ANASTASIOS RAPTIS: Good morning. I'm Anastasions Raptis, hematologist oncologist working at Hillman Cancer Center. I would like to Thank Dr. Donahue and the committee of the annual UIM lecture series for inviting me.

Today we will discuss about MGUS and smoldering myeloma, as well as touch upon multiple myeloma. I have nothing to disclose. We will discuss off label use of lenalidomide in smoldering multiple myeloma.

We will define the monoclonal gammopathies of undetermined significance. We will describe current management of MGUS. We'll describe natural history and risk factors for progression of MGUS to smoldering myeloma and multiple myeloma. We will identify factors that should be considered for risk stratification in smoldering multiple myeloma and updated diagnostic criteria for multiple myeloma. We will describe the current management of smoldering based on best available data.

Dr. Kyle introduced the concept of monoclonal gammopathies of undetermined significance by studying 1,384 patients residing in southeastern Minnesota. The risk features associated with progression of MGUS to higher risk are not stagnant and may evolve over time, making it challenging to determine the pattern of progression. So the term MGUS of undetermined significance might be of unpredictable significance.

The diagnosis is based mainly on laboratory findings and it's an incidental finding established in most of the cases by a non-hematologist. MGUS is a precursor of lymphoplasmacytic malignancies. However, it is also associated with renal, neurologic, and dermatologic disorders of clinical significance.

Monoclonal gammopathy of undetermined significance is characterized by the detection of monoclonal protein, the presence of 10% and less plasma cells in the bone marrow, and the absence of features, characteristics of multiple myeloma or lymphoplasmacytic malignancies. It is a disease of older individuals. It's observed in 3% of patients older than 50 years of age and 0.3% in patients younger than 50 years of age.

There's a higher risk and earlier age of onset in black patients compared to white. There are about 35,000 new cases annually, and there are three subtypes of MGUS, each with a distinct characteristic criteria and diagnosis.

The age adjusted rates are higher in men, 4 per 100, than in women, 2.7 per 100. The rate among men was similar to that among women who were educated older. In both sexes, the prevalence increased with advancing age and was almost four times as high among persons 80 years of age or older as compared to those of 50 to 59 years of age. The prevalence, as you can see in this slide, leveled off after 85 years of age in men and after 90 years of age in women.

We'll move on to discuss the criteria establishing each subtype of MGUS. The IgM MGUS patients have to have all three criteria. They have to have a monoclonal protein, IgM, of less than 3 grams per deciliter, less than 10% plasma cells in the bone marrow, and they should not have any evidence of constitutional symptoms, such as hyperviscosity, lymphadenopathy, hepatosplenomegaly, attributed to the underlying lymphoplasmacytic disorder.

The risk of progression is 1% per year. And usually these patients progress to Waldenstrom macroglobulinemia, AL amyloidosis, rarely to IgM multiple myeloma.

Non-IgM MGUS. Again, all three criteria must be met. Serum monoclonal protein, non-IgM, has to be less than 3 grams per deciliter. Less than 10% plasma cells in the marrow, and absence of end-organ damage, hypercalcemia, renal insufficiency, anemia, and bone lesions. The risk of progression-- 0.5% to 1% per year. And usually these patients progress to multiple myeloma, AL amyloidosis, or plasmacytoma.

Light chain MGUS. All of the criteria listed here must be met. An abnormal free light chain ratio of less than 0.26 or greater than 1.65, with an increased level of involved light chain. Plasma cells less than 10%. The absence of organ damage, and urinary monoclonal protein in a 24 hour unit collection of less than 500 milligrams, and no immunoglobulin heavy chain expression on immunofixation.

The risk of progression is 0.3% per year. And these patients do progress to light chain multiple myeloma or AL amyloidosis.

When should we test for MGUS? The test for the presence of a monoclonal gammopathy is obtained in patients who usually have clinical symptoms and signs, concerning for the presence of multiple myeloma, amyloidosis, or Waldenstrom macroglobulinemia. Most presenting symptoms and signs of lymphoplasmacytic malignancies are nonspecific, with the exception of diffuse lytic bone lesions, microglossia, infiltrating cardiomyopathy, and engorgement of retinal veins.

