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Living with Hodgkin Lymphoma

LEUKEMIA &
LYMPHOMA
SOCIETY

Welcome & Introductions

Dr. Lamar's slides are available for download at www.LLS.org/programs, under the program listing.

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Slide 1: Welcome and Introductions

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I'd like to welcome all of you. A special thanks to Dr. Zanetta Lamar for volunteering her time and expertise with us today.

Before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer, who will share a few words.

Dr. Louis DeGennaro:

Hello. I'm Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancer. For nearly 70 years, LLS has invested more than one billion dollars in scientific research to find better treatments and cures. We have played a pioneering role in the development of groundbreaking targeted therapies and immunotherapies that have led to increased survival rates and improve the quality of life for many blood cancer patients.

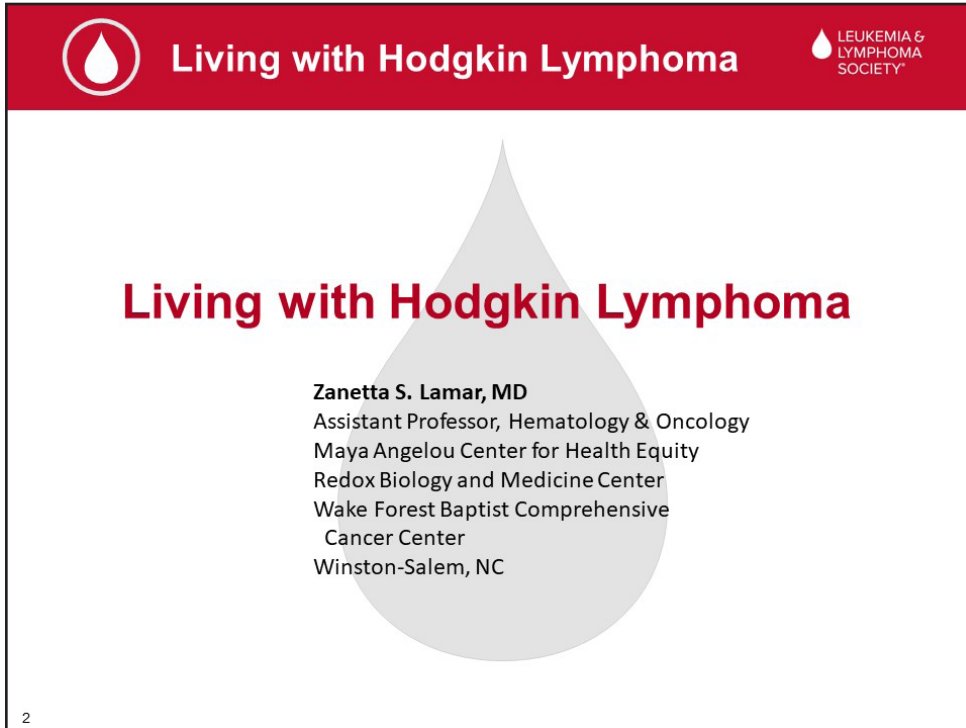
Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support. We also support blood cancer patients in their local communities through our 56 chapters across the United States. And, we fight for lifesaving policy changes at the state and federal level to ensure access to quality, affordable, and coordinated care.

We are committed to working tirelessly toward our mission every single day, until we find a cure. We're fortunate to have esteemed key opinion leaders to present our programs. They each have volunteered their time and we appreciate their dedication to supporting our mission and commitment to caring for patients living with blood cancers.

Thank you for joining us today.

Lizette Figueroa-Rivera:

We would like to acknowledge and thank Seattle Genetics and The Leukemia & Lymphoma Society for support of this program.



Living with Hodgkin Lymphoma

LEUKEMIA &
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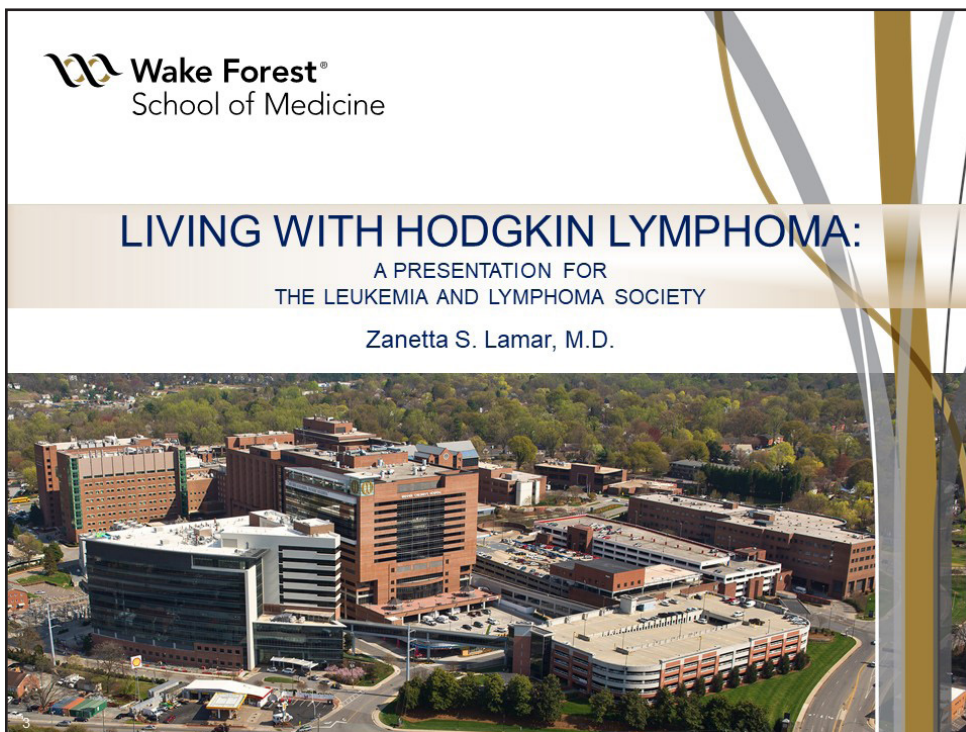
Living with Hodgkin Lymphoma

Zanetta S. Lamar, MD
Assistant Professor, Hematology & Oncology
Maya Angelou Center for Health Equity
Redox Biology and Medicine Center
Wake Forest Baptist Comprehensive
Cancer Center
Winston-Salem, NC

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Slide 2: Living with Hodgkin Lymphoma

I am now pleased to introduce Dr. Zanetta Lamar, Assistant Professor, Hematology and Oncology, at Wake Forest Baptist Comprehensive Cancer Center in Winston-Salem, North Carolina. Dr. Lamar, I'm now privileged to turn the program over to you.




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LIVING WITH HODGKIN LYMPHOMA:

A PRESENTATION FOR
THE LEUKEMIA AND LYMPHOMA SOCIETY

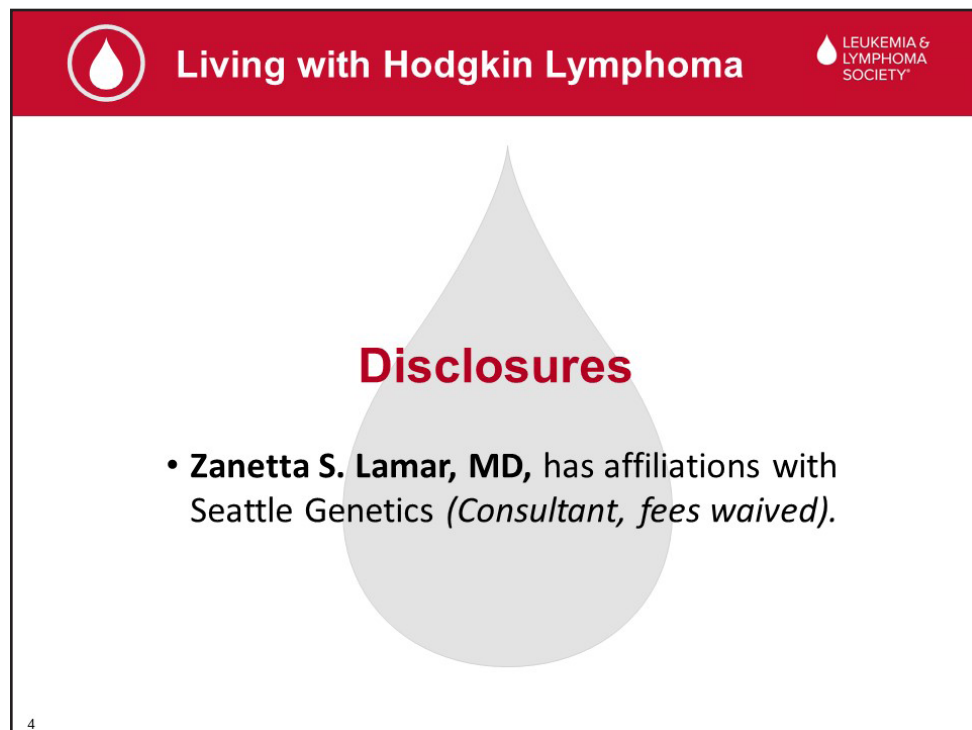
Zanetta S. Lamar, M.D.



Slide 3: Living with Hodgkin Lymphoma

Dr. Zanetta Lamar:

Thank you so much. It is truly an honor to speak with you today about *Living with Hodgkin Lymphoma*.



Slide 4 features a red header with a white drop icon and the text "Living with Hodgkin Lymphoma" and "LEUKEMIA & LYMPHOMA SOCIETY". The main content area has a large grey drop shape in the background. The word "Disclosures" is written in red. Below it, a bullet point states: "• Zanetta S. Lamar, MD, has affiliations with Seattle Genetics (*Consultant, fees waived*)." A small number "4" is in the bottom left corner.

Slide 4: Disclosures


My disclosures.



Slide 5 features a white background with a thin black border. The title "Learning Objectives" is in a brown font. Below it is a list of six bullet points: "• We will discuss", "• History of Hodgkin", "• Epidemiology, presentation, diagnosis", "• Management of early and advanced disease", "• Emerging therapies", and "• Shared decision making". At the bottom left, there is a small number "5" and the text "Wake Forest Baptist Medical Center".

Slide 5: Learning Objectives

In this discussion, we will learn about the history of Hodgkin lymphoma. We'll talk a little bit about the epidemiology, presentation, and diagnosis. Then I'll spend some time on the management of early and advanced stage disease, and we'll spend the last part of the talk talking about new exciting emerging therapies and shared decision making.



Dorothy Reed as a medical student at Johns Hopkins

Thomas Hodgkin, M.D.

ON SOME MORBID APPEARANCES OF THE ABSORBENT GLANDS AND SPLEEN. BY DR. HODGKIN. PRESENTED BY DR. R. LEE. READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.


The Johns Hopkins Hospital Reports, Volume 10, 1902

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Slide 6: Thomas Hodgkin, MD

This is a picture of Thomas Hodgkin. He gave the first description of Hodgkin lymphoma in 1832.



Dorothy Reed as a medical student at Johns Hopkins

ON THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE, WITH ESPECIAL REFERENCE TO ITS RELATION TO TUBERCULOSIS. BY DOROTHY M. REED, M. D., Fellow in Pathology, Johns Hopkins University. [From the Pathological Laboratory of the Johns Hopkins Hospital and University.] (PLATES IV-VII.)

HISTORICAL.—It is seventy years since Hodgkin' called the attention of the medical world to the peculiar enlargement of the lymphatic glands, which has since been designated by his name. Hodgkin's original paper was a simple report of seven unusual cases, which had come under his observation as pathologist at Guy's Hospital. He noted that the cases agreed in glandular tumors and were frequently associated with enlargement of the spleen. He did not attempt any critical analysis of his material, and undoubtedly had no conception that, in one or possibly two of his cases, he was dealing with a peculiar and rare disease. The other cases have no interest for us in this connection, as they are instances of tuberculosis, syphilis and possibly leukæmia.

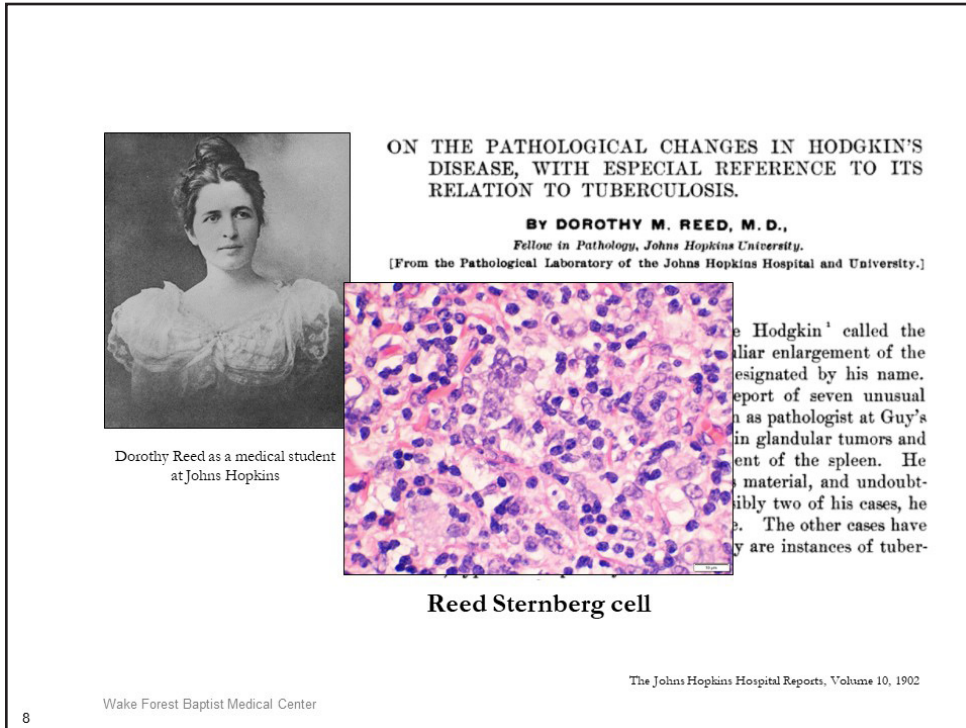
The Johns Hopkins Hospital Reports, Volume 10, 1902

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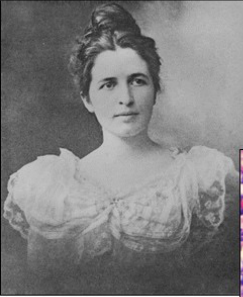
Slide 7: Dorothy M. Reed, MD

I actually like to talk about someone named Dorothy Reed. And, Dorothy Reed was in the early class of Johns-Hopkins. And, during her one and only year there, she was the first person to give a clear and accurate description of Hodgkin. And, she disproved the belief that Hodgkin was a subtype of an infection.

