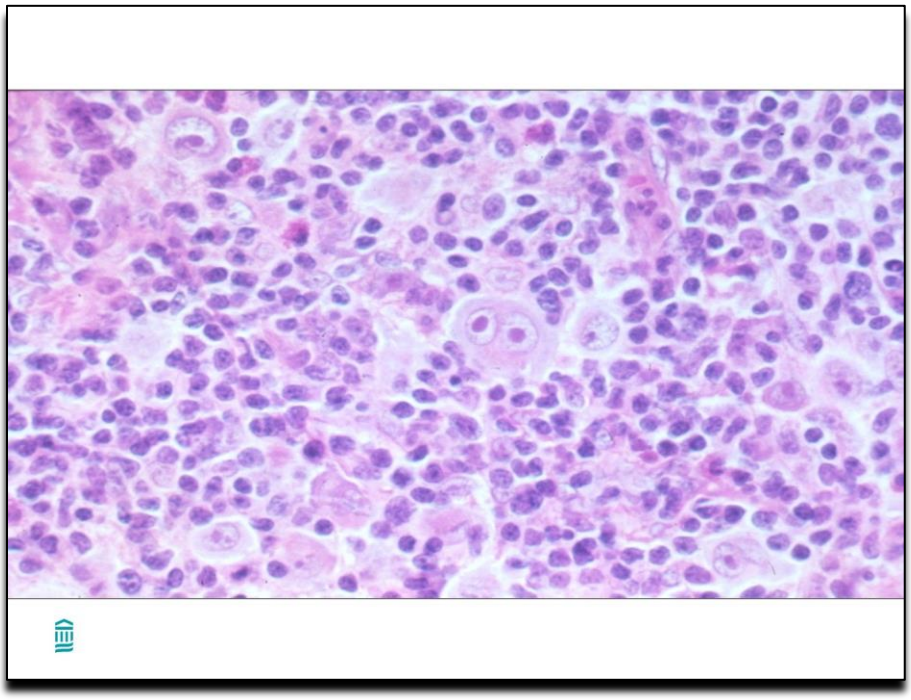
And what she identified in comparing Hodgkin's disease biopsies to those of tuberculosis was in the setting of Hodgkin's disease, the vast majority of the cells in the biopsy specimen were the body's normal healthy inflammatory cells that would otherwise be reacting to an infection, for example. But, they didn't see evidence

of an infection. But, Dorothy Reed did identify that there was very large, unusual looking cells making up a very small minority of the overall cells in the tumor.

And she posited for the first time that these very rare cells, representing only about 1 percent to 2 percent of all of the cells under the biopsy in the microscope, actually represented cancer cells and for the first time proposed that these cells represented malignant cells. And that was what was unique among this disease relative to infections like tuberculosis.

It turns out around the same--actually a few years earlier, Karl Sternberg, in Austria, described the same thing. This was before the Internet, so it took a long time to learn about each other's discovery. And these cells we now recognize to be the malignant cells of Hodgkin lymphoma. Here in the United States, we call them Reed-Sternberg cells, whereas in Austria, they call them Sternberg-Reed cells because of national pride.

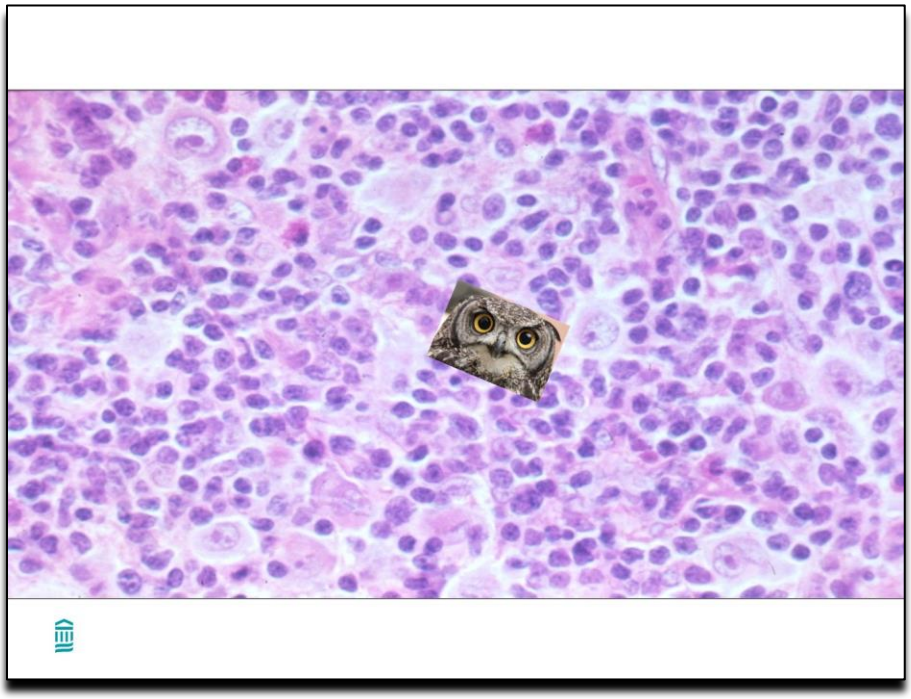
But, Reed-Sternberg cells are now the underlying malignant cause clearly recognized to be the underlying source of Hodgkin's disease. But importantly, that didn't tell us what those malignant cells were. And it took many years. And in fact, it wasn't, believe it or not, until 1994 when the technology became available by Ralf Küppers and Klaus Rajewsky, MD, who micro dissected out these cells, these Reed-Sternberg cells, from within the Hodgkin lymphoma specimen and sequenced their genes. And by sequencing the genes, they determined that these were, in fact, mutated, crippled B lymphocytes. And so, for a disease that was described in 1832, named in 1865 as Hodgkin's disease, it wasn't until 1994 when it was determined officially to be a lymphoma. And so, in 1994, there forward, we now more appropriately call this disease Hodgkin lymphoma.



Image

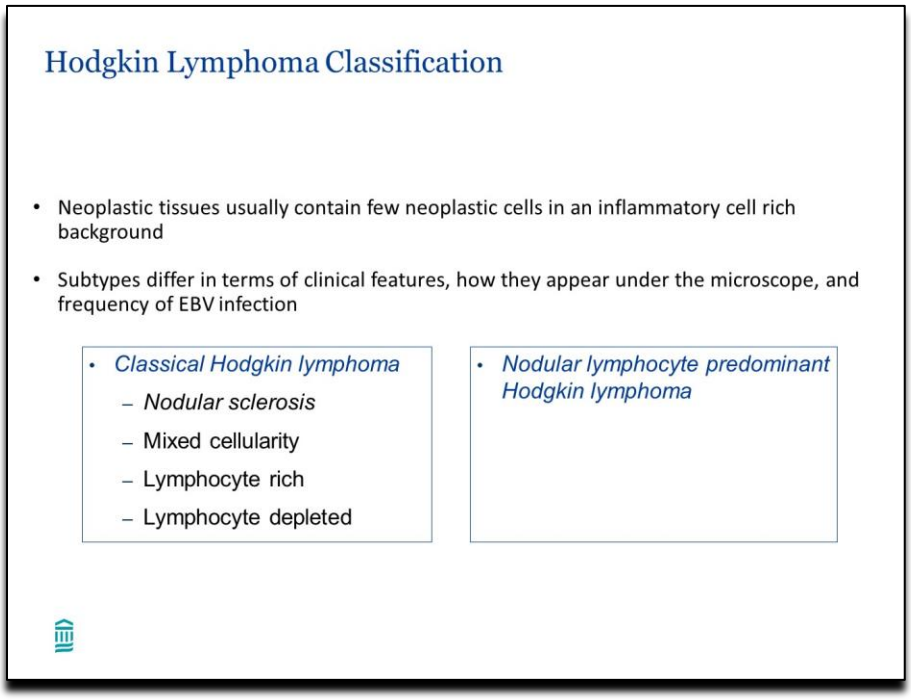
And this is what Dorothy Reed and Carl Sternberg saw under the microscope. The vast majority of the cells that you're seeing there are normal inflammatory cells within the body, normal lymphocytes, histiocytes,

eosinophils, cells that fight off infection in our body. But in the middle of that screen, you'll see a very unusual cell with a lot of what we call cytoplasm surrounding two odd nuclei with big, bright nucleoli within the nuclei that give it a classic appearance of so-called owl's eyes.



Image

And if you look closely, you might be able to discern the image of an owl looking out at you from this biopsy specimen, and that being the classic Reed-Sternberg cell of Hodgkin lymphoma.



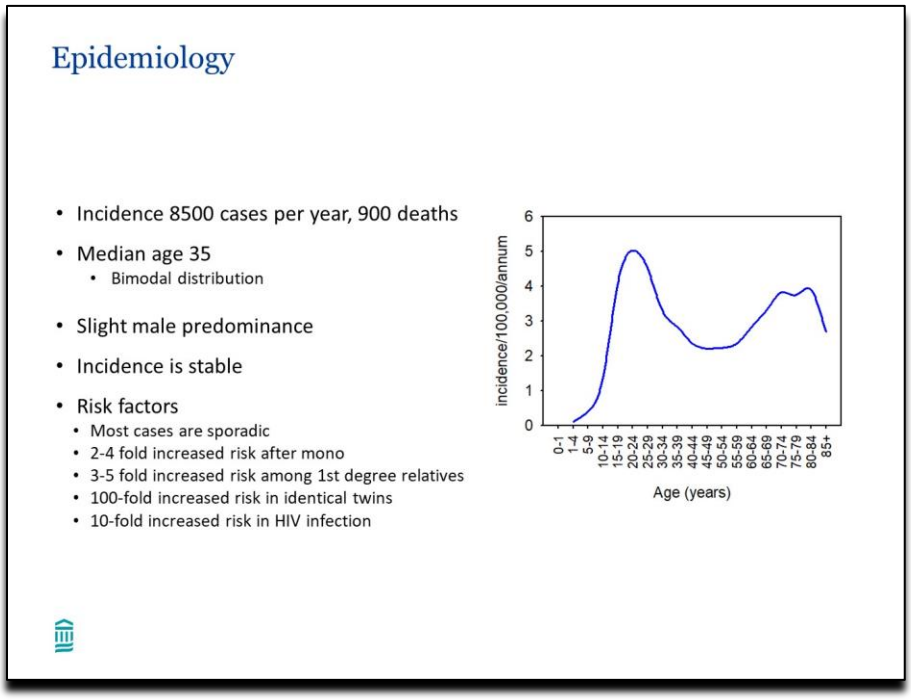
Hodgkin Lymphoma Classification

We now know that Hodgkin lymphoma comes in multiple different subtypes. What is characteristic about all of them are that the biopsy specimens, whether they're lymph nodes, spleens, or bone marrow include these very few actual malignant or neoplastic cells in a dense inflammatory network, which are non-cancerous cells but actually can support growth of the Hodgkin lymphoma.

The subtypes differ in terms of their appearance under the microscope. And we can classify Hodgkin lymphoma in general in two major categories. And 95 percent of Hodgkin lymphoma cases are called classical Hodgkin lymphoma, whereas only a small subset, 5 percent, fit into a very unique disease called nodular lymphocyte-predominant Hodgkin lymphoma, which is really a very separate disease from Hodgkin lymphoma. And we're going to be primarily talking about classical Hodgkin lymphoma today.

Within classical Hodgkin lymphoma, there are four subtypes that are really determined based on how they appear under the microscope. The most common is called nodular sclerosis Hodgkin lymphoma. This is the variant the occurs most commonly in young people, occurs most commonly in the neck and in the middle of the chest, and is characterized by dense bands of these fibrotic tissue, or sclerosis, running through the biopsy specimen.

Mixed cellularity is the next most common subtype, followed by lymphocyte-rich, and then very rare would be lymphocyte-depleted. And so, these are terms you'll see in, for example, biopsy reports that are diagnosing Hodgkin lymphoma.



Epidemiology

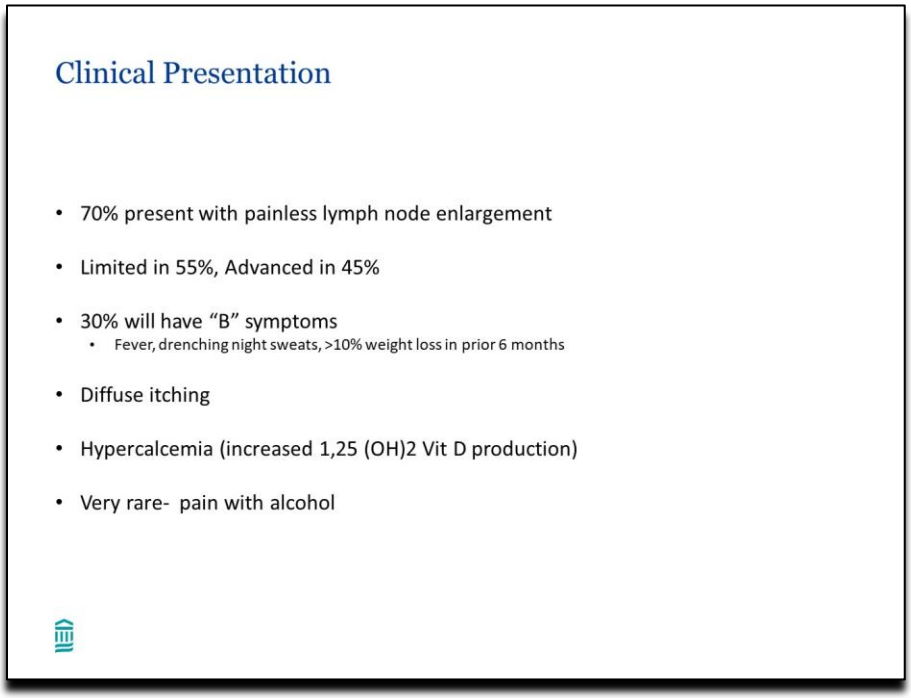
I mentioned that there are just over 8,000 new cases every year diagnosed in the United States, and between 800 and 900 deaths, showing that the majority of patients are, indeed, cured of their disease with very few deaths related to Hodgkin lymphoma in the modern era. This is most commonly a disease of young people. And you can see on this graph that shows you the incidence based on age, on the X axis, the most common age to be diagnosed is in the years really between 15 and 20, where there's been a declining incidence, and then a rising incidence, again, over the age of 60. So, older adults can, indeed, develop Hodgkin lymphoma.