As a result, in most instances when we're testing for M-protein, it's performed. An alternative explanation of the clinical presentation is typically found, and the patients with positive test are labeled as having an incidental diagnosis of MGUS. Evaluation of monoclonal gammopathy is also done if a patient has a non-malignant disease, which is associated with monoclonal gammopathy and if the treatment or eradication of the plasma cell clone will result in control of the disease.

Three are the important tests-- the serum protein electrophoresis, the serum free light chains, the quantitative immunoglobulins. The 24-hour urine protein electrophoresis we'll obtain in patients who have the light chain MGUS.

With a serum protein electrophoresis, we are able to detect the abnormal protein in 82% of patients. With a combination of serum immunofixation, it is up to 93%. And when we combine the serum protein electrophoresis with immunofixation, as well as with the serum free light chains or the urine protein electrophoresis, we can detect up to 98%. There is a small percentage of patients, 1% to 2%, whose plasma cells do not secrete any monoclonal protein.

Here it shows the serum protein electrophoresis, which actually involves a charge and mast-base separation of proteins on a gel, which allows detection of a monoclonal protein because of the characteristic narrow spikes in the gamma and sometimes beta region for the IgH heavy chain.

The immunofixation on the right panel uses antibodies directed against each of the heavy chains and the kappa and lambda light chains. This allows the identification of the type of the monoclonal protein in terms of heavy and light chain isotypes. In a small portion of patients, both the serum protein electrophoresis and the immunofixation can be negative because the plasma cells secrete only the light chains in the middle panel.

Here it shows a bone marrow aspirate with typical plasma cells with the eccentric nucleus on the left panel. In the middle, there is a soft tissue plasmacytoma. And on the right, it shows the presence of plasma cells, even in the peripheral blood, which we see in patients with high-risk myeloma or in patients with plasma cell leukemia.

Dr. Kyle and colleagues reported their findings after studying 1,384 patients and followed them for 34 years. And they noted that at 40 years, the death rates among patients with MGUS were 11%, owing to plasma cell disorders, and they were 87%, owing to non-plasma cell disorders, such as cardiovascular cerebrovascular disease and non-plasma cell cancers. Patients with MGUS had a shorter median survival than was expected in the control population of the Minnesota residents of a matched age and sex-- 8.1 versus 12.4 years.

There are risk factors that have been identified associated with the risk of progression from MGUS to higher grades of plasma cell neoplasm, and these are the M-protein of greater than 1.5 grams per deciliter, and non-IgM protein, and an abnormal serum free light chain ratio.

When patients have all the three factors, as you can see in this slide, they have the higher risk of progression. Patients who have an M-protein of less than 1.5 grams per deciliter, and IgG subtype, and a normal free light chain ratio have the lower rate of risk of progression.

Over the years, guidelines as to how to follow these patients have been established. The UK Myeloma Forum, the International Expert Consensus, the International Myeloma Working Group, and the European Myeloma Network. For the low-risk MGUS, the UK Myeloma Group suggests for the first year to follow them every three to four months and then every six to 12 months. For every other MGUS individual, they suggest to follow at least every three to four months.

The International Expert Consensus for the first two years, they follow every four to six months, and then every six to 24 months. For the IMWG, they follow the patients every six months and then every two to three years, if stable. And for the European Myeloma Network, they follow the patients every six months then every one to two years, if stable or no follow up. And the tests they perform-- the quantitative immunoglobulins, the CBC, BUN, creatinine, and calcium electrolytes.

When should we perform a bone marrow biopsy and obtain skeletal imaging? So for patients with low-risk with less than 1.5 grams per deciliter, IgG isotype, normal FLC ratio, or an IgM of less than 1.5 grams per deciliter, or light chain MGUS with an FLC ratio of less than 8, if they are uncomplicated, the bone marrow biopsy and imaging may be deferred.

If there is presence of unexplained symptoms or laboratory features of concern, then the patient should have a bone marrow biopsy. They should have a skeletal imaging. And here, I want to draw your attention that the skeletal survey is not adequate. We need to obtain a CT/PET scan or a whole body low dose CT scan or an MRI. Because with the skeletal survey, we are going to miss approximately 20% of skeletal events.

There Mayo group here suggested this follow up schedule for patients with MGUS. They repeat the biochemical markers in six months. And if they are stable, they risk stratify to low-risk. And they suggest no MGUS follow up and routine medical care.