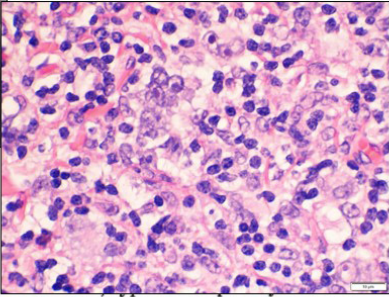


ON THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE, WITH ESPECIAL REFERENCE TO ITS RELATION TO TUBERCULOSIS.

BY DOROTHY M. REED, M. D.,
Fellow in Pathology, Johns Hopkins University.
[From the Pathological Laboratory of the Johns Hopkins Hospital and University.]



Dorothy Reed as a medical student at Johns Hopkins



The Hodgkin¹ called the peculiar enlargement of the cell designated by his name. I report of seven unusual cases as pathologist at Guy's Hospital in glandular tumors and enlargement of the spleen. He has material, and undoubtedly two of his cases, he reported. The other cases have been reported as instances of tuber-

Reed Sternberg cell

The Johns Hopkins Hospital Reports, Volume 10, 1902

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Slide 8: Reed Sternberg cell

The malignant cell, the Reed-Sternberg cell, is partially named after Dorothy Reed. She is a fascinating woman.

Epidemiology

- 8,260 cases diagnosed in 2017
- Represent 0.5% of all new cancer cases
- Five years after diagnosis 86.4% remain alive



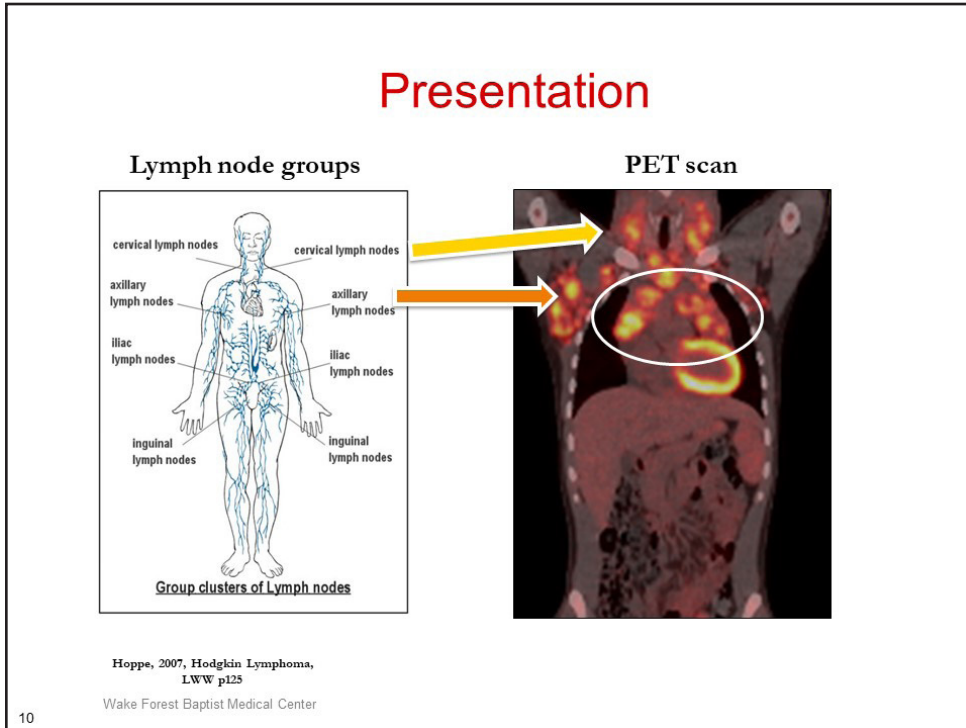
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Based on November 2016 SEER data submission.

Slide 9: Epidemiology

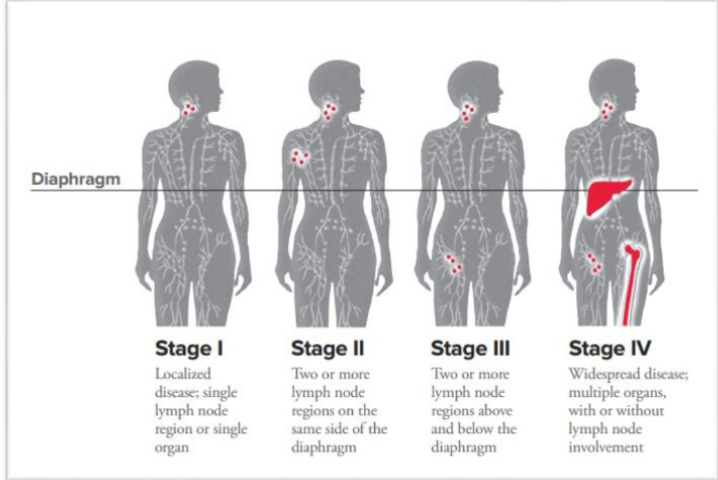
Now, let's talk a little bit about epidemiology. Less than 10,000 cases of Hodgkin lymphoma are diagnosed each year. It is considered a rare cancer. Five years after diagnosis, the overwhelming majority of people remain alive, which is very good news. Hodgkin has something called a bimodal age distribution. And, what that means is that there are a lot of people diagnosed as young adults and a lot of people diagnosed as what I'll call more experienced adults, around the age of 60. There are subtypes of Hodgkin lymphoma and for the purposes of this talk, we will focus on classical Hodgkin lymphoma treatment in those 18 years and older.



Slide 10: Presentation

The most common clinical presentations are enlarged lymph nodes in your neck or chest area. This is a picture of someone who has had a PET scan and the orange dots represent enlarged lymph nodes in the neck and armpit region. This region, highlighted in white, is an area called mediastinum. The mediastinum is an area between your lungs that contains your heart, important blood vessels, parts of your airway, and also lymph nodes. Sometimes, if there are enlarged lymph nodes in the mediastinum, you may experience a cough. Other symptoms associated with Hodgkin include, low grade fevers, drenching night sweats, and a weight loss that you did not intend to have.

Staging



Stage I
Localized disease; single lymph node region or single organ

Stage II
Two or more lymph node regions on the same side of the diaphragm

Stage III
Two or more lymph node regions above and below the diaphragm

Stage IV
Widespread disease; multiple organs, with or without lymph node involvement

Wake Forest Baptist Medical Center Courtesy of the Leukemia and Lymphoma Society

Slide 11: Staging

The stages of Hodgkin lymphoma are from Stage I to Stage IV. Stage I means very limited disease and Stage IV means that there is widespread disease. We generally use a PET scan as a part of staging.

Staging



Bone marrow biopsies are no longer routinely performed

Wake Forest Baptist Medical Center Courtesy of the Leukemia and Lymphoma Society

Slide 12: Staging

We used to routinely do bone marrow biopsies, but now we only do bone marrow biopsies if needed for something else, because bone marrow biopsies are no longer routinely performed as a part of staging.

The distant past....

Hodgkin disease is a systemic disease and invariably fatal

13 Wake Forest Baptist Medical Center Adapted from Saul A. Rosenberg

This slide features a white background with a black border. At the top center, the text "The distant past...." is displayed in a large, black, sans-serif font. Below this, a solid orange rectangular box contains the text "Hodgkin disease is a systemic disease and invariably fatal" in a smaller, white, sans-serif font. In the bottom left corner, the number "13" is visible. In the bottom center, the text "Wake Forest Baptist Medical Center" is present. In the bottom right corner, the text "Adapted from Saul A. Rosenberg" is displayed.

Slide 13: The distant past...

So, in the very distant past, actually in the 1960s and earlier, Hodgkin lymphoma was thought to be a systemic disease and invariably fatal.

The distant past....

Hodgkin disease is a systemic disease and invariably fatal

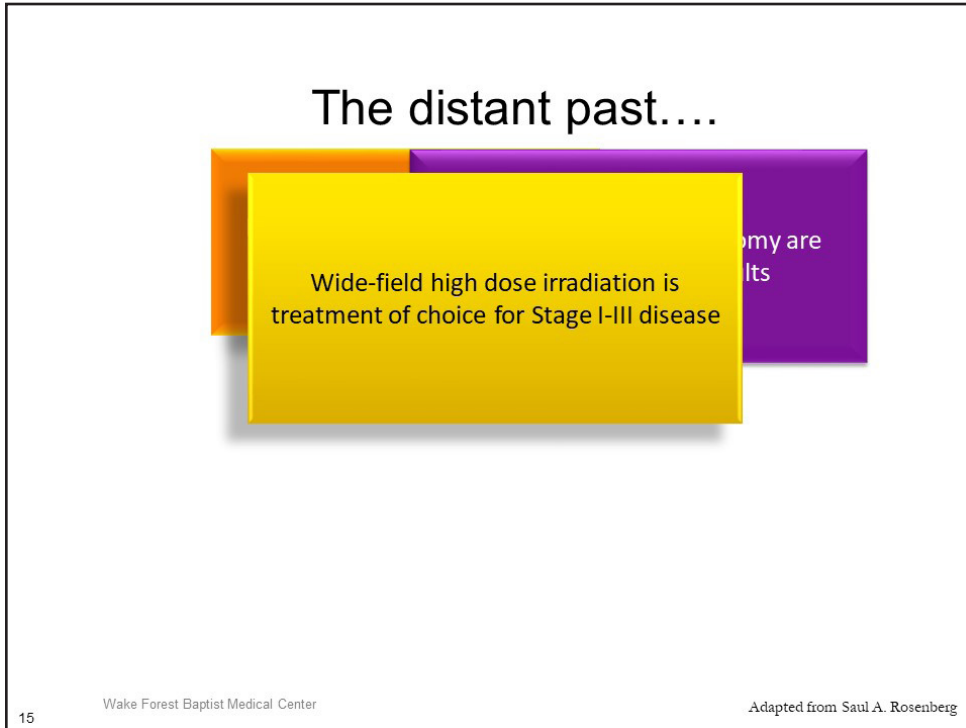
Laparotomy and splenectomy are required for best results

14 Wake Forest Baptist Medical Center Adapted from Saul A. Rosenberg

This slide features a white background with a black border. At the top center, the text "The distant past...." is displayed in a large, black, sans-serif font. Below this, there are two overlapping rectangular boxes. The left box is orange and contains the text "Hodgkin disease is a systemic disease and invariably fatal" in white. The right box is purple and contains the text "Laparotomy and splenectomy are required for best results" in white. In the bottom left corner, the number "14" is visible. In the bottom center, the text "Wake Forest Baptist Medical Center" is present. In the bottom right corner, the text "Adapted from Saul A. Rosenberg" is displayed.

Slide 14: The distant past...

It was thought that big surgeries, called laparotomies, and removal of your spleen, were required for the very best results.



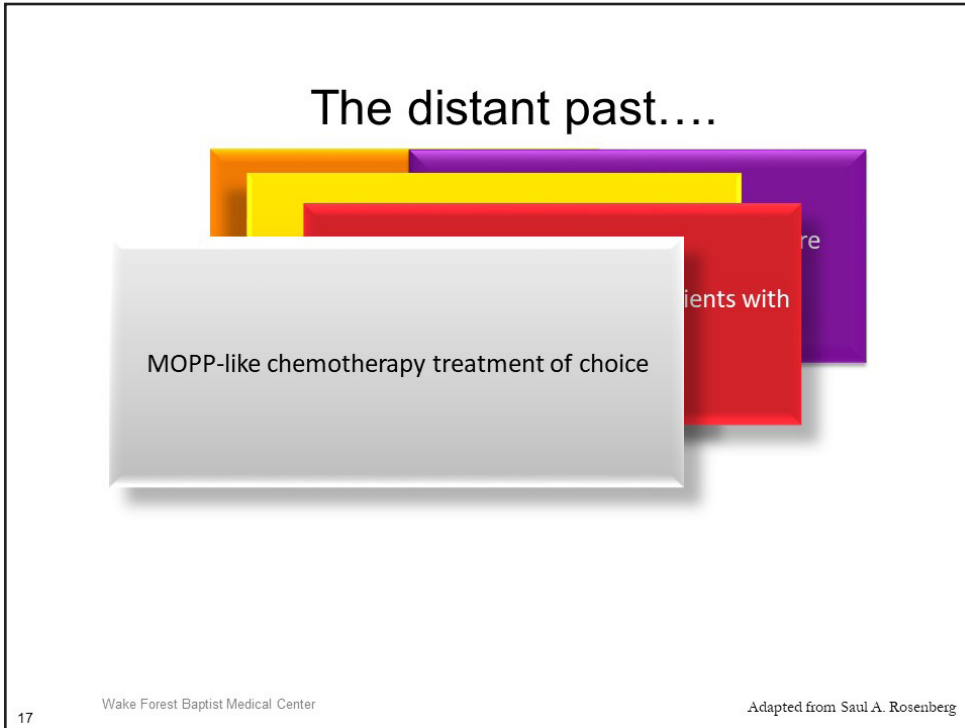
Slide 15: The distant past...