There is a slight male predominance, but it occurs in both genders. There has not been an increasing incidence or decreasing incidence over time. And most patients don't have any underlying risk factors for having developed Hodgkin lymphoma, which means it's a sporadic or randomly occurring disease. Now, some cases of Hodgkin lymphoma will have the Epstein-Barr virus identified within the Hodgkin lymphoma. Epstein-Barr virus is a virus that causes infectious mononucleosis. And virtually everybody has been exposed to the Epstein-Barr virus. It's a ubiquitous virus. But, people who have been exposed have just about a two- to four-fold increased risk of developing Hodgkin lymphoma after previously having been diagnosed with infectious mononucleosis.

But importantly, the vast majority of people who have developed infectious mononucleosis from EBV will never develop Hodgkin lymphoma, so a slightly increased risk of an extremely low risk is still an extremely low risk.

There is a slightly higher risk, about a three- to five-fold increased risk, among first-degree family members. That means parents, siblings, or children. This likely reflects some shared environmental interactions, although discrete environmental risks have not been identified. There's clearly genetic underlying disposition, as highlighted by the hundredfold increased risk of developing Hodgkin lymphoma if an identical twin has Hodgkin lymphoma.

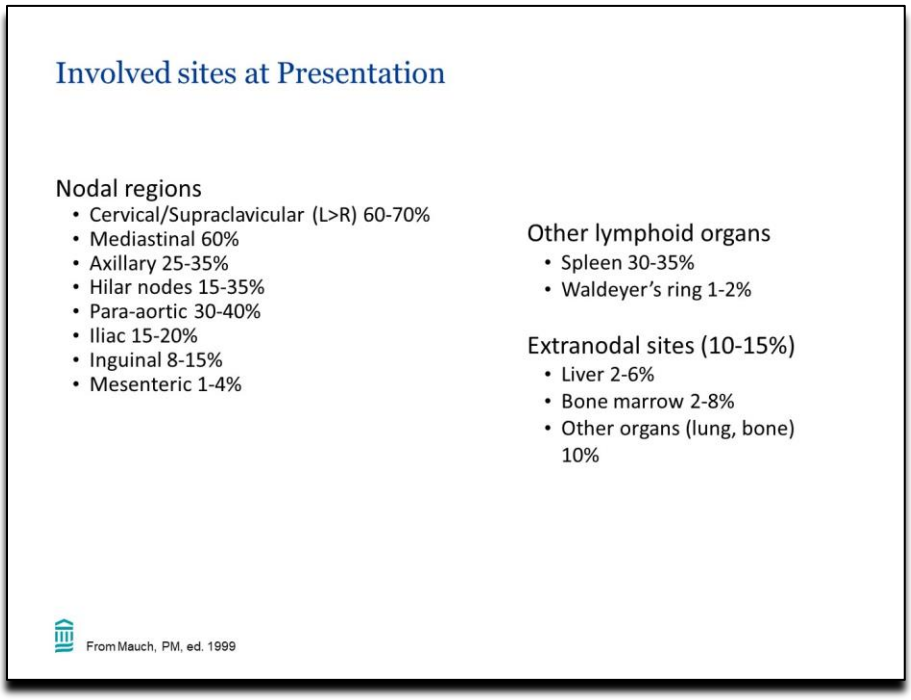
And there is an increased risk in a setting of immune suppression, and most notable in patients with HIV infection, due to the immune suppression they're in--have about a tenfold risk of developing Hodgkin lymphoma in people living with HIV. But, most cases have no underlying risk factors identified.



Clinical Presentation

The most common presentation for Hodgkin lymphoma is a painless and large lymph node, so somebody noticing an enlarged lymph node in their neck or under their arm or in their groin. Most patients will present what we call limited stage and a smaller proportion with advanced stage. And I'll go through in a bit what that means. Just about a third of patients will present with what we call B symptoms. B symptoms are defined as presence of fevers, which have no other cause, drenching night sweats that really soak through the bed sheets or bed clothes every single night, an unintentional weight loss of more than 10 percent of body weight over prior six months. So, these are classic B symptoms of Hodgkin lymphoma but again only present in a minority of people.

Diffuse itching, the medical term is pruritus, can occur in a small minority of people, as can elevated calcium levels due to increased conversion of vitamin D within the Hodgkin lymphoma itself. And very rarely, people will note that they have pain in their lymph nodes when they take sips of alcohol, although that's less than a fraction of a percent of people with Hodgkin lymphoma.

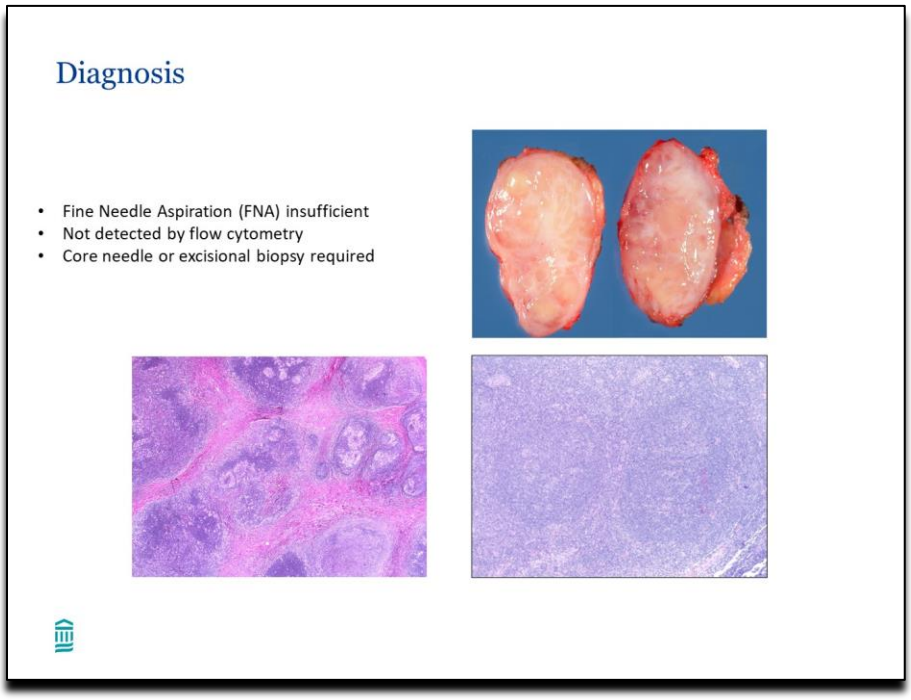


Involved Sites at Presentation

As far as where we see Hodgkin lymphoma identified, the most common location is in the neck. These are so-called cervical lymph nodes, which are present in about 60 percent to 70 percent of people with Hodgkin lymphoma. The middle of the chest, otherwise known as the mediastinum, follows at a close second, and followed there by lymph nodes under the arms, which are called axillary lymph nodes.

Other lymph nodes within the lungs, called hilar lymph nodes, can be involved, abdominal or pelvic lymph nodes less commonly involved, as seen here. Other lymphoid organs, such as the spleen, can be involved in about a third of people. And Waldeyer's ring, which is a fancy term for the tonsillar tissue in the back of the throat, is involved in a couple of percent of people.

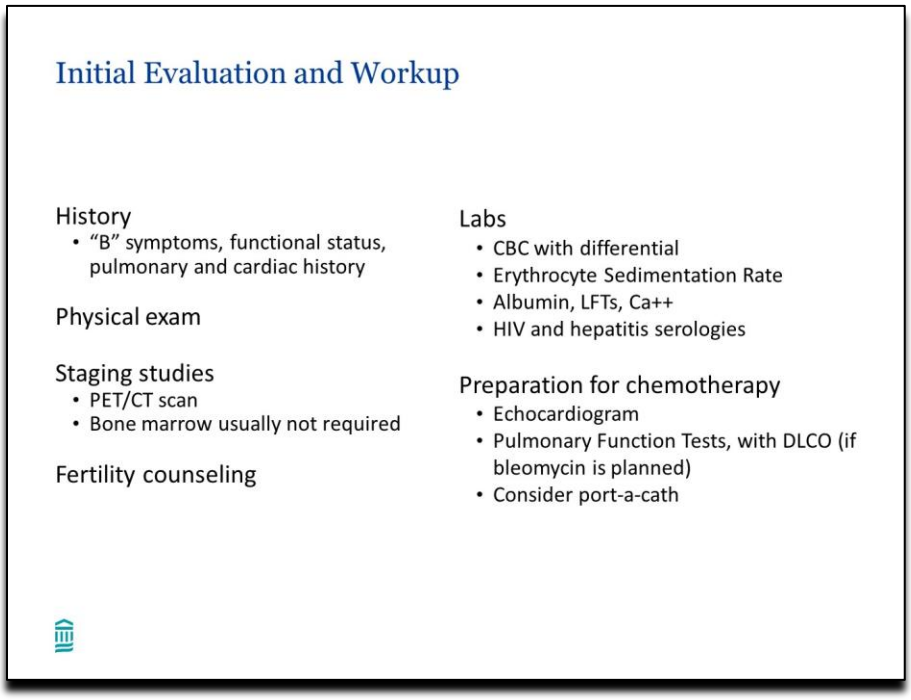
And then, places other than lymph nodes or lymphoid organs, so-called extranodal locations, are involved in about 10 percent to 15 percent of people with Hodgkin lymphoma, not commonly. And that includes the liver, the bone marrow, or rarely other organs such as the lung or the skeleton.



Diagnosis

We make the diagnosis by looking at the tumor under the microscope. You can see an example of a lymph node that has been excised on the upper right. And if you look carefully, you can see that there are these fleshy bands running through that lymph node. And that's the sclerosis of nodular sclerosis classic Hodgkin lymphoma.

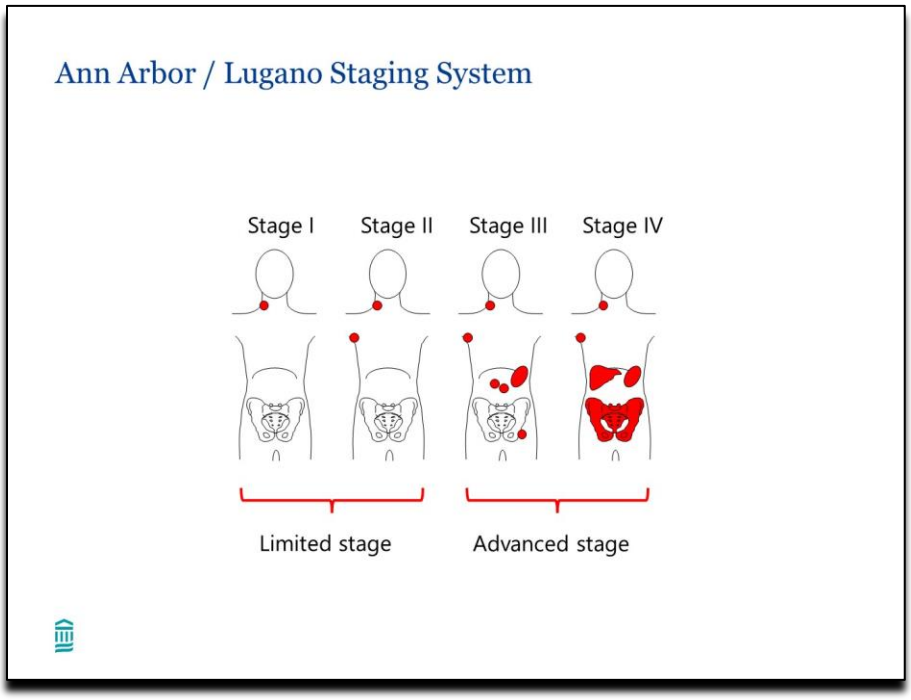
You can see it better under the microscope under the lower left-hand panel, where you can see these sort of areas of lymphoid tissues with these bands of pink running across them. And that's the fibrotic tissue of nodular sclerosis Hodgkin lymphoma, a very characteristic appearance. You can compare that with a low power view to the right of that, where you can see these vague nodules, if you look carefully, these sort of two circles sitting kind of side by side. That vaguely nodular appearance is consistent with the microscopic appearance of nodular lymphocyte-predominant Hodgkin lymphoma. Because the tumor cells are located few and far between, a larger biopsy is preferred. So, I always prefer to have a surgical biopsy, a lymph node actually removed. But if lymph nodes are not easily accessible, then core needle biopsies are utilized, and then we can follow up with surgery if that needle biopsy is insufficiently diagnostic.