If they have intermediate or high-risk, they suggest annual follow up with CBC, calcium, creatinine, serum protein electrophoresis, and free light chains. If there is possible progression, we work up for the lymphoplasmacytic malignancy. If malignancy is identified, it's treated accordingly. If there is no malignancy, then they follow annually with CBC, calcium, creatinine, serum protein electrophoresis, and the free light chain assessment.

So this risk model so far estimates the risk of progression of MGUS to multiple myeloma using data from a single time point of the initial workup. Dr. Landgren and colleagues longitudinally investigated the alterations of serum immune markers with stable versus progressive MGUS. In a prospective cross-sectional cohort study included 77,469 individuals aged 55 to 74 with progression MGUS in 187 or stable MGUS in 498, including light chain MGUS, from November 1993 through December of 2011.

The risk of progression in association with each marker was analyzed using the pre-diagnostic measurements from the time point most proximal to the multiple myeloma diagnosis date. And they also did a longitudinal analysis to define patterns of serum marker changes. And a scoring system was developed based on accumulated points by using the results from the cross-sectional analysis.

And as you can see here, they were able to classify the patients in the low-risk, intermediate-risk, and high-risk, with distinct curves for progression patients, with high-risk in the blue line, patients with a low-risk in the green line, and the intermediate in the red line. The same was observed in patients with the light chain multiple myeloma with a light chain MGUS with a risk of progression to light chain multiple myeloma. The high-risk in the blue line and the low-risk in green line.

And they were able to show that most individuals who developed multiple myeloma after the preceding state of high-risk MGUS have converted from low-risk or intermediate-risk stages within five years before multiple myeloma diagnosis. The light chain MGUS progression showed very similar patterns as the heavy chain MGUS.

A small fraction of cases had rising serum immune markers in less than a year. And only 21% of individuals who progressed from MGUS to multiple myeloma fulfilled the criteria of smoldering multiple myeloma prior to the diagnosis of multiple myeloma.

The next question is, should we screen asymptomatic patients for MGUS. Here is a case of a 65-year-old man who was referred to hematology because of a strong family history of multiple myeloma. His mother was diagnosed with active multiple myeloma at the age of 70 and died seven years later, and his brother was found to have the same diagnosis one year before the visit.

Neither his mother nor brother had risk factors. And prior to hematology referral, he had a serum protein electrophoresis and free light chain, which shows no M-protein. So the current guidelines do not recommend routine screening for MGUS in the general population. Only 20% of prevalent MGUS cases are clinically recognized, and less than 10% of multiple myeloma amyloidosis or Waldenstrom macroglobulinemia have prior diagnosis of MGUS. Thus, about 80% of MGUS are going with no recognition.

Dr. Kristinsson and colleagues reported the iStop study, which was conducted in Iceland. They screened 75,442 individuals with serum protein electrophoresis and free light chains. They identified 3,725 as having monoclonal gammopathy of undetermined significance, and they randomized these to arm 1 with no further workup, arm 2, follow the current guidelines, and arm 3, intensive follow up.

They were able to show that with the intense follow up, they were able to detect more patients with smoldering Waldenstrom macroglobulinemia, more patients with smoldering multiple myeloma, and more patients with multiple myeloma. However, they suggested that at this point this cannot be the standard of care, as we have to wait for data to mature and show the effect of this on the survival of these patients.

However, in my clinic, in patients like the one we discuss who has a very strong family history, particularly if the patient is an African-American and has first degree family member who has history of myeloma, it is important to screen this patient. As well as white individuals who have more than two family members with multiple myeloma.

We also have to consider the psychological distress, which is exactly the same as one due to malignancies, by doing the screening for MGUS patients. We have also to be concerned about the over-diagnosing lymphoplasmacytic malignancies, particularly the smoldering type. And we don't have studies to assess the overtreatment yet.

Also the cost. Over 500,000 individuals with MGUS with annual follow up results in $100 million health costs annually.

So far, we have discussed the effects of the biochemical features. And all the systems we discussed so far are based on the biochemical features to estimate the risk of progression. The whole genome sequencing is the most comprehensive approach to characterize myeloma defining genomic events due to its ability to study the full repertoire of myeloma defining genomic events, such as single nucleotide variants, copy number variants, structural variants, and mutational signatures.

The genomic analysis so far was limited due to low clonal plasma cells in the bone marrow and low tumor DNA until the use of the multiparametric bone marrow plasma cell flow shorting. By using this technique, Oben and colleagues studied 18 MGUS cases and they compared to 14 smoldering myeloma and 80 multiple myeloma cases.