It was thought that big radiation fields were the treatment of choice.



Stage 16: The distant past..

And that chemotherapy was reserved only for those patients with advanced disease.



The distant past....

MOPP-like chemotherapy treatment of choice

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Adapted from Saul A. Rosenberg

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Stage 17: The distant past...

And, if chemotherapy was given, a chemotherapy called MOPP (mustargen, oncovin, procarbazine, prednisone) which is very toxic, was thought to be the treatment of choice.



The distant past....

MOPP-like c

Infertility, leukemia and heart disease are acceptable toxicities

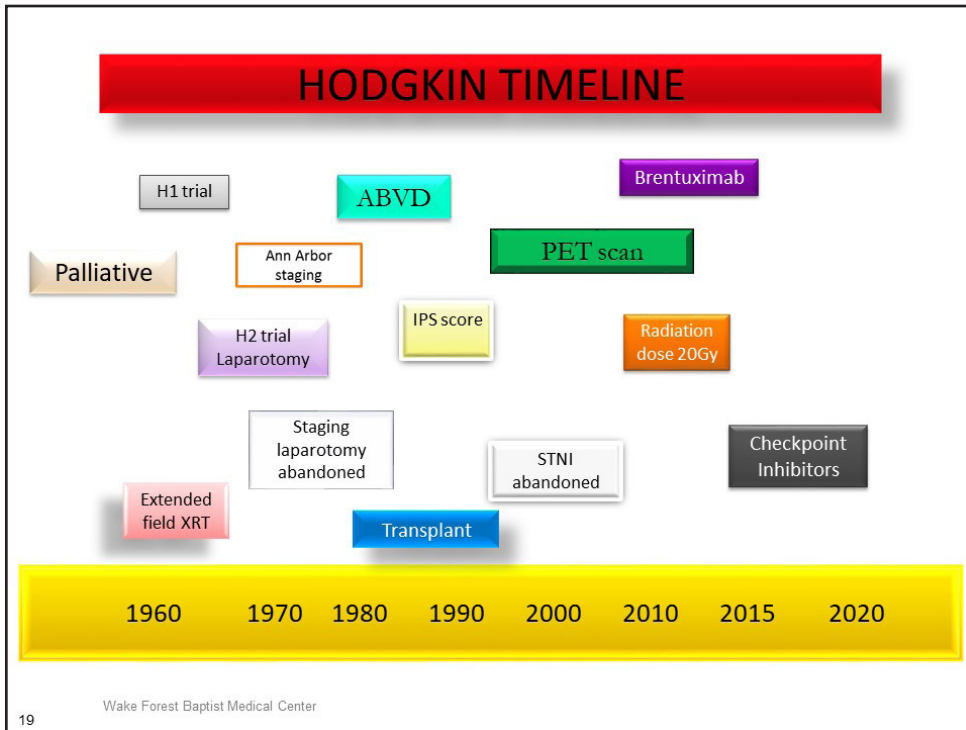
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Adapted from Saul A. Rosenberg

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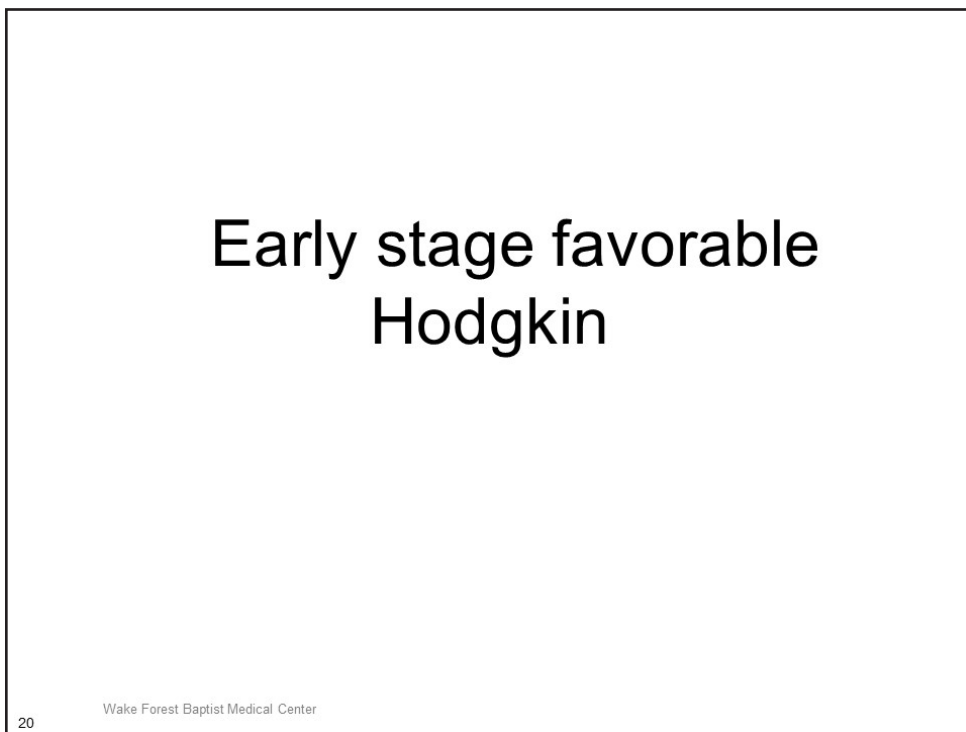
Slide 18: The distant past...

And, we thought that it was acceptable to have side effects that included infertility, secondary cancers, and heart disease. Fortunately, that was the distant past.



Slide 19: HODGKIN TIMELINE

And, this is a timeline that I made that just shows kind of all of the things that have happened over the last 60 years for Hodgkin lymphoma. It is remarkable how things have changed.



Slide 20: Early stage favorable Hodgkin

So, now let's talk about early stage favorable Hodgkin. The term favorable varies by country, but in general it means that this is someone who doesn't have a lot of disease, typically Stage I or II, no symptoms, and normal inflammatory markers.

Early stage favorable Hodgkin

Study	Stage	Treatment	Outcome
NCIC HD.6	IA or IIA	ABVD x 4 – 6 cycles	94% at 12 years

* Excluded for: bulky disease, ≥ 3 nodal areas, elevated ESR

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Slide 21: Early stage favorable Hodgkin

So, one of the trials that gave us the chemotherapy regimen that we typically use for Hodgkin lymphoma was the HD6 trial. This was a trial that evaluated 405 patients with previously untreated Stage I or II disease.

Early stage favorable Hodgkin

Can we safely reduce the chemotherapy or radiation doses?

Study	Stage	Study findings	Outcome
HD10	IA-IIB*	ABVD x 2 cycles then 20 Gy radiation	91% at 5 years
HD13	I-IIA	ABVD x 2 cycles then 30Gy radiation remained standard. Cannot routinely omit Bleomycin or dacarbazine	93% at 5 years

* Excluded for: bulky disease, ≥3 nodal areas, elevated ESR

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Slide 22: Early stage favorable Hodgkin

And, they were randomly assigned to treatment with either 4 to 6 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) alone or to treatment that included radiation. While this study is controversial because of outdated radiation, it gave us very good information on the long-term outcomes in those with early-stage disease with chemotherapy alone. The question we wanted to know, though, was can we safely reduce the chemotherapy or even the radiation doses.

And, the trials that tried to answer those questions are the HD10 trial and the HD13 trial. Let's talk about the HD10 trial. This is a trial that evaluated 1370 patients with newly diagnosed, early-stage favorable Hodgkin. And, patients were assigned to 1 of 4 treatment groups, which included more doses of chemotherapy and radiation. The goal of the study was to evaluate how long the Hodgkin remained in remission. This trial, the HD10 trial, showed that 2 cycles of ABVD, followed by low-dose radiation, was as effective as more chemotherapy and radiation.

Now, what about the HD13 trial? This is a trial that compared 2 cycles of ABVD with variants of ABVD, that omitted either bleomycin, which is the B in ABVD, or dacarbazine, which is the D in ABVD, or both. Each arm of the study was followed by radiation. This trial showed us that an early-stage favorable Hodgkin, dacarbazine and bleomycin should not be omitted at the very beginning of therapy without losing some form of efficacy.



Slide 23: Can we safely use a PET scan to guide therapy?

The next question is can we safely use a PET scan to guide therapy? And, 2 trials tried to answer this question. The first trial is called the RAPID trial. The RAPID trial is a trial that evaluated 602 patients, again with early-stage favorable Hodgkin, who received 3 cycles of ABVD, and if the PET scan was negative, which was considered a Deauville 1 or 2 score, and we'll talk about that more in a little bit, those with a negative PET scan were randomly assigned to radiation or no further treatment. After 5 years of evaluating these clinical trial participants, the overwhelming majority, more than 90% were alive without disease in both groups. Although, those who did not receive radiation had a very slight, almost 4% risk of relapse, as compared to those who did.

Early stage favorable Hodgkin
PET directed therapy trials

Study	Stage	Treatment	Outcome
RAPID	IA – IIA Non-bulky	ABVD x 3 cycles if PET scan (-) (Deauville 1 or 2)	91% at 3 years
EORTC H10	I-II	ABVD x 2 cycles if PET (-) then ABVD x 1 and involved node radiation (INRT)	99% at 5 years
	I-II	ABVD x 2 cycles if PET scan (+) then escalated BEACOPP x 2 cycles and INRT	91% at 5 year

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* Excluded for: bulky disease, ≥3 nodal areas, elevated ESR

Slide 24: Early stage favorable Hodgkin PET directed therapy trials

The next study is the H10 study. This is a study that was used to determine the need for radiation, using a PET scan after ABVD. And, the first part of the study, participants were treated with ABVD times 2 cycles if the PET scan was negative, another cycle of ABVD was given, followed by a kind of radiation called involved node radiation. And, the second part of the trial looked at those who had a positive PET scan, so again they were treated with ABVD times 2 cycles, but this time if the PET scan was positive, then treatment was changed to BEACOPP for 2 cycles, followed by radiation.

So, the first part of the study, in those with a negative PET scan, it showed that there were a little bit higher recurrence rates in those who were PET negative after 2 cycles of ABVD who did not have radiation, and the second part, those with a positive PET scan who were switched to the regimen BEACOPP, had improvement in how long the disease remained away, but this strategy did not improve how long participants lived overall. But, you can see that the outcomes for all of the patients were quite good.

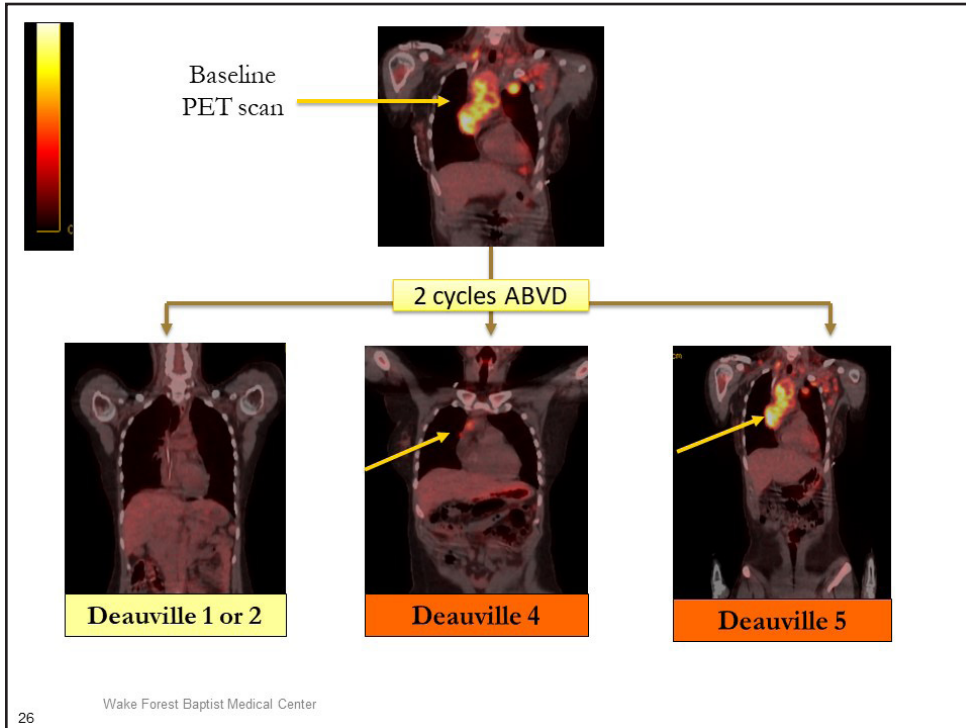
Pet scan Deauville score	
Score	Pet scan findings
Complete response	1 No uptake
	2 Uptake is \leq mediastinal (chest region) blood pool
	3 Uptake is \geq mediastinal blood pool but \leq liver
Partial response or progression	4 Uptake more than the liver
	5 Uptake markedly higher than liver +/- new disease sites

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Slide 25: PET scan Deauville score

Let's talk a little bit about the PET scan and the Deauville score. So, whether or not a PET scan is positive or negative is determined by the Deauville score. Before this scoring system, the PET scan reports were not standardized, and so the Deauville scoring system helps to standardize treatment results. There are different Deauville scores used. For example, a Deauville score of 1 or 2 is the same thing as a complete response. While a Deauville score of 4 or 5 usually means that someone is not in remission or that they may have evidence of progressive disease. You will see that the Deauville score 3 is in gray and the reason why I made the Deauville score 3 gray is because it's a bit of a gray area. It may represent a complete response, depending on when it is done.