Initial Evaluation and Workup

Once we make a diagnosis of Hodgkin lymphoma, we take a careful history and a physical, we have the stage of the Hodgkin lymphoma, which means determining where it is in the body. We do that with a PET CT scan. We used to do more invasive staging techniques, such as with bone marrow biopsies. And really, back in the old days, before CAT scans, we even did open surgeries and spleen and liver biopsies, but that's certainly no longer required. We do basic laboratory testing, including blood counts, chemistry tests. We check pregnancy tests in women of childbearing years and look for infections that might become exacerbated by chemotherapy, such as HIV and hepatitis. We do testing that is necessary prior to starting chemotherapy. That includes an echocardiogram to look at the heart function. It includes pulmonary function tests if we're going to be using bleomycin, one of the long-existing standard drugs in Hodgkin lymphoma.

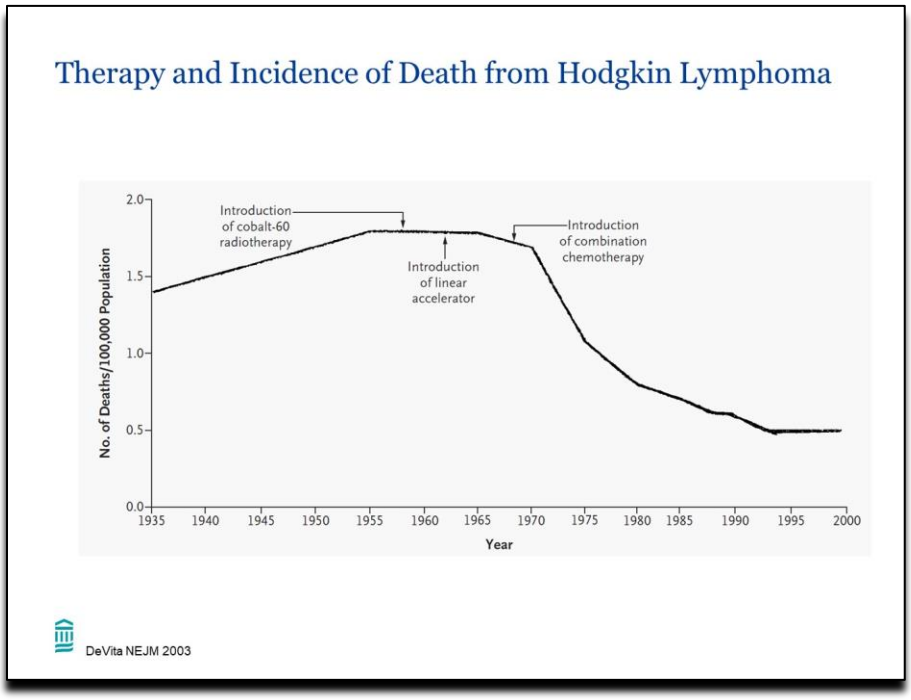
We consider whether we need to give the chemotherapy through a special device called a port-a-cath. And we talk about the risk of infertility and ways to preserve fertility for patients undergoing chemotherapy, though the risk of infertility with the standard front-line treatment for Hodgkin lymphoma today is thankfully quite low.



Ann Arbor / Lugano Staging System

The staging, as I mentioned, is done with a PET-CT scan, which is a modern highly sensitive staging. If lymphoma is in a single region of the body, we call it Stage 1. If it's located in two different lymph--two or more different lymph node regions but all on the same half of the body, above or below the diaphragm, we call that Stage 2. If we have lymphoid disease above and below the diaphragm, we call it Stage 3. And if it's in places other than lymph nodes, meaning extranodal sites, we call it Stage 4.

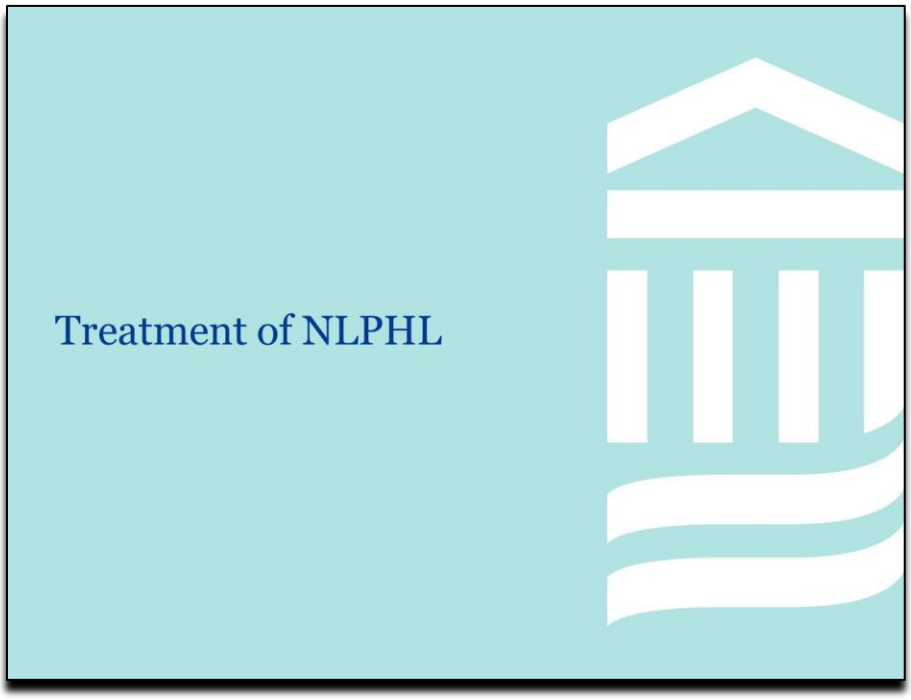
Now, in the setting of Hodgkin lymphoma, we typically group Stages 1 and 2 together and call that limited stage disease, and Stage 3 and 4 together and call that advanced stage disease. And so, you'll commonly hear the terms limited and advanced stage being used as a more simplified way to refer to stages.



Therapy and Incidence of Death from Hodgkin Lymphoma

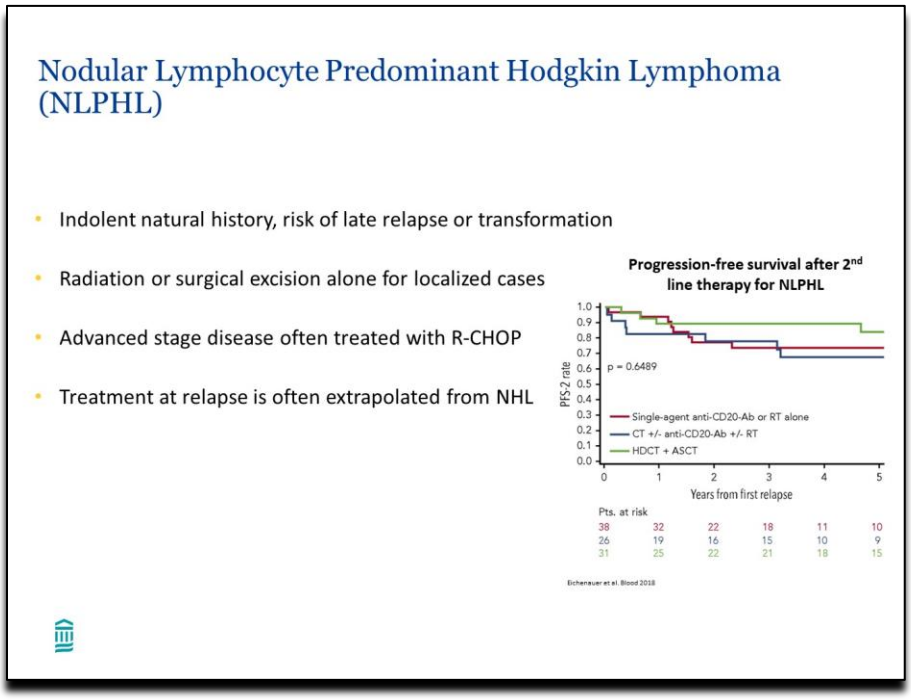
Now historically, when Thomas Hodgkin described this disease, it was a uniformly fatal disease. That has dramatically changed over time. Initial radiation was developed in the 1950s in terms of cobalt radiation, followed by modern radiation with a linear accelerator developed in the 1960s.

But, it wasn't until the advent of systemic chemotherapy, combination chemotherapy, which was developed at the National Cancer Institute in the United States, after which you see a dramatic decline in the incidence of death from Hodgkin lymphoma, making the introduction of chemotherapy for Hodgkin lymphoma one of the greatest advances in modern medicine.



Treatment of NLPHL

Let's think about some specific treatments.



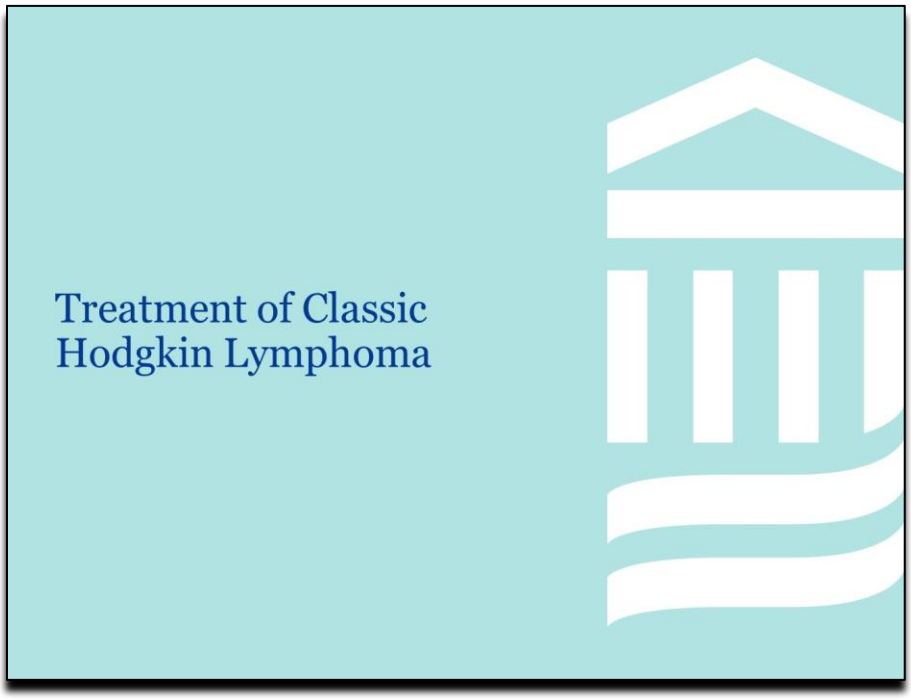
Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

I want to spend just a minute thinking about nodular lymphocyte-predominant Hodgkin lymphoma because it is completely different from classical Hodgkin lymphoma. Unlike classical Hodgkin lymphoma, this disease follows a very indolent natural history. It may progress minimally over time and may never become life-threatening, even without treatment. It does, even after effective treatment, however, have risk of late relapse or even transformation into more aggressive types of lymphoma. So, these patients do require lifelong monitoring.

For patients with localized disease, radiation or surgical removal is all that is required. We don't require chemotherapy for limited stage disease in nodular lymphocyte-predominant Hodgkin lymphoma, but chemotherapy is used in advanced stage disease, but it's not typically the same chemotherapy we use in classical Hodgkin lymphoma. In fact, we usually use the regimen R-CHOP, which is the most common regimen we use in non-Hodgkin lymphomas.

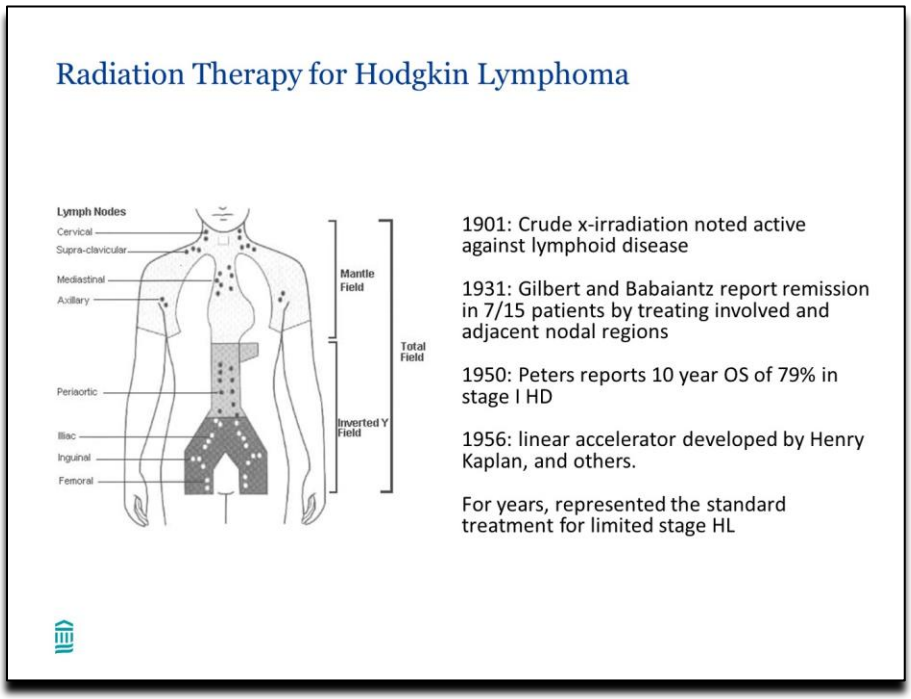
Treatment at relapse is often extrapolated as well for non-Hodgkin lymphomas, but importantly, patients at relapse will usually do very well, regardless of the treatment selected. And I'll show you some curves along the way, called Kaplan-Meier curves, so I'll orient you to what a Kaplan-Meier curve is, so you can interpret them as I go forward. This is a curve showing progression-free survival, which means the number of patients alive and disease-free over time. Time is shown on the X axis. Here it shows years from treatment, so zero, one, two, three, four, five years. And on the Y axis, you see survival probability. So, the top of that means 100 percent of people are alive. The bottom means zero percent.