Here's a cartoon showing how they did the study. They collected marrow samples. They sorted the cells, they lysed the cells, they developed a DNA library, and then they did a whole genomic sequencing.

And what they found is that the distribution of genetic events showed the striking difference and the existence of two biologically and clinically distinct entities of asymptomatic monoclonal gammopathies. One entity is characterized by a sufficient number of myeloma genomic events.

And another entity with a lower burden of genetic events characterized by a high likelihood of a prolonged indolent and clinically stable course, the MG. Future studies are needed to definitely address whether a small proportion of cases with a genomically-defined MG eventually can convert to an EMM status. If there is only a very low rate of conversion, then the term benign monoclonal gammopathy is probably accurate for this genomically-defined clinical entity of MG.

So this slide shows the evolution of SMM, smoldering myeloma, to multiple myeloma. As you can see, the post-germinal B cell acquires primary cytogenetic events, like trisomies and immunoglobulin heavy chain translocations, which triggers an aberrant plasma cell in MGUS. Then secondary genetic hits, such as DNA repair pathway alterations, mixed structural variance dysregulation, copy number alterations and translocations occur, even at the smoldering stage.

Two patterns of clonal evolution have been proposed to drive the progression of smoldering myeloma. Patients with a stable pattern of evolution have a similar genomic landscape as they progress from smoldering to multiple myeloma. Essentially, these patients have early multiple myeloma and they develop the so-called myeloma-defining events as the tumor burden increases.

In contrast, in patients with a branching evolutionary pattern, subclones change significantly as they progress from SMM to MM. These patients have a long time to progression because of the time required to acquire the genetic alterations, leading to overt multiple myeloma. Epigenetic changes, tumor microenvironment dysregulated, immune and cellular compartments, they add to the complexity of the progression of SMM to multiple myeloma.

We will move on now to discuss briefly monoclonal gammopathies of clinical significance, which is the term used to describe non-malignant monoclonal gammopathy scores in important disease. MGCS is the differential diagnosis for any patient presenting with what appears to be a monoclonal gammopathy of undetermined significance, but it is also experiencing other unexplained symptoms. Broadly, these conditions can be separated into symptoms and signs referable to the nerves, the kidneys, and the skin.

The first step in diagnosing these conditions is to consider them. Almost all of the renal and dermatologic conditions are diagnosed by renal and skin biopsies, and it's very important to consult with a highly competent renal pathologist and dermatopathologist. Biopsy is less specific for the neuropathic conditions. Treatment recommendations for many of these conditions are anecdotal because of their rarity, but for several of the conditions IV immunoglobulin, rituximab, and plasma cell directed therapy are the best options. This slide, again, indicates the importance of the clinician, as well as the pathologist, to establish the diagnosis in the variety of these monoclonal gammopathies of clinical significance.

We'll move on now to discuss the need to differentiate the MGUS for smoldering myeloma. As you can see here, unlike MGUS which has a risk of progression 0.5% to 1% per year, the risk of progression of smoldering myeloma is overall 10% per year. But if you can notice here, the first five years, the risk of progression is significantly higher compared to 5 to 10 years, and then is less thereafter, almost mimicking the rate of progression of MGUS.

So we no longer consider the SMM as an intermediate stage between MGUS and multiple myeloma, but rather a heterogeneous entity. We need to identify patients in the smoldering myeloma group who really are not smoldering myeloma, but rather have progressed to multiple myeloma and separate those from the rest of the patients who have smoldering multiple myeloma.

The International Myeloma Working Group has updated the criteria for the diagnosis of multiple myeloma. Here, it shows the previous definition. MGUS, you have to have less than 10% blood plasma cells in the marrow, less than 3 grams of M-protein, no CRAB criteria. Again the CRAB, to remind you, hypercalcemia, renal failure, anemia, and bone lesions attributed to clonal plasma cell disorder.

Smoldering has to have greater than 10% plasma cells, greater than 3 grams of monoclonal protein. And the multiple myeloma patients have to have the CRAB features.

With the updated diagnosis, the IMWG introduced the myeloma-defining events, which is greater than 60% plasma cells, greater than 100 FLC ratio of involved to uninvolved, and more than one lesion identified on MRI. These patients in the previous definition were classified as smoldering myeloma, so we have upgraded this now to multiple myeloma, and thus the definitions of smoldering has also changed.