Slide 26: Baseline PET scan

Let me show you an example. Now, this is a PET scan and the top image is someone at baseline. So, this is before chemotherapy starts. And, you see this is pointing to the area where the lymphoma is. After 2 cycles of ABVD, the next image, over to the left, you see no areas of brightness. This represents a Deauville score of 1 or 2. But, let's look at this middle image in the bottom. You see that this person has responded to chemotherapy, because there's less brightness on the scan, but there's still a small area of uptake. This is not considered a complete response after 2 cycles of therapy, and this would be considered a positive PET scan, meaning that there is still disease on the scan. And, you see the Deauville 5, there's still a lot of cancer after 2 cycles of ABVD.

Early stage treatment		
	Pros	Cons
ABVD	Associated with high cure rates	Side effects, bleomycin lung toxicity
	Low risk of infertility	
	Better tolerated	Results improved with radiation
Radiation	Associated with high cure rates	Associated with increased risk of future cancers
	Doses of radiation has decreased significantly	
Stanford V	Associated with high cure rates	Results similar to ABVD
BEACOPP	Associated with high cure rates	Risk of secondary malignancies, infertility, premature menopause

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Slide 27: Early stage treatment

Now, let's talk a little bit about the pros and cons of therapy. ABVD is considered the treatment of choice in the United States. It's a very good chemotherapy regimen and is associated with very high cure rates. For those that are interested in having children, there is a low risk of infertility, as compared to other chemotherapy regimens. We believe this regimen is better tolerated.

But, what are some of the side effects? Bleomycin lung toxicity is a side effect that scares oncologists the most. There are also other side effects that we'll talk about a little bit on the next slide. ABVD, when given for less than 4 or 6 cycles, sometimes the results tend to be improved with radiation.

Let's talk a little bit about radiation. Now, for Hodgkin lymphoma, radiation is not given by itself. It's typically given after chemotherapy. And, radiation is associated with high cure rates, and the radiation oncologists have done a very good job of decreasing the doses of radiation to try to limit some of the side effects. Unfortunately, not all side effects have been eliminated and radiation sometimes can still be associated with future cancers or even cardiovascular disease. There are some of us that are a little bit reluctant to radiate the mediastinum, particularly in young women, because of the potential risk of a future breast cancer.

I didn't talk about the Stanford V regimen very much, but I know that some of you across the country may be receiving, or may have heard of, the Stanford V regimen. It is associated with high cure rates as well, and the results, however, are similar to ABVD and that's one reason why we prefer ABVD.

You heard me mention BEACOPP. BEACOPP is a regimen that's used more often in Europe. Again, it's associated with high cure rates, but this regimen is much harder to give because of toxicity. There is a risk of having another cancer. Unfortunately, this regimen can also lead to infertility and premature menopause.

ABVD side effects

- Decreased blood counts
- Hair loss
- Nausea/vomiting
- Neuropathy



Component	Value	Ref Range & Units
WBC	2.1	4.8 - 10.8 X1000
RBC	4.11	4.2 - 5.4 X1,000,000
HEMOGLOBIN	11.4	12.0 - 16.0 G/DL
HEMATOCRIT	33.7	37.0 - 47.0 %
MCV	82.0	81.0 - 99.0 FL
MCH	27.7	27 - 31 PG
MCHC	33.7	33.0 - 37.0 G/DL
RDW	12.3	11.5 - 14.5 %
PLATELET COUNT	303	160 - 360 X1000

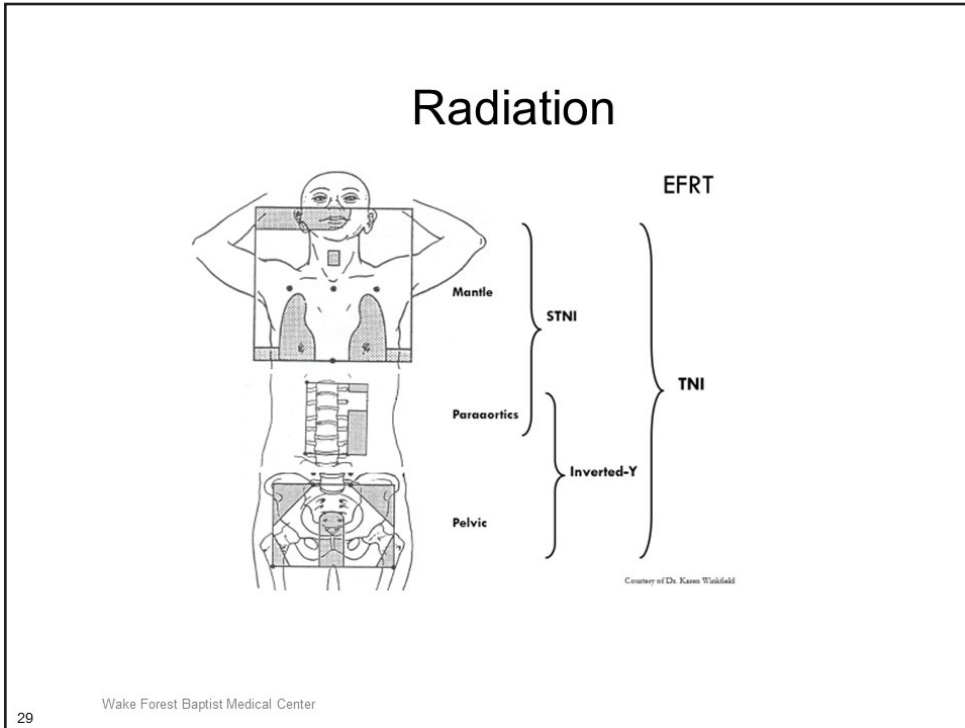
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Slide 28: ABVD Side Effects

A little bit about the side effects of ABVD. You see this picture to the right is the picture of the A in the ABVD, the adriamycin. So, ABVD can be associated with decreased blood counts, hair loss, nausea, vomiting, and neuropathy. And, I wanted to show you just an image of what a CBC or a complete blood count may look like when you're on treatment with ABVD. You will notice that the white count can sometimes lower and a part of the white count is something called a neutrophil. Your neutrophils are your infection-fighting cells. And, for ABVD you may become neutropenic, meaning those neutrophil numbers are low. We generally do not stop chemotherapy for neutropenia and we generally do not give a white count boosting medicine because it may increase the risk of having lung problems.

The next thing that you may see is a lowered hemoglobin. When your hemoglobin is lowered that is called anemia.

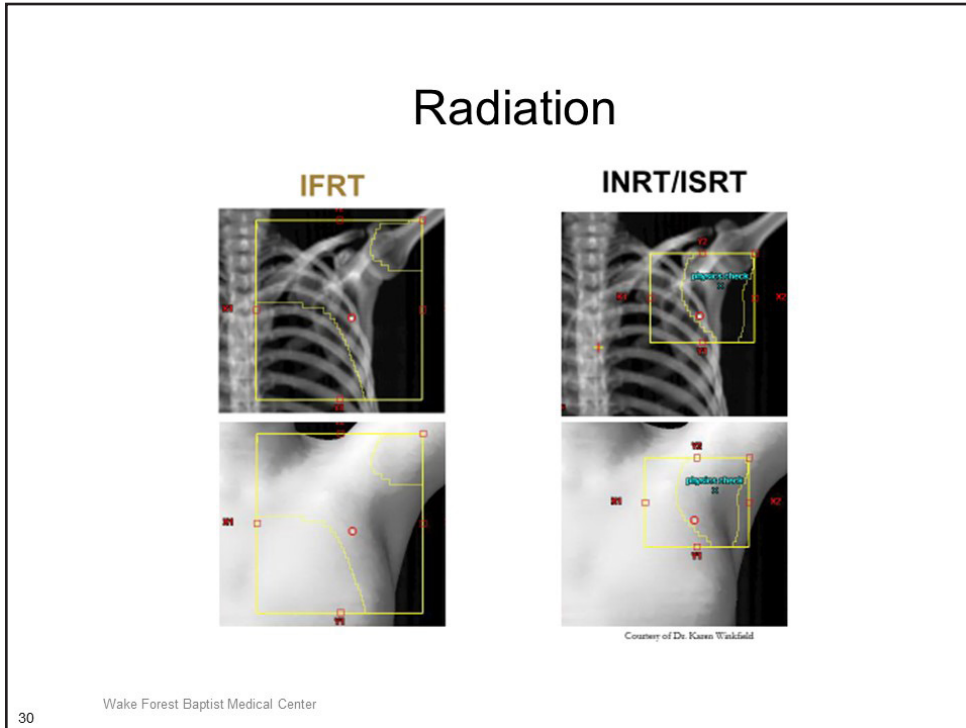


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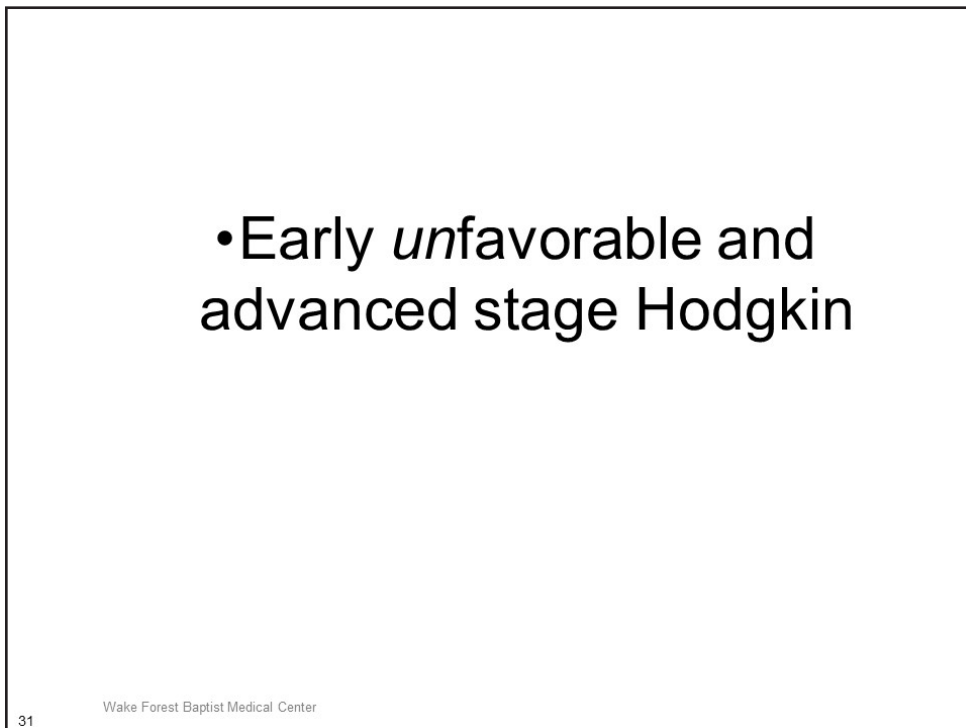
Slide 29: Radiation

Now, let's talk a little bit about radiation. I told you how the radiation fields have changed significantly over the last few decades. This is a picture of something called extended field radiation and you see the radiation fields were quite large. But, over time the radiation oncologists have been able to decrease the radiation field.



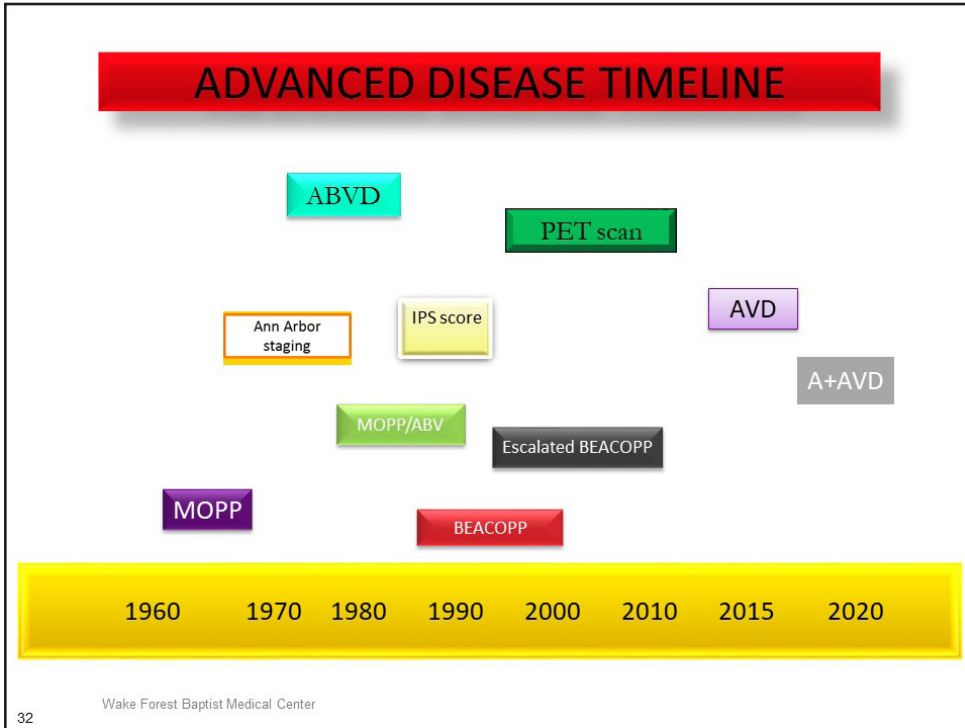
Slide 30: Radiation

So, on the left you see something called IFRT, which is involved-field radiation. And, some of the trials that I mentioned used involved-field radiation. The type of radiation that's more commonly used now is something called involved-node or involved-site radiation. And, that just involves the area that is involved with the cancer and a small area around it. This represents some of the smaller radiation fields that are used for Hodgkin in an effort to decrease side effects.