And so, what you can see over time is that, while the survival decreases somewhat, even five years later, no matter what treatment is administered, more than 70 percent of patients alive and progression-free with nodular lymphocyte-predominant Hodgkin lymphoma. And what that shows is that is an indolent disease with a favorable prognosis.



Treatment of Classic Hodgkin Lymphoma

Let's focus more on classical Hodgkin lymphoma, which is far more common.

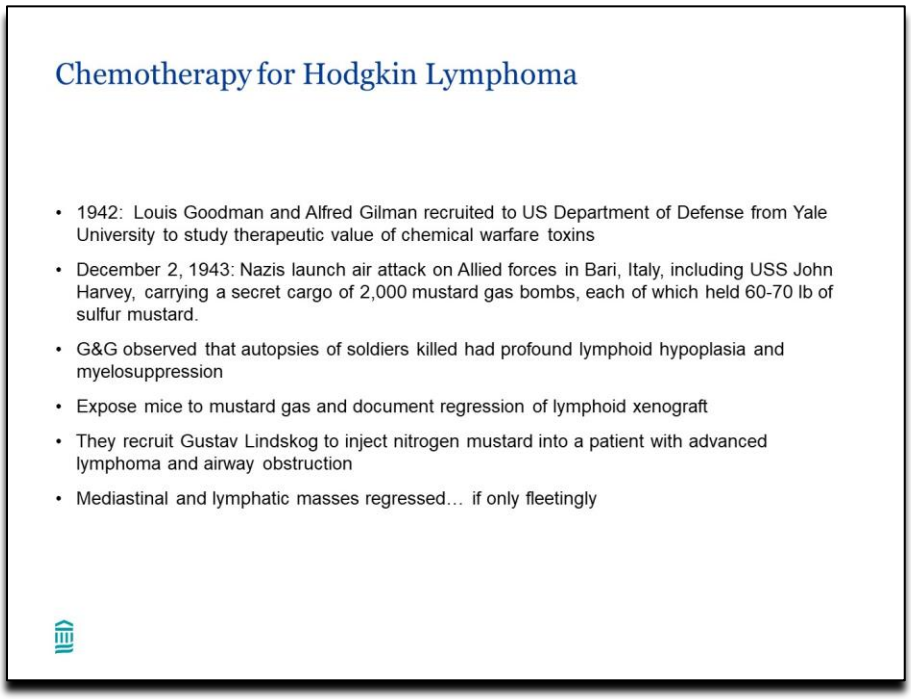


Radiation Therapy for Hodgkin Lymphoma

The initial treatment for Hodgkin lymphoma was radiation therapy. I mentioned that this was developed prior to chemotherapy, and it used to be the only available treatment for classical Hodgkin lymphoma. Initial

radiation waves were shown to be active against lymphoid tissue as early as 1901. It wasn't until 1931 that primitive radiation was used to treat patients with what was thought to be lymphomas at the time. In the 1950s, cobalt radiation was shown to be able to cure limited-stage Hodgkin disease at the time nearly 80 percent of the time. And in 1956, the linear accelerator improved the ability to administer radiation safely. And so, there forward, radiation became the only treatment for limited-stage Hodgkin lymphoma. It was curable in close to 80 percent of people with Stage 1 disease and more like 70 percent of people with Stage 2 disease.

But importantly, at that time, advanced stage Hodgkin lymphoma continued to be incurable because you couldn't radiate the entire body. Radiation could only be given for localized areas of disease.



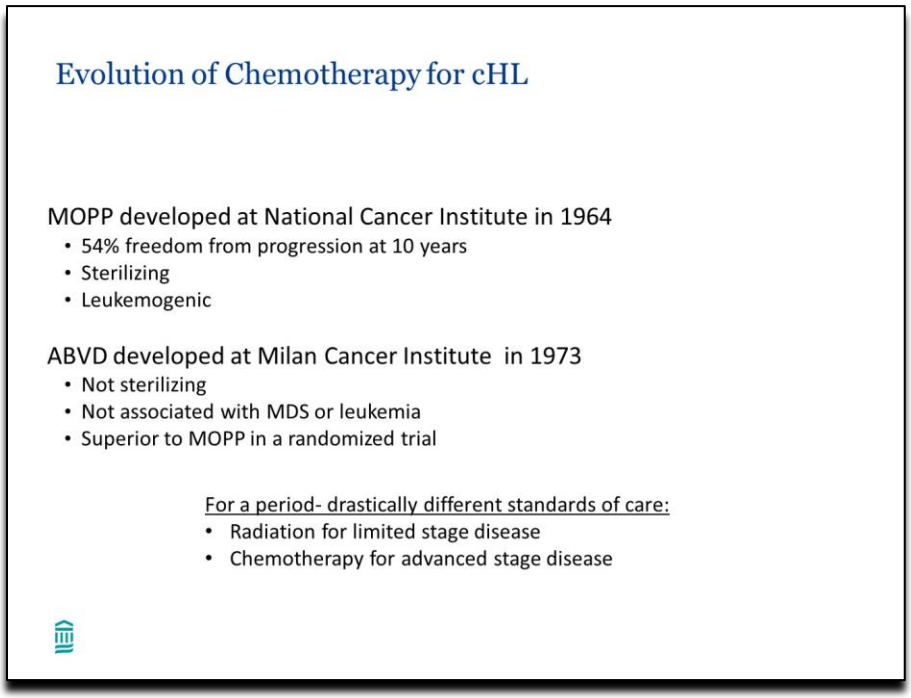
Chemotherapy for Hodgkin Lymphoma

And it was only chemotherapy that actually helped cure the majority of patients with advanced stage Hodgkin lymphoma. And the history of the development of chemotherapy is really linked to the development of Hodgkin lymphoma. In 1942, two pharmacologists by the name of Goodman and Gilman were recruited from Yale University to the Department of Defense. And they were recruited to try and understand if there was any therapeutic value of chemical warfare toxins that were being investigated at the time.

And in fact, in 1943, on December 2, during World War II, the Nazis launched an air attack on allied forces off the coast of Bari, Italy, and attacked a ship called the USS John Harvey. Now, they did not attack the John Harvey with chemical weapons, but the John Harvey was carrying a secret cargo of 2,000 bombs containing mustard gas, each of which contained 60 to 70 pounds of sulfur mustard, a highly toxic agent.

Goodman and Gilman studied autopsies of sailors that were killed during that attack. And what they found is that they had profound shrinking of their lymph nodes, their spleens, and obliteration of their healthy bone marrow, and posited, therefore, that nitrogen mustard, this toxin, might potentially be medicalized and be used to treat cancers of lymphoid organs.

So, they took lymphoma, they inserted it into a mouse, and then exposed that mouse to mustard gas, and indeed found that they could eradicate lymphoma in this mouse. Then, they recruited a surgeon at Yale named Gustaf Lindskog, who, before the age of ethical review panels and informed consent, injected nitrogen mustard into a patient with a very advanced lymphoma that was actually obstructing their upper airway. And in fact, their lymphadenopathy and mediastinal masses did, indeed, shrink. It wasn't a permanent cure, and they ultimately regrew, but this really ushered in the investigation of modern chemotherapy for the treatment of cancer. And so, it really is remarkable that from the bowels of war, modern chemotherapy was born.

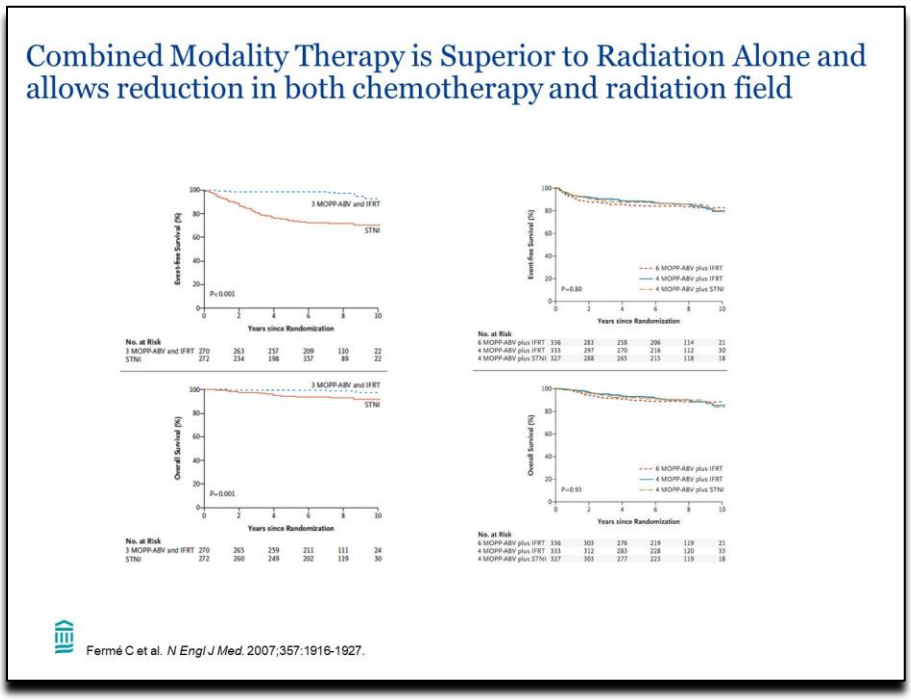


Evolution of Chemotherapy for cHL

Nitrogen mustard ultimately became a drug called mechlorethamine, which is the M in the regimen MOPP. MOPP stands for mechlorethamine, Oncovin® (vincristine), procarbazine, and prednisone. These four drugs were cobbled together at the National Cancer Institute in 1964 and used to treat patients with advanced stage Hodgkin lymphoma. What they found is that more than half of patients were cured, and 10 years later, 54 percent of patients remained alive and free from Hodgkin lymphoma. This was a major advance, given that this disease had previously been uniformly fatal. But, MOPP had serious problems. It made people feel very sick. It caused a lot of nausea and vomiting. It was nearly uniformly sterilizing, which is a major problem for a disease that often affects men and women of childbearing years. And it caused a not insignificant rate of secondary acute leukemia, which is a fine how-do-you-do after you've been cured of your Hodgkin lymphoma.

So, some scientists in Milan developed what they hoped would be a safer regimen called ABVD in 1973. ABVD stands for Adriamycin® (doxorubicin), bleomycin, vinblastine, and dacarbazine. Sure enough, this was highly effective against Hodgkin lymphoma. It did not appear to be sterilizing in people of childbearing years. It was not associated with any significant degree of bone marrow injury or acute leukemia, though there is a very low risk. And when compared head-to-head against MOPP in a randomized clinical trial, it cured more patients with less toxicity. That study published in the early 1990s led to be ABVD becoming the standard of care for advanced stage Hodgkin lymphoma.

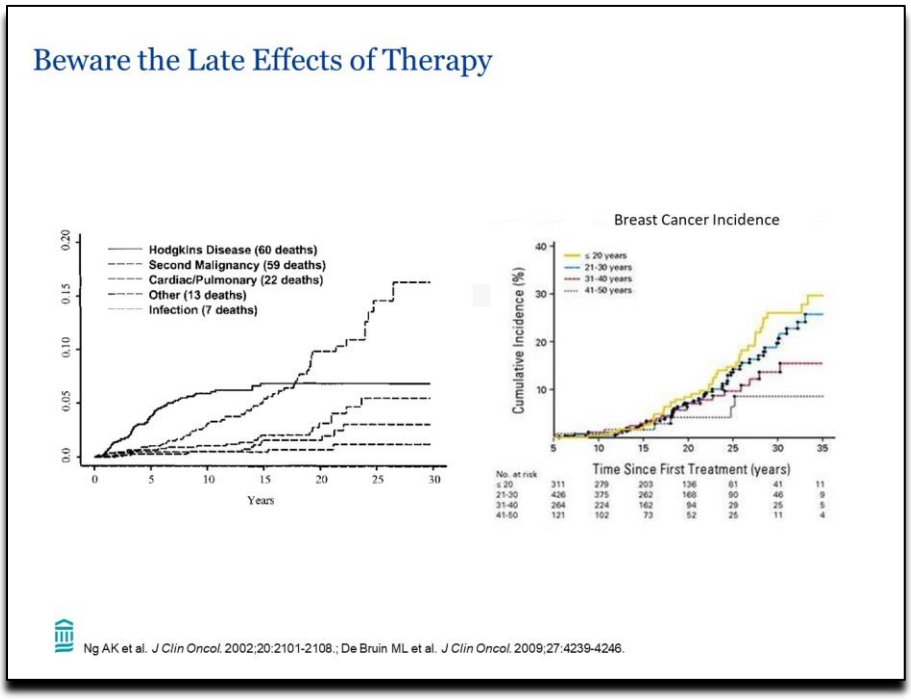
And now, we see an evolution of different treatment paradigms based on stage of disease. Patients with limited stage disease were treated with radiation therapy, whereas patients with advanced stage disease were treated with chemotherapy alone. But, it leads to the question, if we are using chemotherapy to cure the majority of people with advanced stage disease, should we include chemotherapy for limited stage disease, potentially allowing us to improve the cure rate, reduce the amount of radiation, and thus reduce the amount of toxicity?



