Hello. I'm Dr. Romaguera. I am Professor of the Lymphoma/Myeloma Department at The University of Texas MD Anderson Cancer Center.

And today I plan to discuss with you some important issues in terms of the diagnosis, clinical presentation, as well as the x-ray findings and the blood tests in patients that are diagnosed as Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, or multiple myeloma.

We’ll start --- We’ll start first with non-Hodgkin's and Hodgkin's lymphomas. These are the malignant lymphomas. The non-Hodgkin's lymphoma is the most common entity of both and 85% of the non-Hodgkin’s lymphomas originate from a B-cell.

In terms of risk factors for lymphoma, there is no clear known cause of this. There are suspected environmental agents. Pesticides and herbicides have been suspected. There are chemicals that have been already accepted, such as Agent Orange and creosote. The radiation exposure has been suspected it --- even though it is not totally clear. Being immunodeficient also increases the risks of developing lymphoma. And I have put in the lower part of the slide some inf --- examples that might be associated with immunosuppression, such as the HIV, human immunodeficiency virus, which is associated with AIDS, which is acquired immunodeficiency. That has been associated with a subtype of aggressive lymphomas that occur in the brain. Also the HTLV-1, human T-cell lymphoma 1 virus, is associated with leukemia lymphoma. The Epstein-Barr virus has been associated with a pediatric form of Burkitt's in young --- young children in Africa. And the bacteria Helicobacter pylori has been associated with another subtype of lymphoma that is not clinically aggressive, which is MALT, mucosa-associated lymphoid tissue.

The usual clinical presentation as far as the patient can feel, would be a lump that appears either in the neck or under the armpit or in the groin that remains for over two weeks. It does not dis --- disappear and that is nontender. Constitutionally, the patient might feel a temperature, might have drenching night sweats, and could have more than 10% loss in his or her weight over the last six months unintentionally.

It is very important for a diagnosis to be established to get a biopsy. A fine needle aspiration will not be enough. This biopsy can be a needle --- a core needle biopsy. The reason for this is that the classification still rests mainly on how the architecture looks. So some loose cells do not help in identifying which of the 40 types of non-Hodgkin’s lymphoma the patient might have. So it’s very important to get a piece of tissue of that lymph node or any other organ where the findings might have been. Bone marrow is an important part. We do an outpatient procedure with again a needle core biopsy of the bone marrow in the posterior iliac crest to document whether there is involvement in the bone marrow. This will be important in the decision of how far advanced the disease is and it will have prognostic and even therapeutic implications. Other tests that are part of the initial tests include laboratory tests, such as blood tests. Sometimes they are very low, the white counts and the platelets, because the marrow is extensively involved or because of autoimmune problems related to the lymphoma.
Serum chemistries are very important. We want to know how the organs are. Is the liver involved? Is the kidney involved? Some --- Many times these are important facts before we decide what therapies or chemotherapies the patient might have. One of the very important prognostic factors is actually a serum chemistry. It’s the lactate dehydrogenase. So this is an important part of the evaluation.

Also, [it is] very important to find out how extensive the disease is, is to do a chest x-ray, to do computer tomography of the neck, chest, abdomen, and pelvis. And nowadays doing also a physiologic test, such as a PET scan is very important in detecting where the lymphoma might be.

This is just a brief overview of some of the most important non-Hodgkin’s lymphomas. I have classified them just for the clinical purposes into those who have an indolent behavior meaning they might double their size in six months to a year. Those that are aggressive which might double their size in months. And the very aggressive which sometimes double their size in a matter of weeks and I have given some examples. If you see under indolence, the follicular lymphomas are one of the most common types of B-cell lymphomas as we’ll see in the --- in subsequent slides. It’s about 20-30% of them. And the aggressive lymphomas, the most common by far, is the diffuse large B-cell lymphoma. We are finding that this is really a conglomeration of different entities that are slowly being teased away from this diagnosis. One of them was primary mediastinal diffuse large B-cell lymphoma. And I am sure there will be others that will be separated as we learn more about these from this group. Then, as an example of a very aggressive lymphoma, I’ve mentioned already Burkitt’s lymphoma.

This is a representation in a pie chart mode of the different types of lymphoma. I have not included all the lymphomas, just the most representative ones. Most of these lymphomas are B-cell, such as the diffuse large B-cell lymphoma. Follicular lymphomas are B-cell derived. [I apologize for that] Some of them are T-cells, such as the peripheral T-cell lymphoma, the T-lymphoblastic lymphoma, anaplastic large cell lymphoma. These are mostly T-cell lymphomas.