Slide 31: Early *unfavorable* and advanced stage Hodgkin

Now, let's talk about early unfavorable and advanced-stage Hodgkin.



Slide 32: ADVANCED DISEASE TIMELINE

And, this is just a timeline of what has happened for advanced-stage Hodgkin over the last 60 years. We've had a lot of very good improvement.

Treatment options for early *unfavorable* or advanced Hodgkin

Name of study	Treatment	Outcome
ECOG 2496	ABVD x 6 cycles	74% at 6 years
Viviani	BEACOPP x 8 cycles +/- radiation	85%
RATHL	ABVD x 2 cycles, PET scan (-) then AVD x 4 cycles	84% at 3 years
ECHELON-1	Brentuximab and AVD	82% at 2 years



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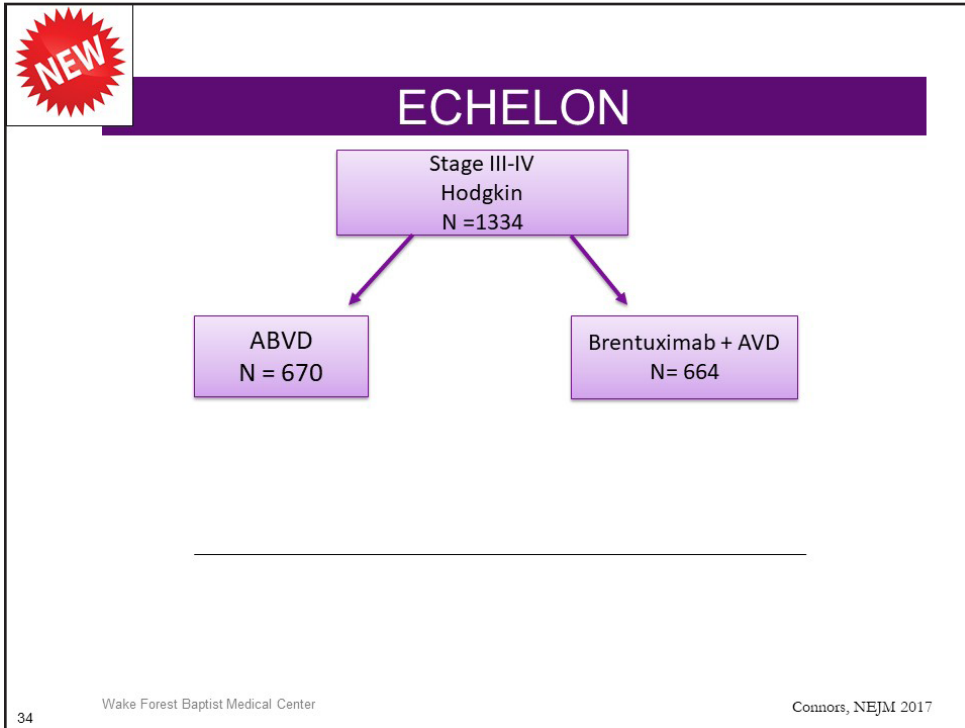
Slide 33: Treatment options for early *unfavorable* and advanced Hodgkin

The first study, the ECOG 2496 study, is a study that compared ABVD to the Stanford V regimen. And, this trial showed that there was no difference in response rates between the 2 regimens and in early-unfavorable or advanced-stage Hodgkin, ABVD remained standard.

The second trial is a trial that compared ABVD and BEACOPP in advanced stage disease, and it showed although that BEACOPP was better at initial tumor control, the long-term outcome, meaning how long the participants on the trial lived, the long-term outcome was no different.

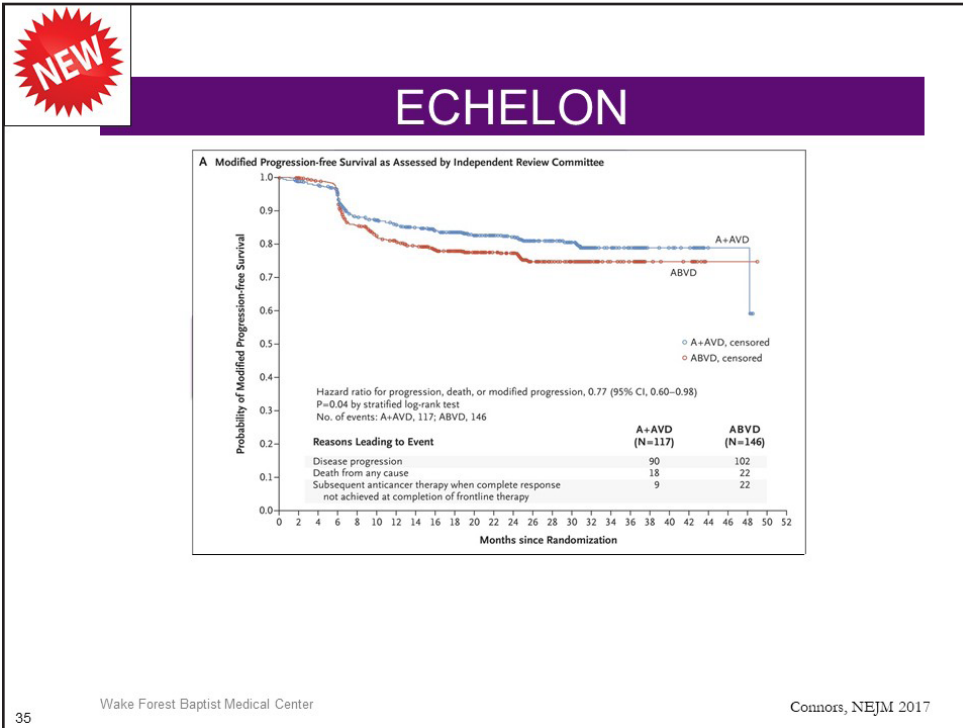
I want to spend a little bit more time talking about the last 2 trials. The RATHL study. In the RATHL study, ABVD was given for 2 cycles and then a PET scan was performed. If the PET scan was negative, and in this trial a negative PET scan was defined as a Deauville score of 1 to 3, then bleomycin was taken away and AVD was continued for 4 cycles. This trial showed in advanced stage disease, dropping bleomycin, did not lower the efficacy after the PET scan was negative, and it tended to improve lung toxicity. Although the study did not meet its endpoint, this study showed us that you can effectively drop bleomycin for those who have a negative PET scan in advanced stage disease.

Now, let's talk about the ECHELON study. The ECHELON study was very recently published, and it compares a drug called brentuximab. Brentuximab is a monoclonal antibody and it binds to a protein on Hodgkin cells called CD30.



Slide 34: ECHELON

This drug was combined with AVD. You will notice that the bleomycin was not included in the experimental arm of the study. And, the reason why, the combination of brentuximab and bleomycin given at the same time, can substantially increase lung toxicity. So, in the ECHELON study those with Stage III or IV disease were randomized to either ABVD or brentuximab and AVD.



Slide 35: ECHELON

And, this study showed, the blue line is the brentuximab plus AVD arm, it showed that there was a 5% lower risk of Hodgkin getting worse, coming back, or the need for more cancer treatment at 2 years. So, this is a very intriguing study and will likely become a part of standard of care for Hodgkin lymphoma. We'll talk a little bit about the concerns on the next slide actually.

Advanced stage treatment		
	Pros	Cons
ABVD x 6 cycles	High cure rates	Bleomycin toxicity Side effects worse in >60 yrs
BEACOPP x 8 cycles	Better disease control	Toxic, less experience in the US
ABVD x 2 cycles, PET scan (-) then AVD x 4 cycles	Slightly reduced risk of bleomycin toxicity	If PET scan positive, ideal treatment less clear
Brentuximab and AVD	No risk of bleomycin toxicity	Cost of brentuximab
	May be slightly more effective than ABVD	Requires growth factor
		Risk of neuropathy
		More follow up needed

Slide 36: Advanced stage treatment

So, let's talk about the pros and cons of therapy. So, ABVD times 6 cycles. It's associated with very high cure rates. But, there's that risk of bleomycin toxicity. And, the toxicities associated with ABVD tend to be worse in our more experienced population.

What about BEACOPP? BEACOPP does a very good job of controlling the disease, but there's not a lot of experience in the US and this regimen is very difficult to give.

What about the RATHL study that looked at ABVD times 2 cycles, then if your PET scan was negative, the bleomycin was dropped, and you continued AVD times 4 cycles? This trial was able to slightly reduce the risk of bleomycin toxicity, however, if the PET scan is positive then the ideal treatment is less clear.

Now, what about the ECHELON study? The study that I said was very intriguing. Some of the pros of this trial is that there's absolutely no risk of bleomycin toxicity because there's no bleomycin in the regimen. And, this regimen may be slightly more effective than ABVD. Some of the concerns are with the cost of brentuximab, a monoclonal antibody that would need to be given with each dose of therapy. This regimen actually requires a white cell medicine to increase your white cell count and we call this a growth factor. Remember, I said we do not routinely give growth factor for ABVD because of the risk of lung toxicity with the bleomycin. But, in this regimen brentuximab and AVD, there is no bleomycin and growth factor is required because the addition of brentuximab tended to lower the counts more than typical ABVD.

Brentuximab is also associated with something called neuropathy. Neuropathy can be numbness and tingling of your hands or feet, or weak, achy muscles. Brentuximab substantially increased the risk of neuropathy, although it was low grade and was able to improve once the medication was stopped. This is something that would need to be followed up on. And, right now, we have 2 years of information. We are waiting to see if this regimen helps those with Hodgkin to live longer. And, we should have that information in the next few years.

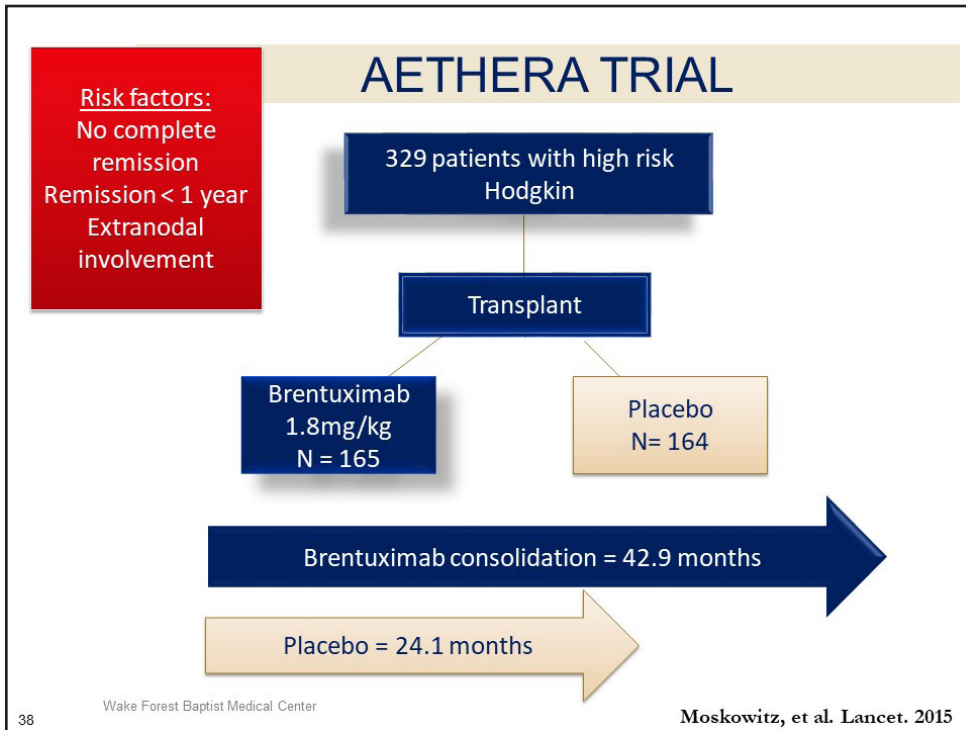
- What if the cancer does not go away or what if it comes back.....

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Slide 37: What if the cancer does not go away or what if it comes back...

But, now what if the cancer does not go away or what if the cancer comes back?



Slide 38: AETHERA TRIAL

This is the trial called the AETHERA trial. This is for those who had high-risk Hodgkin that returned. And, high-risk Hodgkin was defined as those who did not achieve a complete remission, the remission was less than a year, or the cancer was located in somewhere outside of the lymph nodes, such as in an organ.

So, the participants in this trial were given a second-line chemotherapy regimen, and then if they responded, they went on to something called an autologous transplant. This is a kind of transplant that uses your own stem cells and it allows oncologists to give higher doses of chemotherapy that you would normally not be able to tolerate, and then your stem cells are returned to you. That's called an autologous transplant.