Combined Modality Therapy is Superior to Radiation Alone and Allows Reduction in Both Chemotherapy and Radiation Field

And sure enough, several clinical trials were done that looked at these very questions. And what this clinical trial shows is, in the upper left-hand panel, you can see that this is a progression-free survival curve, number of patients alive and free of disease over time for patients treated with chemotherapy plus radiation versus radiation therapy alone. And you can see that the patients who received both chemo and radiation, which we call combined modality therapy, that blue dash line stays higher over time, meaning more patients at any given time are cured to a larger degree than patients treated with radiation alone in the orange curve, showing that there is an ongoing risk of relapse over time. Here, with these limited stage patients, you see about 70 percent cured with radiation alone, whereas it's over 80 percent for patients treated with combined modality therapy. The lower panel shows--overall survival shows that more people are also alive, not only alive and disease-free.

And then, the next question asked in this trial, on the right-hand panels, were, if you add chemotherapy to the radiation, can you lower the amount of chemotherapy and radiation? And the answer was yes, you can give fewer cycles of chemotherapy if combining with radiation therapy with no differences in terms of progression-free and overall survival because the curves on the right-hand side of the slide are directly overlapping. But, these patients all still got four cycles of chemotherapy. They all still got a fairly high dose of radiation.

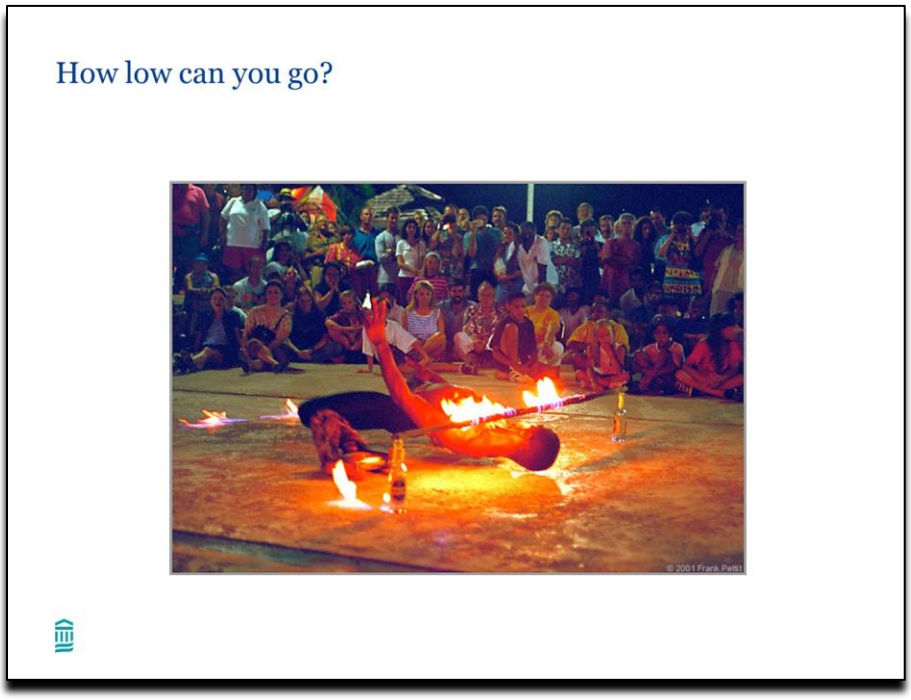


Beware the Late Effects of Therapy

So, the question is, when combining chemotherapy and radiation, can you reduce the doses further? And there is reason to think about doing that. And the reason is that radiation therapy can have significant late toxicities, and we heard about them from the patient story that led into our program. So, if you look at incidence of death over time in patients with Hodgkin lymphoma treated with radiation-based approaches on your left, what you can see is the risk of dying from Hodgkin lymphoma starts to stable out after 5 to 10 years, whereas the incidence of death from secondary cancers, cardiac disease, lung disease, and others continues to rise steadily, particularly the late risk of cancers from radiation therapy, which is more common than dying from Hodgkin lymphoma 15 years after treatment.

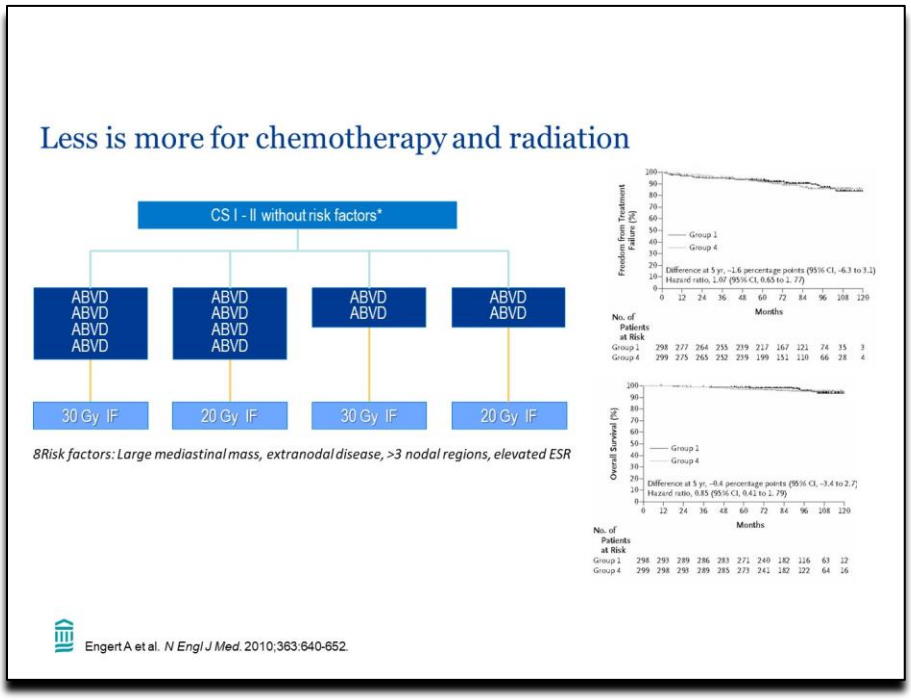
The risk is highest among young women treated with radiation in the middle of their chest, which exposes breast tissue. And here you can see that, over time, and this curve goes out to 25 years, that the incidence of breast cancer continues to rise after patients receive radiation therapy for Hodgkin lymphoma. The risk is highest if patients are treated at younger ages. So, you can see the highest risk are patients who received radiation under 30 years of age with lower risks as they get older. But, you'll see that risk continues to rise in about a third of patients who had mediastinal radiation, ultimately developing a second malignancy in the breast.

So, we really need to think carefully not only about the short-term cure rate of Hodgkin lymphoma but the long-term side effects, particularly in terms of secondary cancers, lung disease, and heart disease, which can complicate radiation therapy.



How Low Can You Go?

Which leads to the question, really, of how low can you go? How much can we decrease chemotherapy and radiation, particularly for the treatment of limited stage Hodgkin lymphoma?

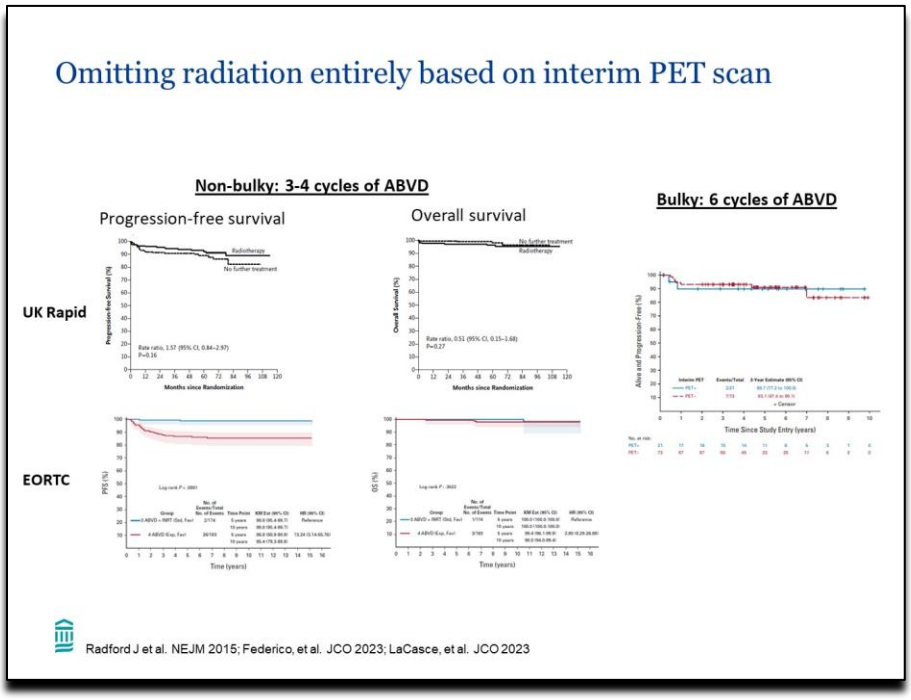


Less is More for Chemotherapy and Radiation

Well, this important trial from Germany asked this in two ways. They took patients with fairly low risk limited stage Hodgkin lymphoma and randomized them to two different chemotherapy strategies and two different radiation strategies. So, patients were initially randomized on whether they received four versus two cycles of chemotherapy. And then, they would be randomized to receive either 20 or 30 gray of radiation. Gray is the unit of radiation. And so, what you ultimately had was a group that got the highest dose treatment, four cycles of ABVD, followed by 30 gray of radiation, and then the lowest intensive group of two cycles of ABVD, just two cycles of chemotherapy, followed by 20 gray of radiation therapy.

And what you can see, based on those curves on your right, which are completely overlapping, is that the highest intense group and the lowest intense group had directly overlapping outcomes. And so, there was no benefit to four cycles compared to two cycles or higher dose radiation therapy in this study, meaning just as few as two cycles of chemotherapy followed by lower dose radiation therapy emerged as a reasonable and appropriate standard of care for low-risk, limited stage Hodgkin lymphoma.

But, of course, any radiation dose to any site of the body could theoretically be associated with late risk of secondary malignancy in others. And so, the major question we've been focusing on since is whether we can omit radiation therapy entirely.



Omitting Radiation Entirely Based on Interim PET Scan

And the answer is that we can in the vast majority of patients. I put up two different studies here, the U.K. study on the upper panel and the European ORTC study on the lower right-hand panel. Both of these studies asked a similar question. They said if we do a PET scan after just three cycles of treatment, can we take the patients who had a negative interim PET scan and avoid radiation for just those patients?

And so, patients with a negative interim PET scan, meaning a complete remission on a PET scan after just three cycles of ABVD, were randomized to get radiation or to get chemotherapy alone. And in the chemotherapy-alone arm, it was three cycles of ABVD on the U.K. study, four cycles of ABVD on the EORTC study, so slightly different, but both asking the question of how much value does radiation provide?

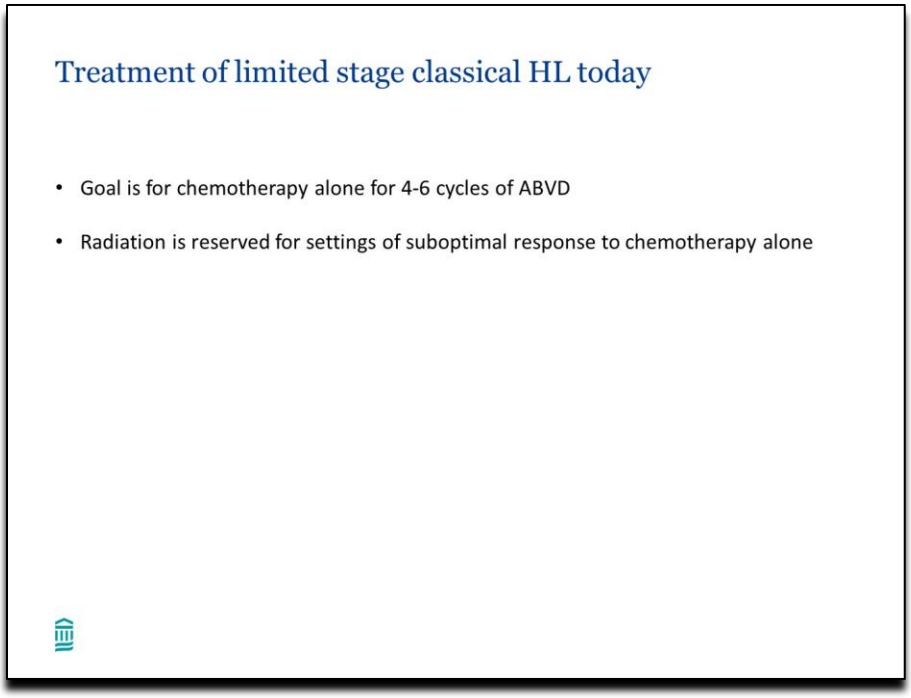
Now, what you can see in terms of progression-free survival, meaning how many people are remaining in remission, there is a small difference in those two groups. You can see that there are separate curves on both the upper study on the right and the lower study on the left, meaning there are still slightly more patients cured if they get radiation therapy. That is in the 3 percent to 5 percent range, which means you would have to expose 95 to 97 percent of patients to radiation therapy that will benefit only 3 percent to 5 percent of them. And in fact, if you look at the overall survival, meaning how many people are alive and well in both of these studies on your right, it's identical, meaning that that small group of patients that relapsed because they did not get radiation therapy are also likely cured in the relapsed, refractory setting.