Patients have to have 10% to 60% plasma cells in the marrow, greater than 3 grams of protein, or greater in the 500 milligrams in 24-hour uterine. But they should not have any myeloma-defining events. Which, again, are the greater than plasma cells in the marrow, greater than 100 FLC ratio, and more than one lesion in the MRI.

Risk factors for progression of the SMM to MM. So after we upgraded the patients from SMM to multiple myeloma, which is approximately 20% of patients, the remainder of the smoldering myeloma are still in a heterogeneous group of patients. Patients who have greater than 10% plasma cells plus an M-protein in the 3 grams, absence of normal plasma cells, less than 5%, or immunoparesis, which means decreased levels of the non-involved immunoglobulins.

Abnormal FLC ratio 8 to 10, deletion 17p, translocation 4 14, or gain of 1q 21. IgA isotype and evolving pattern, meaning that we follow these patients if they have an increase of the M-protein by 0.5 grams or they have a drop in hemoglobin by 0.5, then these patients have an evolving pattern, and if we have increased circulating plasma cells in the peripheral blood.

The myeloma group have proposed 20 to 20, this is a typo, it's 20 to 20 model, based on plasma cells greater than 20%, and protein gradient at 2 grams, and FLC ratio of greater than 20. And as you can see here, they were able to sort out a group of patients with a high risk and who have almost 50% chance of progression within two years.

The International Myeloma Working Group further stratified these patients based on the level of the FLC, the M-protein, and the plasma cells in the bone marrow. However, it introduced the cytogenetic features, and they were able to identify patients with a high-risk, with a 73% chance of progression in two years, and with intermediate-risk, with a 50% chance of progression in two years.

What can we do about these patients to prevent them from developing the CRAB features by progressing into multiple myeloma? This is a prospective study by the Spanish group, the thin group. They studied 119 patients with high-risk smoldering myeloma.

They randomly assigned them to treatment versus observation. The treatment was with lenalidomide and with dexamethasone. And the primary endpoint was time to progression to symptomatic multiple myeloma.

As you can see here, in panel A shows the progression to symptomatic disease, which favors the treatment group. Panel B is the overall survival from date of inclusion in the study. And the panel C shows the overall survival from date of diagnosis of smoldering myeloma. All these favor the treatment group versus the observation. And in a follow up updated study, with a median follow up of 76 months, they showed the survival advantage on the treatment group compared to observation.

A second randomized study, ECOG E3A06, studied 222 patients randomized. 92 patients received lenalidomide with no dexamethasone and 90 patients, they were observed. The primary endpoint was progression free survival with the disease progression requiring development of end organ damage.

And again, here the panel A shows progression free survival, favoring the treatment group. The panel B shows the cumulative incidence of progression, favoring the treatment group. However, the overall survival was not different between the two groups. When they looked at this data based on the Mayo risk stratification tool, they noted that in panel A that most of the benefit was observed in patients who had the high risk myeloma, according to the Mayo risk stratification.

There are ongoing trials at this point studying the high risk smoldering myeloma patients, utilizing the treatments that we use in patients with full blown myeloma, like the KRd regiment. And also they use the daratumumab, which is a monoclonal antibody, as well as bortezomib, Revlimid, and dexamethasone. The results of these studies are still pending.

So how do we approach a new patient with multiple myeloma or smoldering? If the patient has any of the myeloma-defining events or CRAB, we treat as myeloma. If the patient has high-risk smoldering with a median time to progression of two years, then we discuss early treatment with Revlimid and dexamethasone, or Revlimid alone, or participation in clinical trials, with intermediate or low-risk, we do observe.

How do we monitor these patients? This slide shows the list of biochemical markers that we monitor every three to six months or every year. The skeletal imaging is obtained every six to 12 months, and if M-protein is rising. Otherwise, there is no need to obtain skeletal imaging. And also, bone marrow biopsy aspirate is obtained only if there is a concern of disease progression.

So in summary, we discussed today the definition of monoclonal gammopathy of undetermined significance. And we discussed the different models of risk stratification. Then we discussed the recommended follow up and management of MGUS, the revised definition of smoldering myeloma, as well as multiple myeloma, and the classification of smoldering myeloma and the management. I would like to thank you for inviting me in this presentation.