After the transplant, participants were randomized to either brentuximab given for 16 cycles or placebo. And, the reason why there was a placebo arm on this trial is because generally after a transplant no further treatment is given in Hodgkin.

So, what did this trial show? This trial showed that brentuximab consolidation improved something called progression-free survival or how long the disease remained away, as compared to those who had no treatment after a transplant. Although progression-free survival was improved, there was no difference in overall survival or how long people lived after treatment. And, some of that is because those in the placebo group were able to get brentuximab at the time of progression. And so, they likely had a benefit, which is the reason why there may not have been a survival benefit in this study.

PD-1 inhibitors

- Also called checkpoint inhibitors
- Acts as gatekeepers on T cell function
- Nivolumab
- Pembroluzimab

Slide A: Chen, et al, JCO 2017
Slide B: Ansell, et al, NEJM 2015

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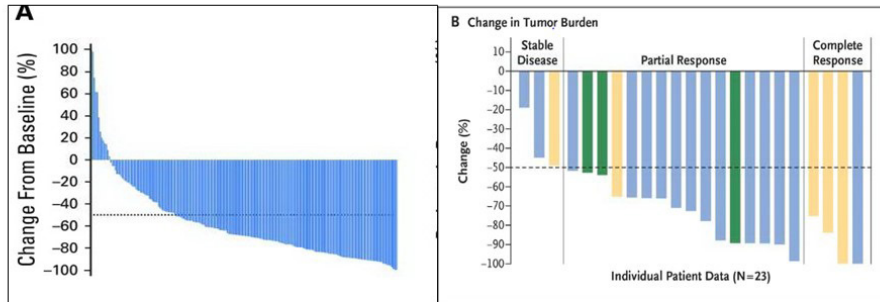
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Slide 39: PD-1 inhibitors

Now, let's talk about PD-1 inhibitors. PD-1 inhibitors are also called checkpoint inhibitors. Just for some background, T cells. T cells are special cells that go on surveillance in the body, looking for bad cells. And, these bad cells are – examples are viruses or cancers. When T cells see those bad cells, they create a signal that leads to an attack. Sometimes, however, cancer cells can be sneaky, and they know how to camouflage themselves using something called PDL-1. And, they're able to avoid the body's natural T cell defense system. So, cancer cells essentially are hacking the body's normal checkpoint defense to avoid attack and remain alive. Checkpoint inhibitors, they reveal those hackers, basically unmask those hackers, so that the T cells can then attack.

So, the checkpoint inhibitors that are approved for Hodgkin are nivolumab and another drug called pembrolizumab.

PD-1 inhibitors



Slide A: Chen, et al, JCO 2017
Slide B: Ansell, et al, NEJM 2015

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Slide 40: PD-1 inhibitors

The first slide is from the study that used pembrolizumab. And so, you'll see blue lines going down and what that means is the depth of response. So, as participants were treated with the pembrolizumab, they responded to therapy. And, the same is true with nivolumab. These drugs are associated with very good response rates in those where the Hodgkin has come back or if it did not go away with initial therapy.

Therapy combinations under investigation

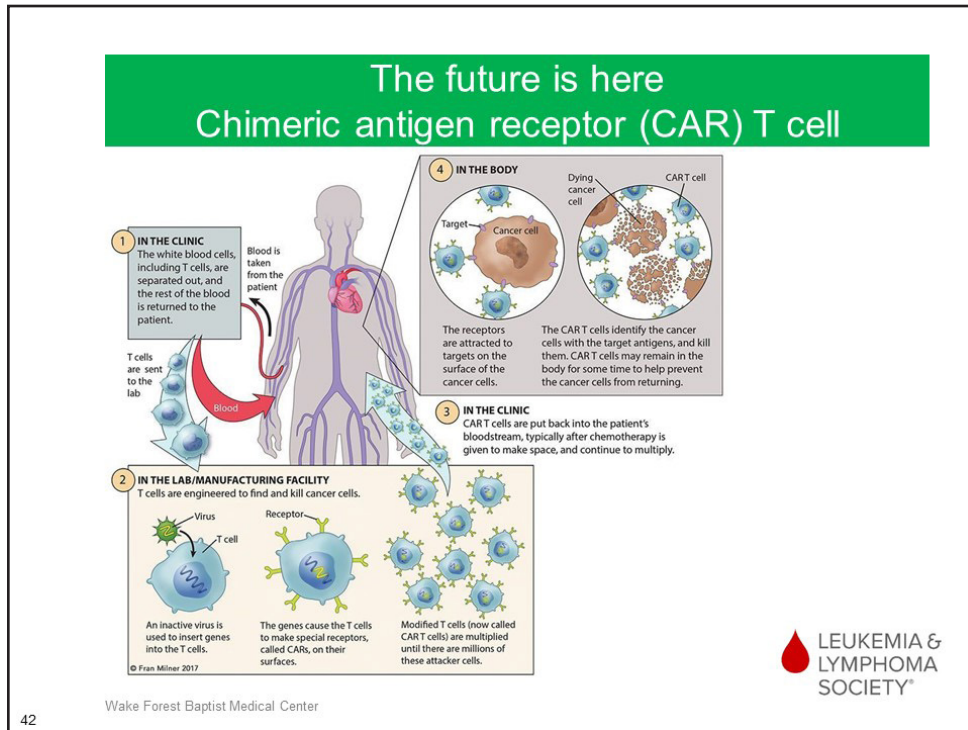
Brentuximab +	Nivolumab+	Pembroluzimab+
ICE	AVD	Acalabrutinib
Bendamustine	Ibrutinib	Brentuximab
Dacarbazine	ICE	Lenalidomide
Ipilimumab	Ipilimumab	
Nivolumab	Lenalidomide	Lenalidomide

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Slide 41: Therapy combinations under investigation

Some of the therapy combinations under investigation, and there are a lot, so I separated the therapy combinations into those that are combining the monoclonal CD30 antibody brentuximab with ICE. There's also very good emerging data for brentuximab and bendamustine. You also will see the combination of brentuximab and nivolumab in trial. And also, our checkpoint inhibitors, nivolumab and pembrolizumab. There are trials looking at nivolumab with AVD. And also, other oral drugs that are currently on the market. So, there are very exciting emerging therapy combinations that we'll learn more about over the next few years.



Slide 42: The future is here Chimeric antigen receptor (CAR) T cell

Now let's talk about CAR T-cell therapy. CAR means chimeric antigen receptor, and this is actually a picture that was taken from The Leukemia & Lymphoma Society website. There's very good information on this website. And so, for CAR T-cell therapy, it is approved in certain subtypes of B cell non-Hodgkin lymphoma and it's also been FDA approved in certain types of leukemia.

Now, what is CAR T-cell therapy? Remember we talked about those T cells, those surveillance cells that are checking your body, looking for bad cells. So, with CAR T-cell therapy, blood is taken from you and the T cells are separated out. And so, then those T cells are engineered to produce artificial receptors, hence the name chimeric antigen receptors. Chimeric just means a mixture of things. So then, these receptors are multiplied to target tumor cells in a specific area, such as a CD30 on Hodgkin cells. Before the CAR T-cells are given back to you, you receive chemotherapy to try to deplete your own lymphocyte cells. That's called lymphocyte depletion. So then, the CAR T-cells are given back to you to recognize and attack cancer cells that have the specified target on their surface. There are side effects associated with CAR T-cell therapy, but fortunately over time, these side effects are now starting to be minimal and don't last as long. And, this form of therapy is in clinical trials right now and we are looking forward to more information on CAR T-cells in Hodgkin.

Shared decision making

- Newly diagnosed
 - How will treatment affect....
 - Fertility, cardiovascular disease, risk of another cancer (skin, breast, lymphoma)
 - Finances??
 - Herbal supplements...
 - Interim PET scan
 - Will treatment change based on the results?



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Slide 43: Shared decision making

Now, let's spend the very last part talking about shared decision making. This is when you have a conversation with your healthcare provider about your needs. If you are newly diagnosed, the questions that you should ask are how will treatment affect fertility? If you're interested in having children, you should make sure that this question is asked up front. Cardiovascular disease? We know that some of the chemotherapies can affect your heart. We know that radiation, especially to your mediastinum, can affect your heart. If you already have a history of cardiovascular disease, you want to ask your healthcare provider about how to minimize this. And also, you want to ask about your risk of other cancers. Common cancers that can occur after a Hodgkin diagnosis are actually skin cancers. We know that breast cancer, I've mentioned that, and we do recommend breast surveillance strategies for those who have finished treatment. But how can we minimize that up front?

Finances? We know that sometimes the cost of cancer care in the United States can be expensive. The Leukemia & Lymphoma Society has good information to help you with this. I would also ask you to talk with your healthcare providers about the resources within your own area.

Herbal supplements? There are many people taking herbal supplements and they may not know that sometimes these medications can interact with chemotherapy and potentially make it less effective. You want to tell your healthcare provider about anything that you are ingesting or taking as a part to help with treatment.

Now, what about that interim PET scan? You want to ask how will this change your treatment, if at all, based on the results of the scan.

Shared decision making

- Post-treatment
 - How often will scans be performed?
 - How long will I deal with memory problems, sexual dysfunction, fatigue, peripheral neuropathy?
 - When should I transition to primary care?



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Slide 44: Shared decision making

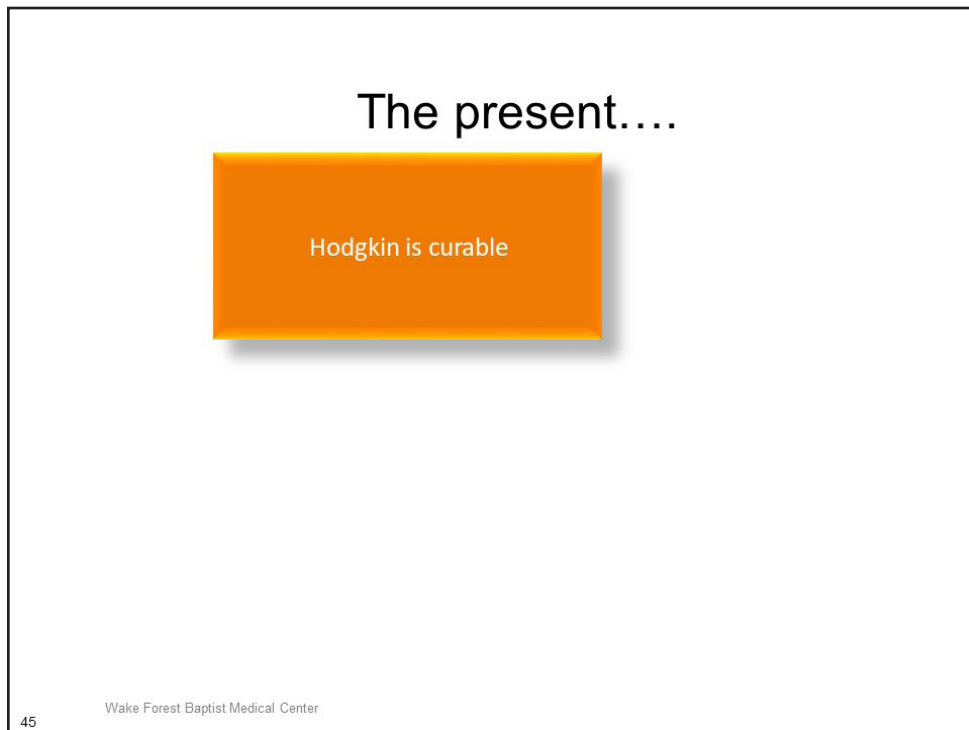
After treatment, I am often asked, how often are scans performed? So typically, we perform an early interim PET scan after 2 cycles and then at the very end of chemotherapy. Once a PET scan is negative, then we perform a CT scan twice the first year after completion of chemotherapy, and then once their second year. After the second year, we no longer perform imaging studies if there are no symptoms. We do not recommend routinely performing PET scans once chemotherapy has finished and the PET scan is negative because of the radiation associated with it and the risk for false positives.

So, we know that survivors are reporting higher incidences of things like fatigue, sexual dysfunction, and peripheral neuropathy.

Let's talk a little bit more about neuropathy. Neuropathy can be difficult to treat and we typically, if we can, try to avoid it. If you have neuropathy, which is numbness, tingling of the hands or feet, or weak, achy muscles, we recommend that if the pain or the discomfort is severe, you may want to consult with a pain medicine provider or an integrative medicine specialist. Sometimes yoga and massage can be helpful. For those who have difficulty with sensation, it's very important that if you're cooking, you want to do things like use potholders. You want to make sure that your home is protected so that you could decrease the risk of falls.