And so, based on these data, most of us have moved away from radiation therapy in patients who have a negative interim PET scan. So, for my patients, if they have a negative PET scan for non-bulky limited stage disease after three cycles, I'll typically do one more cycle, as they did in the EORTC study, and stop at four total cycles without radiation therapy. For patients who still have detectable disease on their PET scan, however, those are patients with higher risk of relapse or progression. And so, for somebody with a positive interim PET scan, we do typically still favor radiation therapy at the end of treatment, but those radiation doses have gotten lower and to smaller areas over time. I will tell you that over 80 percent of people do

achieve a negative interim PET scan, so by using this approach, we typically only require radiation in 10 percent to 15 percent of patients in the modern era.

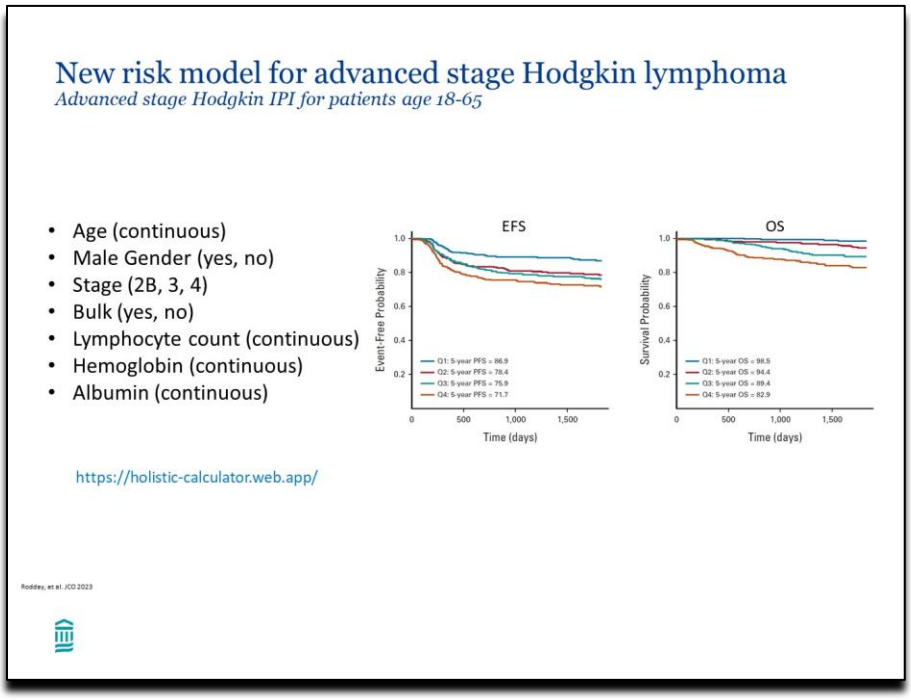
Now, patients with bulky disease, which in the U.S. we define as 10 cm or greater, do still need a full six cycles of chemotherapy. When this clinical trial looked at patients who had a negative interim PET scan after two cycles of ABVD, and if they had a negative interim PET scan, they got no radiation after six cycles of chemotherapy, what you can see is their outcomes were excellent. So, as of today, I would avoid radiation in limited stage non-bulky patients. I typically do a PET scan after two cycles of ABVD. If it's a PET complete response, I'll do two more cycles then follow with observation, and I'll consider including radiation if the interim PET scan is positive. For bulky limited stage disease, we still do an interim PET scan after two cycles.

If that PET scan shows complete remission, then we'll complete six total cycles of ABVD with no radiation therapy. Thus, in the modern era, we're providing radiation to only a very small group of Hodgkin lymphoma patients.



Treatment of Limited Stage Classical HL Today

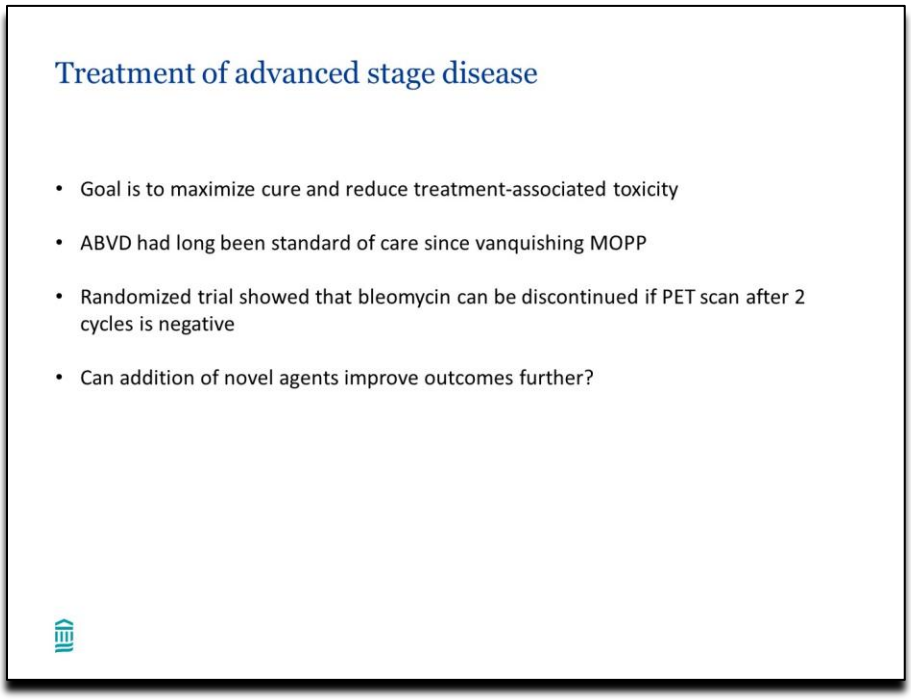
So today, our goal for most patients is four to six cycles of ABVD and reserving radiation only for patients with suboptimal responses to chemotherapy alone.



New Risk Model for Advanced Stage Hodgkin Lymphoma

Shifting our attention to advanced stage disease, I'll highlight that we do have a recent updated risk model, using modern data to assess sort of prognosis in patients with advanced stage Hodgkin lymphoma, meaning Stage 3 or Stage 4. This model included bulky Stage 2B, as also an advanced stage disease, and looked at a series of risk factors and generated a risk score.

And what you can see, importantly, in the modern era, the progression-free survival, number of people alive without the disease or needing new cancer treatment, even the highest risk group, over three-quarters of those patients are cured with modern treatment. And the vast majority, close to 80 percent of patients, even in the highest risk group, remain alive several years later. So, I think this shows we've made dramatic advances over time, and even the highest risk patients are likely to be cured with modern treatment.

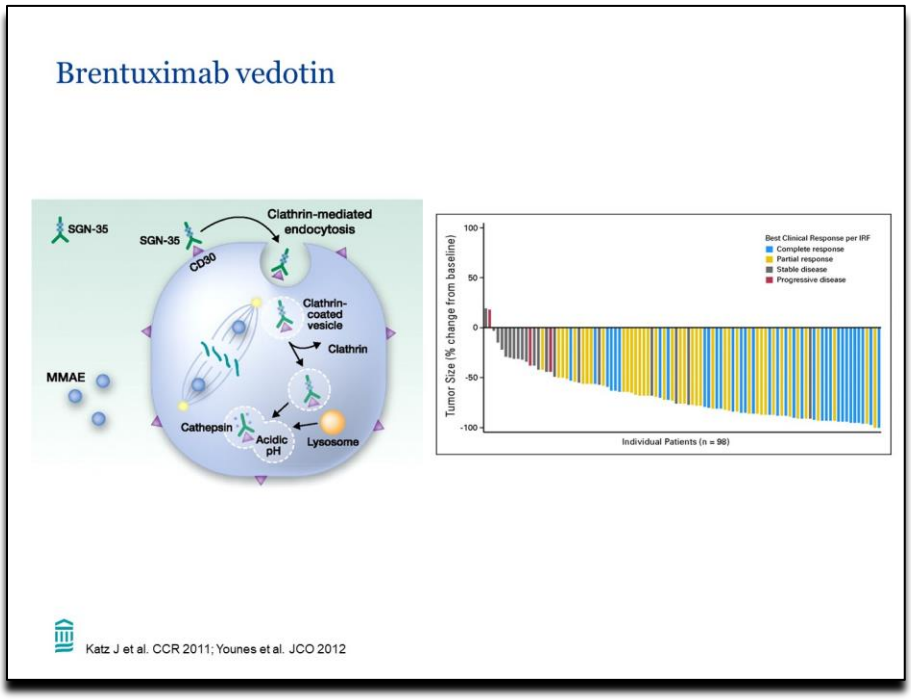


Treatment of Advanced Stage Disease

Now, advanced stage disease treatment has evolved significantly over time. Our goal is obviously to maximize the cure rate as well as reducing treatment-associated side effects. I said that ABVD has long been our standard of care since it vanquished MOPP in the initial randomized trial.

We also have a randomized trial looking at trying to eliminate as much bleomycin, the B in ABVD, because bleomycin in ABVD can risk lung injury, including long-term lung injury. And so, we do have a randomized trial that's, again, a PET scan after two cycles of ABVD. And patients with a complete response after two cycles were randomized to continue standard ABVD or stop the bleomycin after two cycles and just continue AVD for the remaining four cycles. And in fact, that study showed that those two groups did exactly the same. So, for patients with advanced stage disease getting ABVD, if the PET scan is negative after two cycles, we discontinue the bleomycin and continue AVD, which leads to decreased risk of bone marrow side effects and decreased risk of bleomycin lung injury.

The more pressing question in modern treatment is whether newer, novel, targeted drugs directed at the underlying biology of Hodgkin lymphoma can improve outcomes further than historic chemotherapy drugs like ABVD.



Brentuximab Vedotin

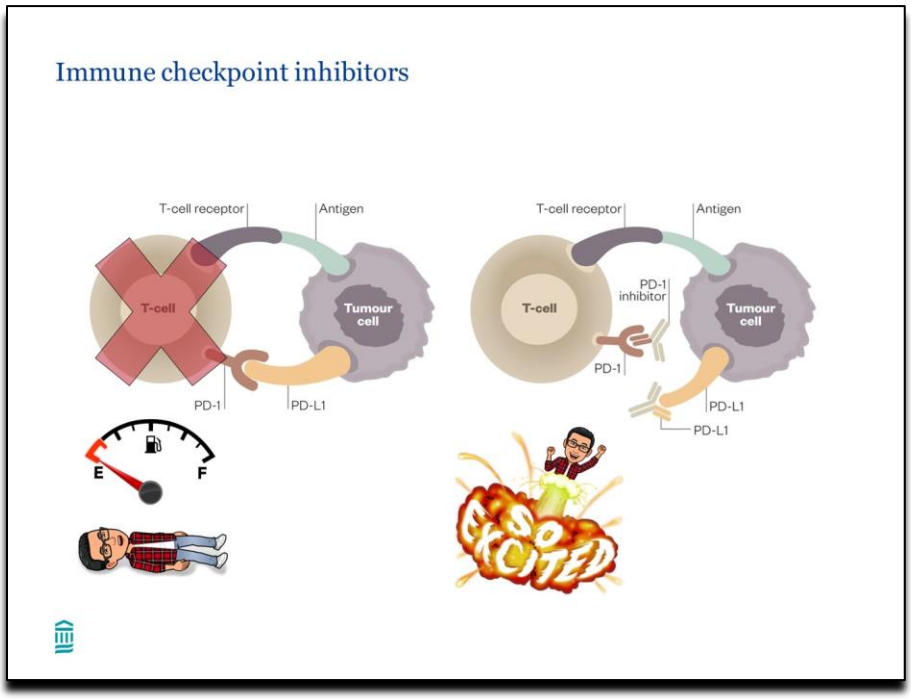
Now, this is an example of one of the drugs that's now a targeted therapy, part of our treatment armamentarium for classical Hodgkin lymphoma. This is a drug called brentuximab vedotin (Adcetris®). Brentuximab vedotin is an antibody drug conjugate. And what that means is it's an antibody. An antibody is a biological protein that is targeted specifically towards a protein on the surface of a lymphoma cell. Now, our bodies produce antibodies all the time, and those are antibody-targeted proteins on the surface of viruses, bacteria, fungus, infections. But, this is an antibody designed to target Hodgkin lymphoma cells. And it's specifically against a protein on the surface of virtually all classic Hodgkin lymphoma cells called CD30.