This is an example of how a follicular lymphoma would look under the microscope on a low powered field. As you can see, this is a biopsy, not a fine needle aspirate. We can see architecture. We can see the follicles that are enlarged and replaced by malignant cells. So in this type of lymphoma the lymph node retains its follicles --- its architecture but the follicles are enlarged and involved by lymphoma, ...

...as compared with the diffuse large cell lymphomas where what you see is just a complete effacement of the lymph node. You don’t distinguish any follicle inside the lymph node. This is just a couple of examples of different types of cells that can be included in the diffuse large cell category, the immunoblastic and the centroblastic. There are some studies suggesting that the immunoblastics have the worst outlook. So all of this information, especially the blood tests and the CAT scans, lead us to Stage the lymphoma and find out how advanced it is. So sing --- stage I will be lymphoma that presents in a --- in one or more nodes regions either above or below the diaphragm. I
apologize in one --- in one nodal region. Stage II will appear in two or more, but always in one side of the diaphragm.

Stage III will involve nodal regions both above and below the diaphragm. And Stage IV will have disease outside of the lymph nodes whether it be an organ, whether it be the bone marrow, that will be a Stage IV.

This is an illustration. Here we have Stage I disease where one nodal region is involved. You have Stage II where you have two nodal regions involved. You could have more than two nodal regions involved as long as they are in one side of the diaphragm. In this case, they are above. Stage III you have above and below the diaphragm and Stage IV you have disease outside of the lymph nodes. Here the diagram illustrates the liver or a bone marrow involvement.

It is important to have all this information so we can tell the patient in advance of starting therapy what the likelihood that they'll respond to therapy and perhaps change therapy if we think the standard therapy won't be good enough. We might offer them some clinical trials. This is the most widely used prognostic model for the aggressive lymphomas. It has five variables in it. Age of the patient and this the adverse feature. You have performance status. There is a performance status model which assigns 0, 1, 2, 3, 4 for how well the patient is physically. This actually should be more than two, not just equal or more than two. Actually, this means that the patient is more than 50% bedridden. This is the blood test I mentioned earlier, the lactate dehydrogenase. It has to be above normal to be a bad prognostic factor. If the patient has two or more sites outside of the lymph nodes that is also a poor prognostic feature and if the patient has advanced Stage III or IV. And you can see that based on this model if you have zero to five of these variables, it'll give you an estimate of what are the chances of the patient being free of recurrence at five years and alive at five years.

Another example is with another subtype of lymphoma called Mantle Cell International Prognostic Index. Again, you have a series of factors. Age. This is the performance status that I've discussed earlier. They call it ECOG, Eastern Oncology Group. Device is zero to five model. You have the lactate dehydrogenase and in this case the initial white cell count is also prognostically important and depending upon how advanced these four features are you will increase the number in points and you will give the patient the prognosis.
And this is the graph that shows according to whether they have three or less of these points, they will be in this curve. Whereas if they have five or more points, they'll be in this curve. This is after therapy with standard treatment mostly cytoxan based, some of it with adriamycin.

So this concludes the part of the non-Hodgkin’s lymphoma. It’s a brief overview. I also want to briefly overview the Hodgkin’s. In terms of the Hodgkin's, we still have the four categories. This has not changed a lot. This is a morphology on how the biopsy looks under the microscope. You have the two most common which are the nodular sclerosing and the mixed cellularity and these comprise 90% or more of the lymphomas that we see. And these are two rare variants.

This is a slide that shows one of the typical features of Hodgkin’s lymphoma, which is the Reed-Sternberg cells, so-called, after the two physicians that described the cell where you have the cell with these two nuclei. It’s looks like two little eyes in the --- in the cell.

In terms of trying to --- In terms of the staging testing, they are very similar. You’re going to do the same types of x-rays and CT scans and PET scans. You're going to do basically the same laboratories. The only laboratory that you will add is this erythrocyte sedimentation rate which has importance in one of the models that has been published so that you can tell the patient how they’ll do with therapy. This is particularly for the early Stage 1’s and 2’s. Again, the staging system for Hodgkin's is the same one that I showed you before for Stage 1, 2, 3, 4. Actually the stage --- the model was devised with Hodgkin's and it was later included in the non-Hodgkin’s. So if you have an early stage Hodgkin’s, but you have a large mediastinal mass and you have outside of the nodes disease or more than three involved nodal regions then even though you have early stage, therapy will be more extensive than if you didn’t have any of these.