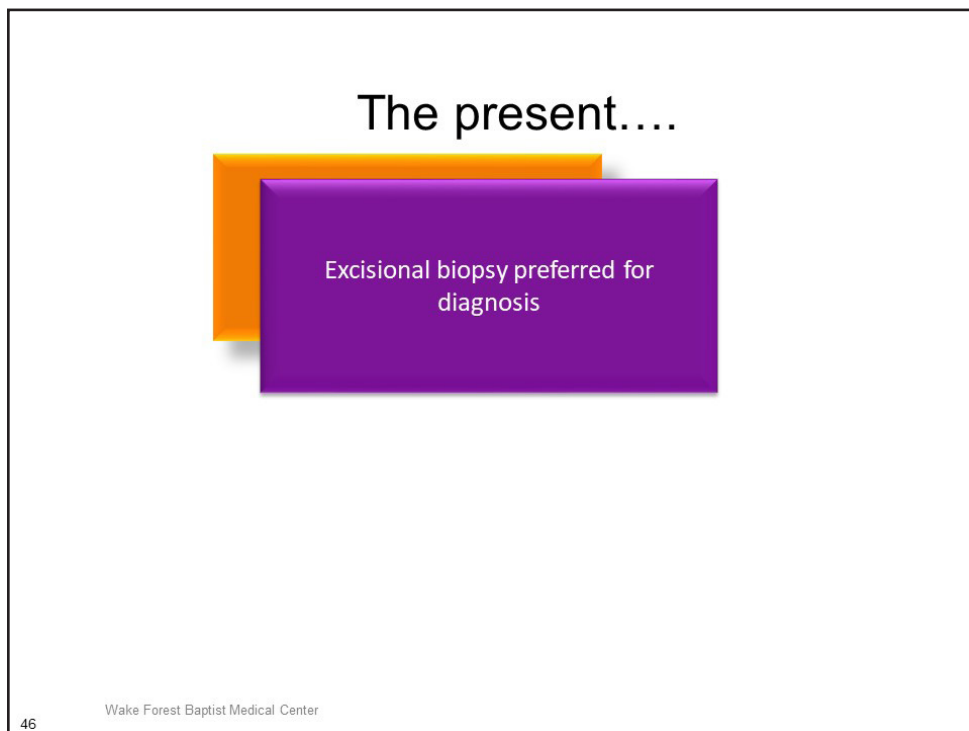
Something else that comes up are memory issues, which can be memory loss, difficulty concentrating. Exercise and meditation are sometimes helpful. You want to make sure that you make a list. Sometimes if memory problems are severe, we will refer for something called neuropsychological testing.

The last question, when should I transition to my primary care physician? Usually after you've been followed for 5 years, you will transition back to your primary care physician. Before that happens, you want to make sure that you have a treatment summary that details all of the treatments that you had and the follow-up that your oncologist recommends.



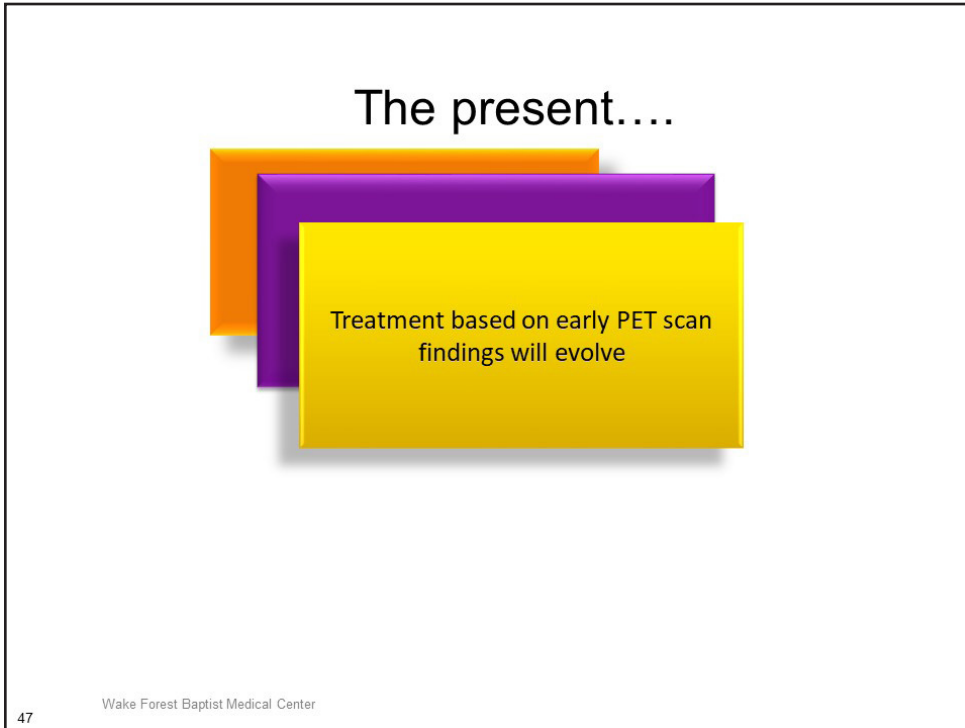
Slide 45: The present...

So, now let's talk about the present. We know absolutely that Hodgkin is curable.



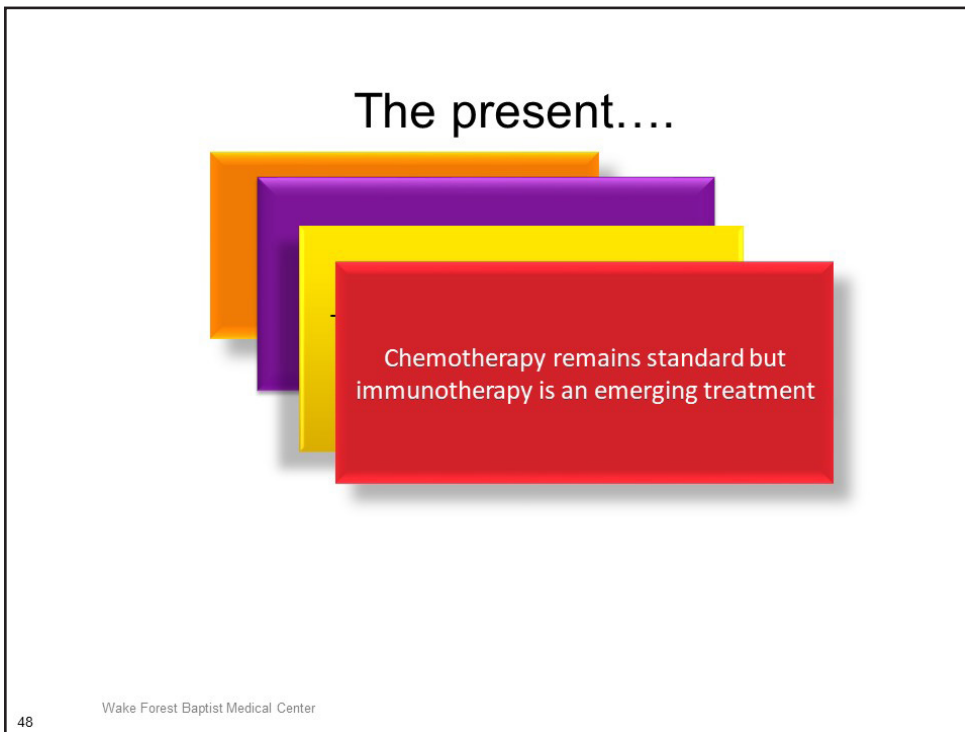
Slide 46: The present...

We still prefer an excisional biopsy for diagnosis.



Slide 47: The present...

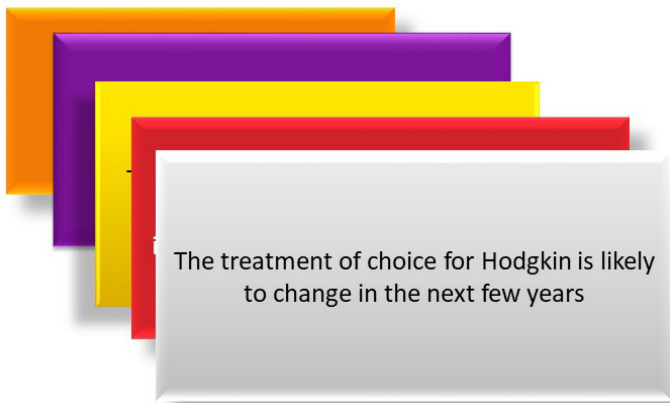
We believe that treatment based on the early interim PET scan will continue to evolve.



Slide 48: The present...

And, although chemotherapy remains standard, particularly in the up-front setting, immunotherapy is an emerging and exciting treatment.

The present....



The treatment of choice for Hodgkin is likely to change in the next few years


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Slide 49: The present...

And, the treatment of choice for Hodgkin is likely to change in the next few years.

The present....



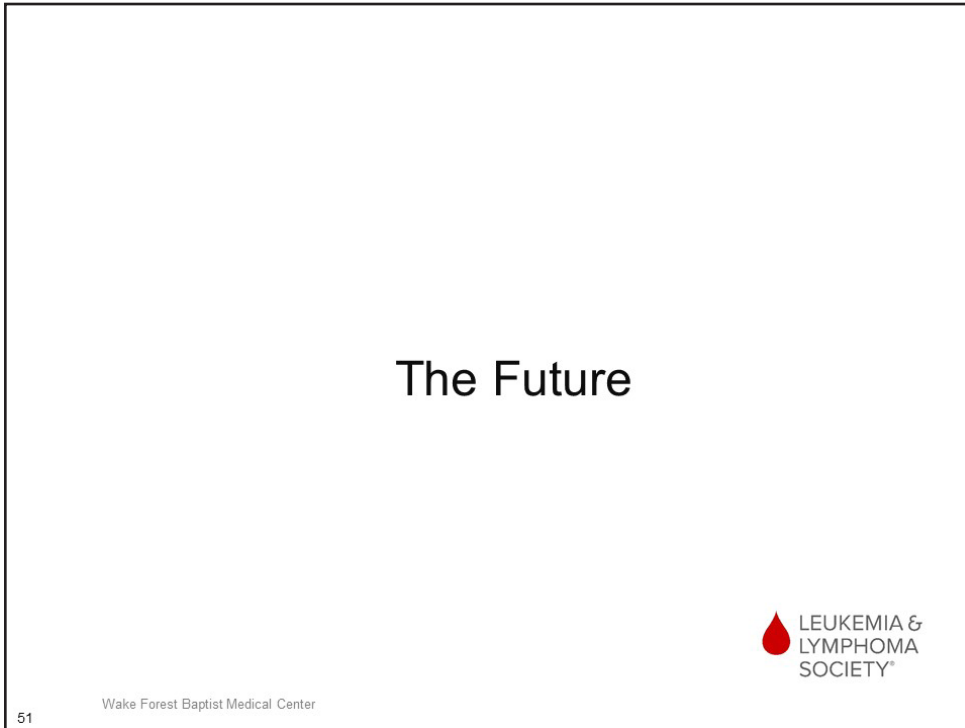
Treatment goal is not only cure of Hodgkin but also improving quality of life during and after therapy

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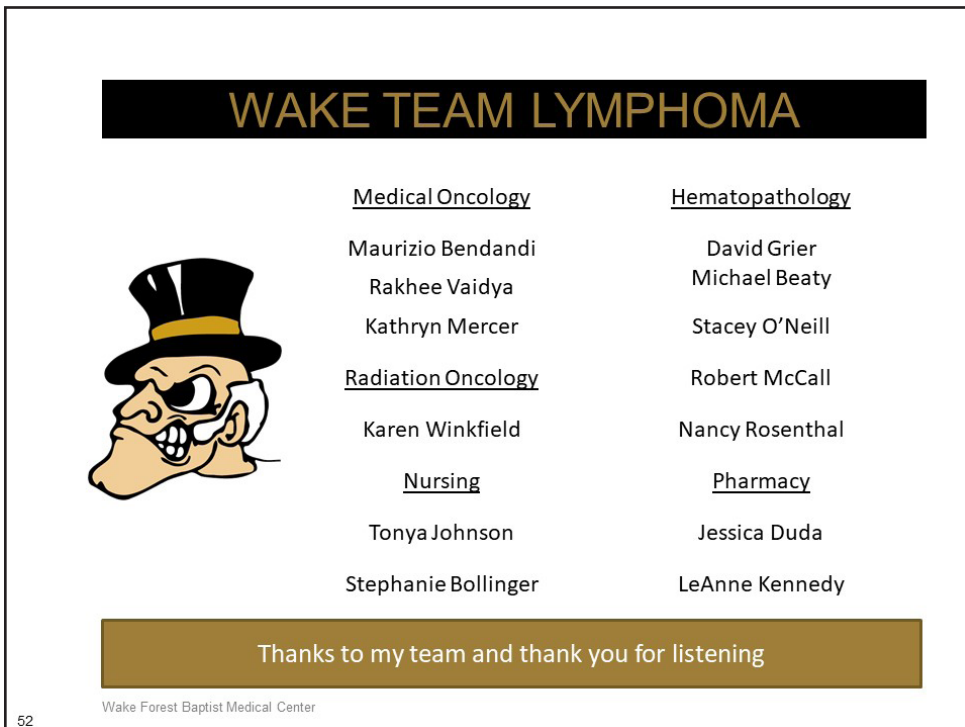
Slide 50: The present...

Our treatment goal is not only cure of Hodgkin, but also improving quality of life during and after therapy.