Now, that antibody is designed to be a targeted drug delivery mechanism, and it's linked to a molecule of chemotherapy called MMAE, or monomethyl auristatin E. Auristatin was originally investigated as a chemotherapy. But unfortunately, it was far too toxic to give systemically, and so it sat on a shelf for a long time. But with this technology, it's linked to the antibody CD30. That antibody drug conjugate then binds to the lymphoma cell. The lymphoma cell then gobbles up that complex, internalizes it. Once internalized into the cell, the MMAE is released from the antibody, and it attacks the DNA of the Hodgkin lymphoma cell, thus killing the cell from the inside out. And I think of this much akin to the Trojan horse getting taken into the city walls of Troy and releasing the soldiers inside the city walls.

This drug was initially approved for multiple relapsed classical Hodgkin lymphoma. These were patients who had received initial therapy like ABVD, had relapsed, gotten additional therapy and a stem cell transplant, and relapsed again. So, these were multiple relapses. The curve I showed you on your right is the initial Phase 2 study of brentuximab vedotin as a single drug for multiple relapsed classical Hodgkin lymphoma.

This is what's called a waterfall plot. Each of these columns represents a patient's lymphoma over time. And so--and the zero access is no change. So, if the bar goes up, then it means the lymphoma has grown, if the bar goes down, that the lymphoma has shrunk by 50 percent to 100 percent. And so, you can see among all patients treated on this study, all but two patients had a significant reduction in the amount of Hodgkin

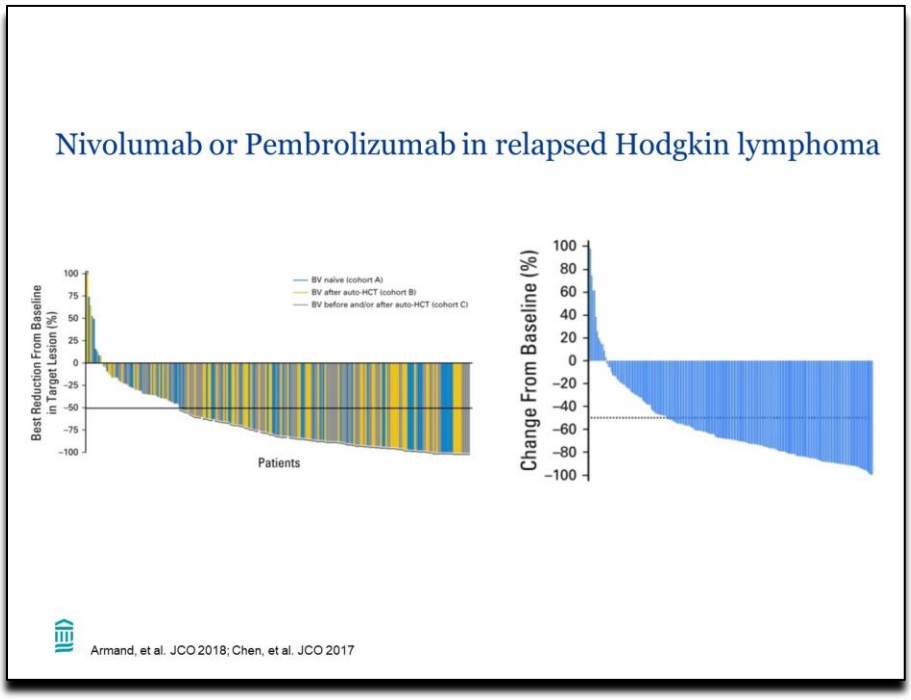
lymphoma, and showing remarkable single-agent activity, which led to FDA approval for brentuximab vedotin for the treatment of relapsed and refractory classical Hodgkin lymphoma.



Immune Checkpoint Inhibitors

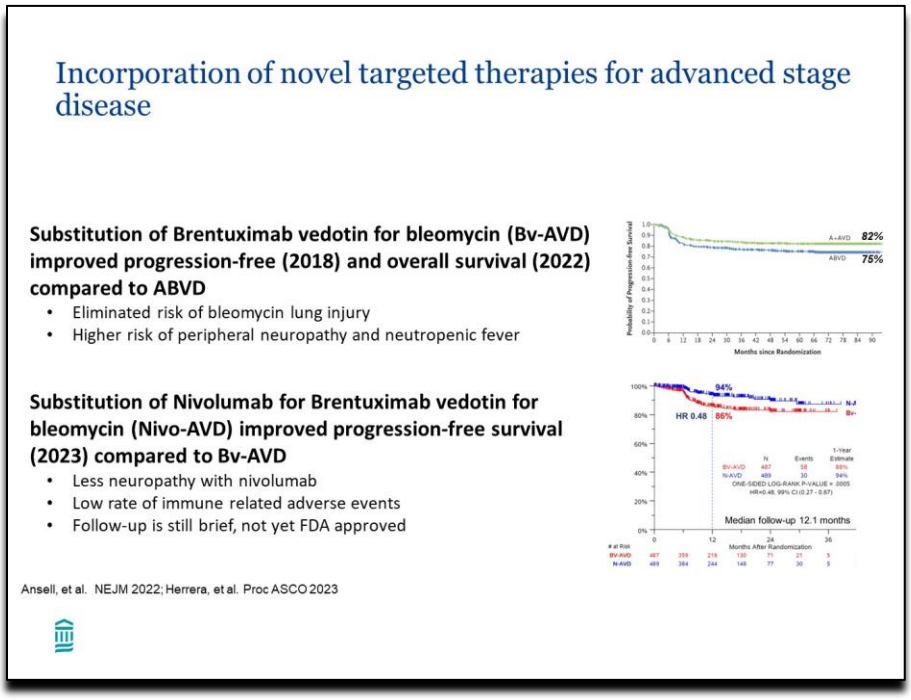
Now, another novel targeted drug is called an immune checkpoint inhibitor or a PD-1 inhibitor. Now, one thing that was recognized, and you'll remember back when I showed the histology views, the microscopic views of Hodgkin lymphoma, the tumor cell is surrounded by the body's own inflammatory cells. And it turns out that the body's own inflammatory cells have a protein on their surface called PD-L1. And PD-L1 binds the PD-1 on the surface of the patient's T cell. And when it does that, what the tumor cell does is it effectively deactivates the patient's T cell, because PD-1 shuts down that patient's T cell. And so, if you deactivate the T cell using PD-1, you lead to what's called T cell exhaustion, as shown here by my exhausted emoji.

So, one question then is what if you can block PD-1? What if you can use a separate antibody and actually prevent the tumor cell from exhausting the T cell? Well, now you see an activated version of myself, now that T cell is indeed activated, and can do what T cells are supposed to do, which is kill things that don't belong there. And what the goal of PD-1 or checkpoint inhibition is to remove the invisibility cloak from the lymphoma cell and allow the body's own immune system to destroy it.



Nivolumab or Pembrolizumab in Relapsed Hodgkin Lymphoma

So, does adding either brentuximab vedotin or an immune checkpoint inhibitor help treat advanced stage Hodgkin lymphoma? Well, there are now two immune checkpoint inhibitors, FDA approved, for the treatment of relapsed classical Hodgkin lymphoma. These are, again, waterfall plots showing nivolumab (Opdivo®) on your left and pembrolizumab (Keytruda®) on your right lead to tumor reduction in the vast majority of patients with multiple relapsed classical Hodgkin lymphoma, and this is purely by reactivating the patient's own immune cells against their Hodgkin lymphoma.

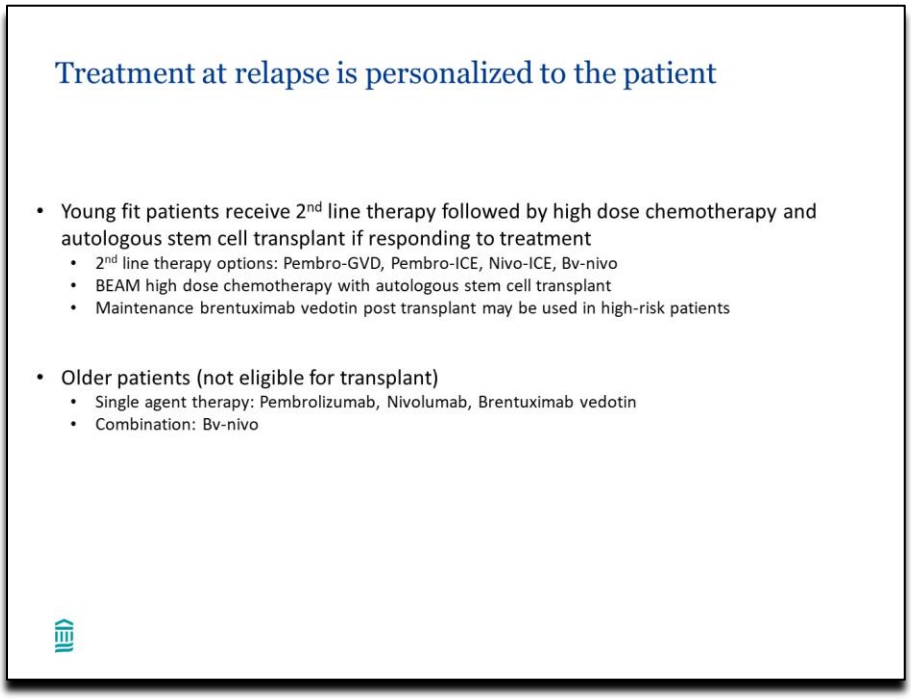


Incorporation of Novel Targeted Therapies for Advanced Stage Disease

So, can we incorporate one of these drugs into standard chemotherapy and try and cure more patients upfront rather than saving these drugs for patients with relapsed, refractory disease? And sure enough, if we add brentuximab vedotin to AVD, substituting it for bleomycin, we see an increased cure rate favoring brentuximab AVD compared to ABVD. And this led to brentuximab AVD being a preferred standard treatment for advanced stage Hodgkin lymphoma.

But, it did have a fair amount of increased risk, particularly peripheral neuropathy and more effects on the bone marrow. And so, an additional trial more recently presented instead substituted an immune checkpoint inhibitor, nivolumab, to AVD and compared it to brentuximab AVD, so one novel agent compared to another in combination with chemotherapy. And it turns out that Nivo AVD cures more patients than brentuximab AVD with less toxicity. So nivolumab AVD has now emerged as our standard Hodgkin lymphoma treatment in advanced stage today.

Relapsed cHL

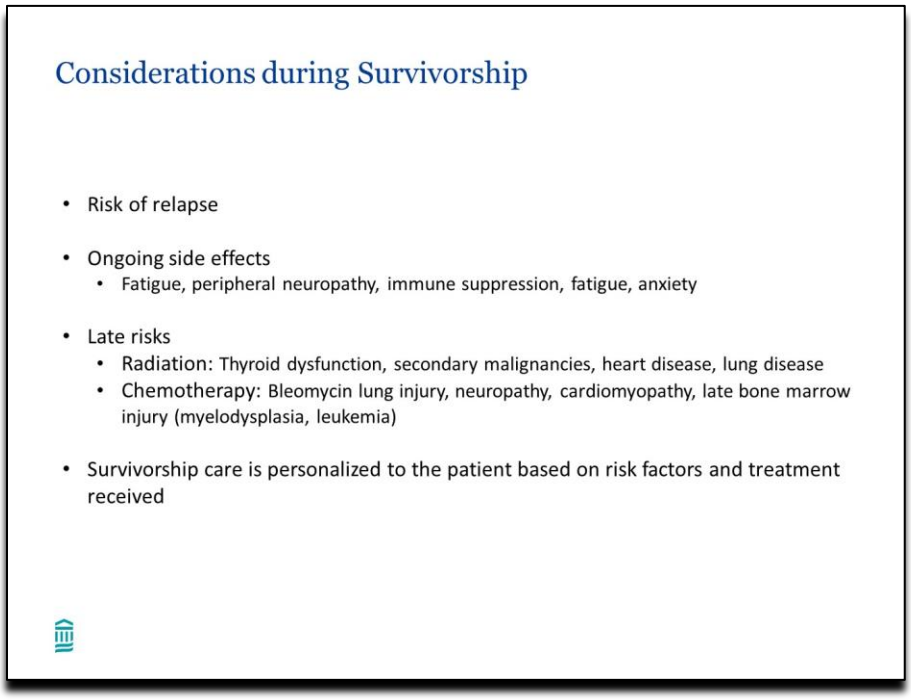


Treatment at Relapse is Personalized to the Patient

And I'll close by saying that the management of relapsed Hodgkin lymphoma today has really evolved a great deal. It does have to be personalized to the patient, so I'm not going to go into great detail today.

Survivorship

And spend my remaining few minutes on thinking about survivorship, which is where most people with Hodgkin lymphoma end, which is alive and well in remission from Hodgkin lymphoma.