If you have already advanced Hodgkin’s Stage IV disease --- Stage III or IV disease ---, there is a model that you can use to try to tell the patient how they will do with the standard treatment which is usually adriamycin, bleomycin, vinblastine, and dacarbazine. And there are seven variables and you can see how they might be poor prognosis if the albumin is less than 4 grams, if hemoglobin is less than 10.5, etc. And depending upon how many of these factors you have, you can tell the patient the chances that he or she will be alive without recurrence at five years.

So this ends the discussion about Hodgkin’s lymphoma. I will briefly discuss multiple myeloma. This is a disseminating malignancy of plasma cells which all derive from the same mother cell. That's why we call them monoclonal. It is a --- a second most common hematologic entity. And usually the patient will present with recurrent infections, many times urinary infections. They might have symptoms of elevated calcium, such as confusion, constipation. They might have failure of the kidney because the --- of the myeloma involving the kidney or having one of its proteins that it produces damage the kidney. You will have either fractures of the bones for no reason
without having had any trauma. And if you don’t and you just do x-rays you will find lytic lesions meaning like holes, because one of the hallmarks of myeloma is that there is demineralization of the area where the lymphoma is in the bone.

Again, very important to do x-ray studies but in this entity, it’s really more important to look at the blood. You want to know how high the --- this what so-called M protein is in the blood. There is a high production of a protein that can be detected in the blood by protein electrophoresis and immunofixation. You can also look at the free light chains of these proteins. And they will give you an idea of how number one, to confirm the diagnosis, but also to tell the patient the extent of --- of the disease --- of the tumor burden in his --- in his body. You can also look at the urine, again, looking at these proteins as they are excreted sometimes in the urine.

You will do a blood test to see if you have low counts…

…because the bone marrow is involved extensively. You will want to know, like I said before, in the chemistries how high is the lactate dehydrogenase, which is not shown here, but is important, the calcium levels, whether the kidney has been affected. And you do that by measuring the blood urea nitrogen and the creatinine. Very important you will do a skeletal survey. You want to identify bones that have not been fractured yet but might be at risk. You want to show these lytic lesions where they are through the different bones of your body. You want to prove in the bone marrow that the patient has myeloma. This is a disease that is always present in the bone marrow. Very rarely, it is not present in the marrow and it’s only a solitary lesion elsewhere in the body. And as part of the attempt to predict how well the tumor will do, you want to do special testing on the bone marrow. You want to find out how the chromosomes are. And you want to find out any additional genetic abnormalities by these now very well established tests which is called fluorescent insitu hybridization. Another very important blood test in myeloma is the serum levels of Beta-2 microglobulin.

So based on some of this information, you can try to tell the patient whether he has a lot --- a very small amount of myeloma or whether he has a high amount of myeloma in his body or her body. These are some of the blood tests that I’ve just mentioned before that you can do to try to answer this question. And depending upon how they are elevated or not, you can tell the patient whether he has a lot or not too much disease in his or her body.

Another system that has been reported that is sort of easier because there’s less things to remember is you can simply look at the Beta-2 microglobulin levels in the blood and the level of albumin which is an important protein in the blood. And just based on these two, there have been models that have been able to predict how well the patient will do with standard therapy.

As I said before, it is becoming important to look at the chromosomes and the DNA of the patients. We know that problems with chromosome 13 are usually poor prognostic features, translocations between chromosomes 4 and 14 or 14 and 16. Deletions of
part of chromosome 17 mainly 17q13 are important because this is where the p53 gene resides. And gain of 1q21 is also poor prognostic value.

If you try to combine this information with the already established ones, in other words if you add these genetic abnormalities to other already mentioned features, you can see how they worsen the prognosis. So be --- without and with the cyt --- the chromosome abnormalities you can see how the survival decreases at four years.

So in summary, I’ve really briefly mentioned some of these hematologic malignancies that are every year increasing in --- in knowledge and we are adjusting every year new prognostic factors in lymphoma --- in Hodgkin’s and multiple myeloma. Based on this information, I’m hoping that you’ll be able to diagnose and help assess what type of therapy should the patient have and how well they will do. And we’re always --- thank you very much and we always welcome any --- any input from you. Thank you.