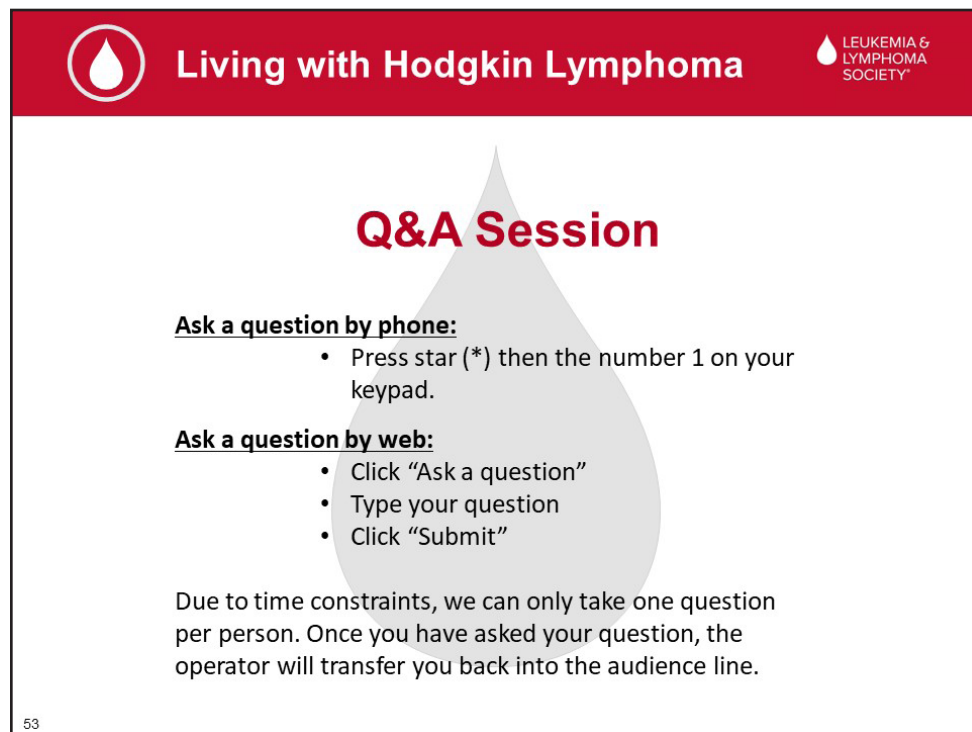
Slide 51: The Future

What about the future? The future is bright. Our outlook is so positive. And, we hope that one day everyone is cured without any short- or long-term side effects.



Slide 52: WAKE TEAM LYMPHOMA

I would like to thank my Wake Team Lymphoma. I would like to thank The Leukemia & Lymphoma Society for doing a great job of getting information out to you. And I would like to thank you all so much for listening. This concludes my presentation.



The slide features a red header with a white drop icon and the text "Living with Hodgkin Lymphoma" and "LEUKEMIA & LYMPHOMA SOCIETY". The main content is white with a large grey drop graphic in the background. The text is centered and includes instructions for asking questions by phone and web, and a note about time constraints.

Living with Hodgkin Lymphoma LEUKEMIA & LYMPHOMA SOCIETY

Q&A Session

Ask a question by phone:

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

Ask a question by web:

- Click "Ask a question"
- Type your question
- Click "Submit"

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

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Slide 53: Q&A

Lizette Figueroa-Rivera:

Thank you, Dr. Lamar. It is now time for our question and answer portion of our program.

We'll take the first question from our web audience. Doctor, Jerry asks: How soon after treatment is bleomycin toxicity manifested?

Dr. Zanetta Lamar:

That's a very good question. Sometimes bleomycin toxicity can occur during treatment. But, it can also be delayed. So, usually it will manifest within the first 6 months.

Lizette Figueroa-Rivera:

Okay, we'll take our next question from the web audience. Doctor, Sarah asks: Has Hodgkin lymphoma been tied to exposure of any environmental hazards?

Dr. Zanetta Lamar:

That is a very good question. Hodgkin lymphoma is quite rare. We know that those who have a family member with Hodgkin can sometimes have an increased risk. Whether that's related to genetics or because they're in the same environmental area, it's hard to say. We know that there are some viruses, such as Epstein-Barr virus, that can be associated with Hodgkin. But a clear environmental source has not quite been delineated yet. Good question.

Lizette Figueroa-Rivera:

Thank you. And, the next question comes from the web. Nancy wants to know: If it is common, if anyone is experiencing blockages in the carotid arteries due to radiation in the neck?

Dr. Zanetta Lamar:

That is common actually. And, as a part of follow-up, we actually recommend that if you received radiation to your neck, you should get an ultrasound of your carotid at 10-year intervals. So, 10 years after you've received the radiation to your neck, you should start getting an ultrasound of your neck and then repeating that every 10 years to look for blockages. Fantastic question.

Lizette Figueroa-Rivera:

Yes. And, we'll take the next question from our phone audience, please.

Operator:

Thank you. Our next question comes from Maria from New York. Please state your question.

Maria:

Yeah, I want to know the frequency of autoimmune deficiency after treatment.

Dr. Zanetta Lamar:

It's actually not very common to have autoimmune deficiency after treatment. There are some people who may be predisposed to Hodgkin who have autoimmune disorders before therapy. But, it's not very common to suffer autoimmune deficiencies post-treatment.

Lizette Figueroa-Rivera:

Thank you for your question. And, our next question comes from the web. Hillary is asking about fertility post-treatment.

Dr. Zanetta Lamar:

So, fertility is a very big issue. We know that women tend actually to have better fertility after a treatment, such as ABVD than men. We routinely recommend that our patients, even with ABVD, even though your fertility can be preserved, we still recommend that they're seen by a reproductive endocrinologist. If you have been exposed to chemotherapy and you are having any issues with fertility, I actually recommend that you go ahead and go to a reproductive endocrinologist instead of waiting to see what may be the issue. But, typically after ABVD, fertility is preserved in the majority of patients. After things like a transplant or BEACOPP, then we know that these things tend to make those exposed infertile. Another good question.

Lizette Figueroa-Rivera:

Thank you. And, Mary Jo on the web is asking about nodular lymphocyte predominant Hodgkin lymphoma, a rare subset. And, just asking more about the prognosis for someone of her gender and a young adult age.

Dr. Zanetta Lamar:

Sure. So, what we call NLP Hodge or nodular lymphocyte predominant Hodgkin, is rare. It only represents about 5% of Hodgkin subtypes. And, it behaves nothing like Hodgkin lymphoma actually. So, nodular lymphocyte predominant Hodgkin is very responsive to treatment, depending on your stage and really, we tend to individualize treatment in those who have NLP Hodge. But, the prognosis is actually excellent. There is a risk, about 25% to 30%, after treatment, you may have to be treated again, but still prognosis is very good for NLP Hodgkin.

Lizette Figueroa-Rivera:

Thank you. And, on the web Darla is asking about long-term effects of mantle radiation. Her daughter is a 28-year survivor of Hodgkin lymphoma, Stage 3B, and she received only radiation after staging laparotomy at age 15.

Dr. Zanetta Lamar:

And so, this really shows you how the treatment has changed over the past 30 or 40 years for Hodgkin lymphoma. So, mantle radiation can cure Hodgkin, as it did for this young lady. In those who received mantle radiation, we actually do aggressive follow-up. So, I don't know how old she is, but I typically recommend very aggressive breast screening. So, we perform mammograms and MRIs yearly. I recommend that there is a heart evaluation with either an ultrasound of the heart. Sometimes we will refer to cardiology just because of the history of mantle radiation, because of the risk of cardiovascular disease. We check for thyroid issues. We make sure that vaccinations are given each year. And so, as long as we are taking kind of a preemptive approach, her daughter should do quite well.

Lizette Figueroa-Rivera:

Thank you. And, our next question from Jennifer: Any advice on patients who have undergone radiation and now suffering from radiation fibrosis syndrome?

Dr. Zanetta Lamar:

Radiation fibrosis syndrome, it depends on kind of where she had the radiation. I believe I have an idea. It's very difficult to treat and I would recommend that she have a discussion with her radiation oncologist and even specialist to try to help. Unfortunately, we do not have therapies to reverse radiation fibrosis, unfortunately.

Lizette Figueroa-Rivera:

Thank you. And, we did receive a lot of questions in regard to nutrition. Ricardo is asking: Are vitamins and training supplements, protein shakes, creatinine intended for muscle growth recommended upon completion of treatment and when in remission?

Dr. Zanetta Lamar:

I think nutrition is incredibly important. We know that those who exercise and live a healthy lifestyle physically tend to do better, but it also helps with kind of emotional things like depression and other things that can happen post-therapy. So, most things in moderation are very good. I would make sure that he has a conversation with his healthcare providers about everything he's taking. Moderation, I have learned, means different things for different people. And, The Leukemia & Lymphoma Society has very good resources on nutrition as well. But, most things in moderation are okay after completion of therapy.

Lizette Figueroa-Rivera:

Thank you. Our next question comes from Senette: After reoccurrence, what is the treatment for early-stage Hodgkin?

Dr. Zanetta Lamar:

Sure. So, after recurrence, one of the things that we like to know is how long did the Hodgkin stay away. We know if you're able to go over a year without having disease, people tend to do better. Having said that, usually we will do a kind of therapy called second-line therapy and that really depends on where you are across the country. But, our second-line therapies are generally pretty good. If there is a response to the second type of chemotherapy that's given, then we would recommend an autologous transplant, and that's the kind of transplant where you use your own stem cells. If this is not an option or there is not a good response to second-line therapy, that's where some of the newer drugs, like brentuximab and the PD-1 inhibitors come in. And, if for whatever reason, if that is not a good option, that's when you can look for clinical trials that include things like CAR T-cell therapy.

Lizette Figueroa-Rivera:

Thank you. And, our last question today comes from Christian. Christian is asking about cancer-related fatigue in Hodgkin lymphoma, how long will it last?

Dr. Zanetta Lamar:

Cancer-related fatigue I think is the bane of an oncologist's existence. It's very, very difficult to treat, but it can improve, and it will improve over time. So, what I recommend for fatigue is to track your fatigue. Sometimes it may be improving, but it's occurring so slowly that it's hard to tell. So, I want you to keep a diary, track your fatigue so that you can tell your healthcare provider about what's going on. You want to try to take scheduled short naps. Try to have very good sleep hygiene. You want to try to go to sleep eight hours a day. And also, exercise and eat healthy, that will help kind of speed up that cancer-related fatigue. But it does, it takes a very long time for that to improve.

Lizette Figueroa-Rivera:

Thank you so much Dr. Lamar for your continued dedication to patients. And, for those of you who participated in today's program, we hope this information presented today will assist you and your family in your next steps.



The Leukemia & Lymphoma Society Offers:


- **LLS Information Specialists:** Master's level oncology professionals who can assist you through cancer treatment, financial and social challenges, and give accurate up-to-date disease, treatment, and support information.
 - EMAIL: infocenter@LLS.org
 - TOLL-FREE PHONE: 1-800-955-4572
- **Free Education Booklets:**
 - www.LLS.org/booklets
- **Free Telephone/Web Programs:**
 - www.LLS.org/programs
- **Live, Weekly Online Chats:**
 - www.LLS.org/chat



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Slide 54: The Leukemia & Lymphoma Society Offers:

And, if we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM eastern time or reach us by email at infocenter@LLS.org.



The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance, and more: www.LLS.org/support
- **LLS Podcast, *The Bloodline with LLS*:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org
- **Education Video:** Free education videos about survivorship, treatment, disease updates, and other topics: www.LLS.org/educationvideos
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask

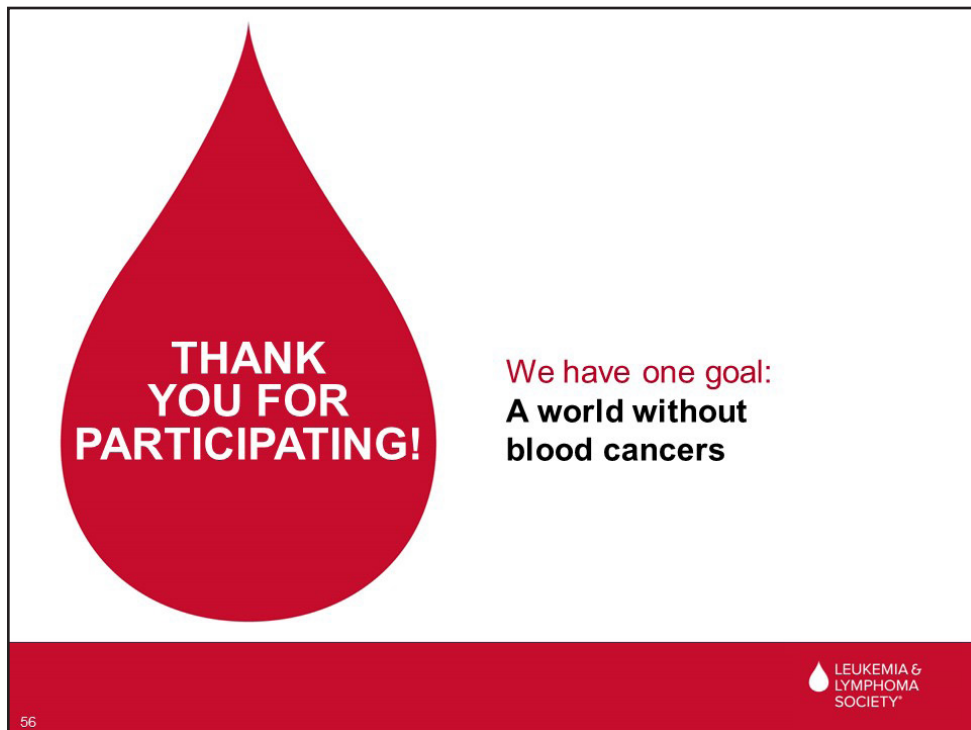


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Slide 55: The Leukemia & Lymphoma Society Offers:

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment. Information Specialists can also discuss and refer you to a free personalized nutrition consult with our Nutrition Educator.

Again, we would like to acknowledge and thank Seattle Genetics and The Leukemia & Lymphoma Society for support of this program.



Slide 56: THANK YOU FOR PARTICIPATING

Dr. Lamar, thank you again for volunteering your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

END