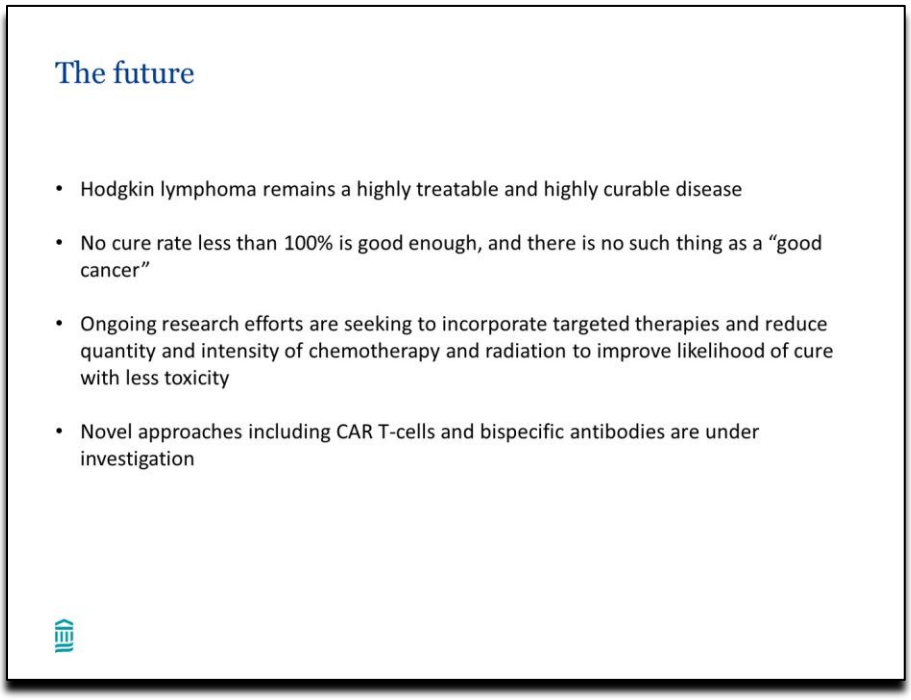


Considerations During Survivorship

So, what do we think about during survivorship? We think about monitoring for relapse. The risk of relapse is low, since the majority of patients are cured. In my practice, I typically do a clinical check-up every three months with a CAT scan every six months for two years after remission. After two years, the risk of relapse is so low that I then do check-ups with clinical visits and a physical exam every six months until five years, but no further scans after the two-year mark. And after five years, we typically follow with an annual survivorship visit. Survivorship also has to pay attention to potential side effects such as fatigue, peripheral neuropathy related to potentially the brentuximab or vinblastine, immune suppression, which can last quite a while after chemotherapy for Hodgkin lymphoma, and the anxiety of survivorship because of fear potentially for relapse or late toxicity.

And then, there's risks that we think about that can occur late after treatment, and that includes radiation effects that we talked about, secondary malignancies, heart disease, lung disease, and I'll include thyroid dysfunction with that as well for radiation of the neck. And then, late effect risks with chemotherapy include bleomycin lung injury, peripheral neuropathy from vinblastine or brentuximab, heart injury from Adriamycin®, or a late bone marrow injury, and even that very low risk of leukemia from chemotherapy.

For that reason, we monitor organ function over time and blood tests as well. And ultimately, survivorship care is highly personalized to the patient, based on what risk factors they had and the specific treatments they received, since the treatments will guide their potential short- and long-term toxicity.

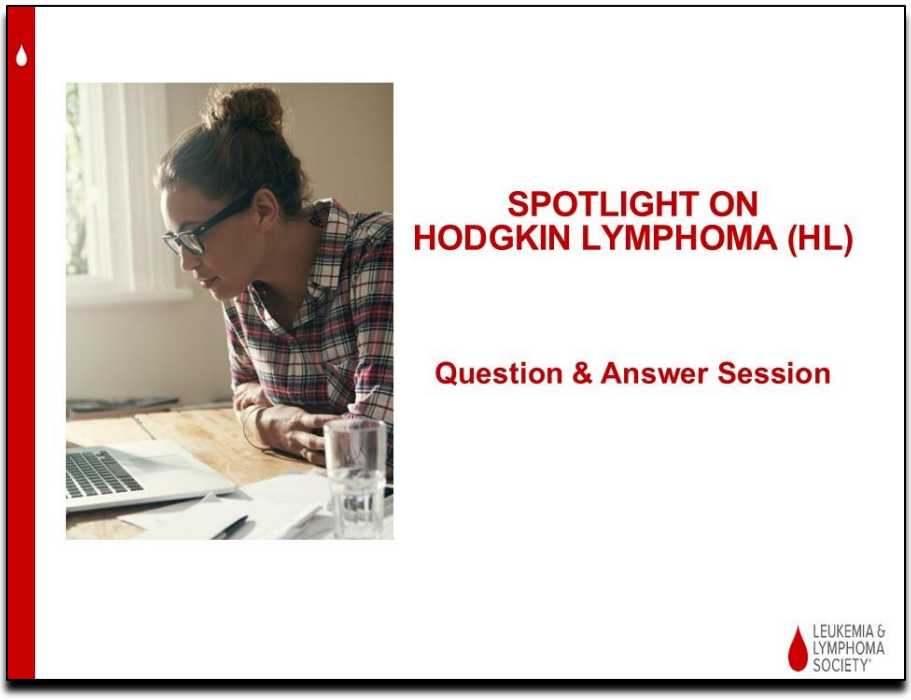


The Future

So, I'll close now by saying that Hodgkin lymphoma remains a highly treatable and highly curable disease, but no cure rate less than 100 percent is good enough. There's no such thing as a good cancer. We still need to do better. We take this very seriously, and our goal is to cure 100 percent of patients with zero toxicity over time. Ongoing efforts to do that are increasingly relying on novel agents and immune-activating therapies as opposed to traditional chemotherapies and radiation.

And some of these are in current investigation, including something called the CAR T cell, our bispecific antibodies that really directly harness the power of the patient's own system to fight lymphoma.

With that, I'll thank you for your attention. I'll turn the program back over to Lizette and happy to take any questions.



Question & Answer

Lizette Figueroa-Rivera
Well, thank you so much, Dr. Abramson, for your very informative presentation. It is now time for our question-and-answer portion of our program.

Doctor, you answered many questions throughout your presentation, so thank you. Debra is asking, I had strong B symptoms. Did that make my disease any worse for late effects or for recurrence?

Dr. Jeremy Abramson
So, the presence of systemic B symptoms, in terms of prognosis, has really a minimal effect. In limited stage Hodgkin lymphoma, Stage 1 and 2 Hodgkin lymphoma, having B symptoms is--does predict a slightly lower risk of cure, but still the vast majority of people are cured. There is no prognostic impact of B symptoms in patients with advanced stage disease. So overall, I'd say the importance of B symptoms is really very minimal and does not predict for a significantly worse outcome over time and also does not predict for worse side effects over time.

Lizette Figueroa-Rivera
Thank you. And Diana is asking the best method for monitoring for late effects and possible cancer recurrence after the five-year mark for Hodgkin lymphoma patients.

Dr. Jeremy Abramson
So, this is very much personalized. The major one that I would say is actionable are people who have received mediastinal or chest radiation that's included breast tissue, so young women. Particularly young women who have dense breasts, it's hard to look with mammography. So, for women who have received radiation therapy that included breast tissue, we typically do an annual mammogram as well as an annual breast MRI, which is more sensitive than mammograms in younger women.

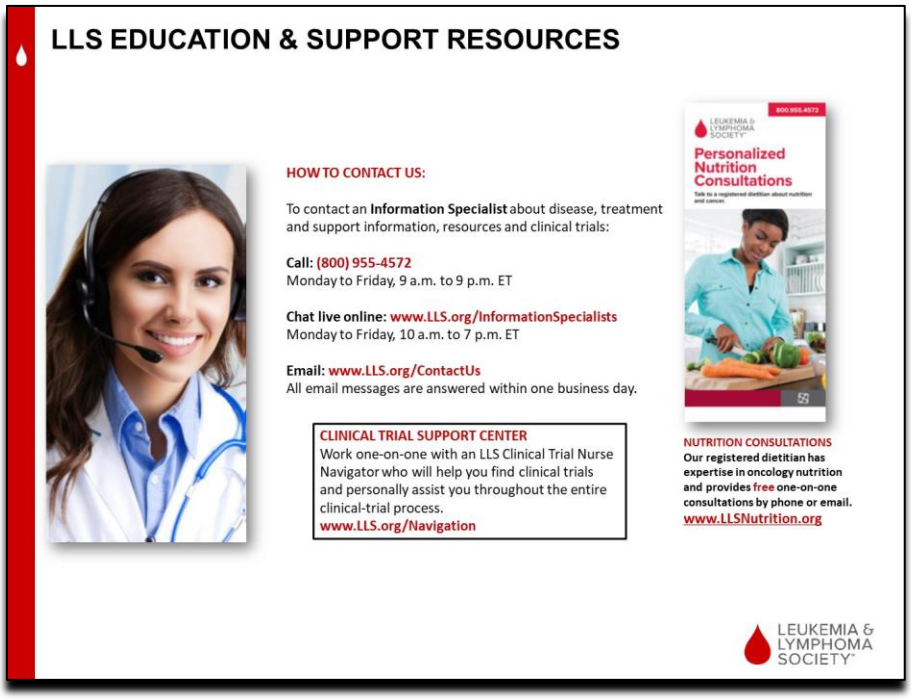
And so, I usually alternate those, so every six months, a young woman who got mediastinal radiation will get a breast MRI. Six months later, they'll get a mammogram. Six months later, they'll get a breast MRI. Other than that, it's age-appropriate cancer screening, so colonoscopies beginning as early as age 40. And if new masses or symptoms develop, they're being evaluated. But, the only specialized cancer monitoring is really for breast cancer.

Lizette Figueroa-Rivera
Thank you. And Brett asks, do you have any recommendations for managing neuropathy? I know that you've mentioned neuropathy, Doctor, for example, any exercises that may help, things to avoid?

Dr. Jeremy Abramson
Neuropathy is a tough one. Nerves heal very slowly over time, and sometimes they don't fully heal. Certain medications can help if it's painful neuropathy, sort of electric shock type sensations. That's where a drug called duloxetine (Cymbalta®) can be helpful or a drug called gabapentin (Neurontin®) sometimes. More commonly, neuropathy is more of a numbness, tingling sensation. That cannot be helped with medications, unfortunately.

Some people have reported that they feel improved with some acupuncture techniques, so that can be recommended as a try. But otherwise, most neuropathy, if it's existing--if you still have neuropathy a year or two years after treatment, you're kind of stuck with it, unfortunately. And it's more sort of coping mechanisms more so than actually making the neuropathy go away because that damage is likely permanent, unfortunately. But for painful neuropathy, there are drugs that can help. And I do always think acupuncture is worth a shot.

Lizette Figueroa-Rivera
Well, thank you so much, and thank you, Brett, for your question, which was our final question today. Again, a special thanks to Dr. Abramson for sharing his expertise with us and for his continued dedication to our blood cancer patients.

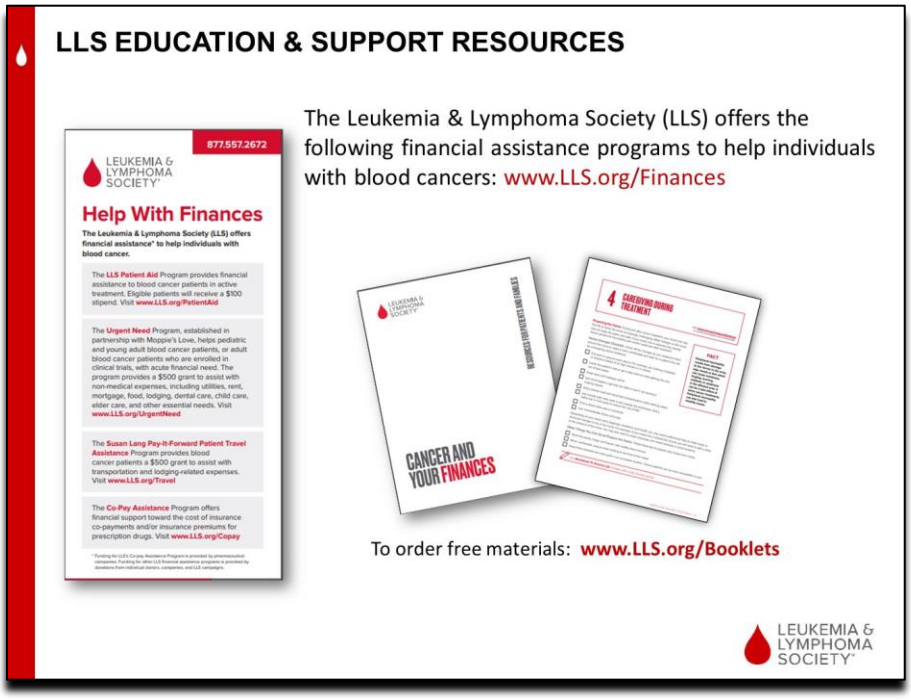


LLS Education & Support Resources

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 9:00 a.m. to 9:00 p.m. Eastern Time or go to lls.org/Information Specialist to chat online, or e-mail them at LLS.org/ContactUs.

LLS also has a Clinical Trial Support Center (CTSC) where clinical trial nurse navigators will personally assist you throughout the entire clinical trial process. And you may reach them at LLS.org/Navigation. And if you haven't already, please schedule a free nutrition consult with one of our registered dietitians. It's free, and it's open to all cancer patients and to their caregivers. You may go to LLS.org/Nutrition for more information.

LLS Education & Support Resources



LLS Education & Support Resources

And The Leukemia & Lymphoma Society is proud to partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free. Please visit LLS.org/DollarFor. That's LLS.org/DollarFor for more information.

Thank You

Now, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program, and please consider sharing your story with us. Your words of encouragement can bring hope and confidence to others, and you may submit your story at LLS.org/voices-of-lls-submission.

Thank you so much and take good care.