[MUSIC PLAYING]

SPEAKER 1: Task today is to go over some of the salient points with respect to the management of well-differentiated thyroid cancer. And by this, we are basically talking about papillary thyroid cancer or papillary thyroid carcinoma, which is a very, very common disease entity that is being diagnosed and seeing more and more frequently.

I will discuss some of the updates of concepts in management and diagnosis for this disease entity. There are no disclosures. By way of background, papillary thyroid carcinoma is a common disease entity that we encounter. As far as malignancies goes, it comprises about 4% of newly diagnosed cancers per year in the US. It is the ninth most common carcinoma, in terms of incidence in the US.

And interestingly, despite this relatively high incidence for this cancer and being of relatively common cancer, deaths due to thyroid cancer are infrequent and relatively uncommon. Here's a recent article published by Louise Davies in 2015. And this article shows that over the past 40 years or so, the incidence of thyroid carcinoma has increased relatively exponentially, in terms of all histology seen. This is showing the solid line. Papillary thyroid carcinoma, you can see it mimics it very, very closely. So the vast majority of thyroid cancer is that a practitioner will encounter during his or her practice is really papillary thyroid carcinoma.

Now there are several other disease entities that can arise in the thyroid, such as follicular carcinoma or anaplastic thyroid carcinoma. And those are shown at the bottom of the graph. And you can see they range between 1 to less than 1 per 100,000 people in Asia, adjusted rates. And interestingly, despite this relatively steep incline in the incidence of thyroid cancer or, in fact, papillary thyroid cancer, the mortality remains uniformly low. It has not changed significantly in the last 40 years.

This leads us to surmise that if there are only 0.5 deaths per 100,000 from thyroid cancer, but the age-adjusted incidence is rising from about 4 per annum to now almost 14 annum. So that's a threefold increase over the last few decades. But the death has not changed. It leads us to wonder whether, a, we're overdiagnosing these carcinomas. Or b, whether many of these thyroid carcinomas are so well-behaved that we are, in fact, overstaging them or giving them a diagnosis that might pretend a dismal outcome for a patient, although that may not necessarily be true.

As far as size, this is again data from that same paper by Louise Davies, which shows that the vast majority of thyroid cancers that we find are 2 centimeters or less in size. And this speaks to that first question that I raise, which is are we overdiagnosing these patients with thyroid cancer? In other words, if we subject every patient with a thyroid nodule to a biopsy, regardless of size, then, statistically speaking, we're more likely to identify small thyroid carcinomas or papillary microcarcinomas.

And these microcarcinomas may, in fact, never pose a significant problem to the patient. And so this might account for that to change in incidence that I showed in the prior graph. However, we should note that there is still an increase of cancers that are between 2 to 5 centimeters in size. And so this leads us to now postulate that maybe this is not simply an overdiagnosis situation. But maybe there are, in fact, tumors are growing to this size and are being, therefore, being identified.

Taken altogether, these data have translated into the new American Thyroid Association guidelines, which suggests, which really puts forward the idea that we should not be biopsying patients with thyroid nodules that are smaller than 15 millimeters or 1.5 centimeters, assuming that they don't have any high-risk feature, such as microclassifications, irregular borders, or being taller than wide on ultrasound axial imaging.

So what this has led us to do now is to number 1, hopefully not biopsy so many patients and, therefore, reduce the number of microcarcinomas that we detect. And in fact, what Dr. Davies has found-- and this is another one of her papers from 2014-- that when you look at the size distribution of the tumors that are seen, the vast majority of these tumors tend to be 10 millimeters or less in size. And are, therefore, very likely to be these microcarcinomas, which may never grow and may never really pose a problem for these patients.

And so by virtue of doing too many needle biopsies by subjecting too many patients to these sorts of investigations, we may, in fact, be identifying smaller and smaller and smaller tumors, which, in essence, may not really change the patient's disease outcome. And, in fact, may subject the patient to increased interventions.

Interestingly, we note also that the mean size also has decreased slightly from 22.8 to 19.0 millimeters. And again, this is statistically significant at p-value 0.001. And similarly the median size also has decreased from 20 to 50 millimeters, suggesting again that maybe we were just biopsying too many small nodules. And so again, when we think about the size distribution of less than 10 millimeters, it's really about almost 25% of patients that fall within this microcarcinoma range.

So this leads us to the very important and clinically relevant question-- do we need to operate in all of these people with relatively small well-differentiated thyroid carcinomas, especially if they have such a good survival. If they're deaf, it's somewhere in the range of 0.5 per 100,000 patients. Then that translates to about a 98% survival for these patients with thyroid cancer.

And so if they have such a good survival-- they enjoy such a good survival, do we really need to operate in every single one of these patients? And how can we tease that apart? So some of the seminal studies on this topic were really led by the Kuma Hospital in Japan by doctors Yasuhiro Ito and his Chairman Dr. [INAUDIBLE], who have published over the past few years, some landmark papers showing that they can, in fact, observe papillary microcarcinomas.

And they have been observing well-differentiated thyroid carcinomas that are papillary microcarcinomas for almost 20 years. And in fact, Japan, unfortunately, has a very high rate of thyroid carcinoma as a result of exposure to radiation, both from World War II and later. And so they unfortunately have a greater number of patients with these relatively small thyroid carcinomas that were biopsied quite vigorously.

And so Kuma Hospital, along with two other centers in Japan, have now observed almost 1,500 patients. And they have been leading the charge, in terms of observation for patients with small thyroid cancers. Here are some of their recent data that shows that if these patients are observed for papillary thyroid carcinoma, they actually do not have any difference in disease at specific mortality, nor in local regions of occurrences when compared to patients that underwent immediate and definitive surgical intervention for this disease.

The disease specific mortality for patients with small thyroid carcinomas is less than 1% in a cohort of patients who underwent immediate surgery. Whereas those that elected for observation, either active surveillance at 5 years or the 10-year mark, there was still only a 1% rate of disease specific immortality.

And this is because those patients who do progress over the course of observation-- that's shown in this bottom row greater than 3 millimeters increase in size, which, of course, it would be 7%. And at five years, it increases the longer we observe these patients. They were still able to be salvaged by having a total thyroidectomy at a later point in time.

And you might ask, well, why 3 millimeters? Why is that a magic number? Well, there is really no magic number here. 3 millimeters was chosen as an arbitrary cut off, because most of these tumors were 10 millimeters in size or less. And it was felt to represent roughly a 30% increase in tumor size.

And so the reality is that if we observe these patients, according to the Japanese data, there's about a 7% rate of growth over 5 years or 16% over 10 years. But these patients can still be salvaged, which still means that over 10 years, we will avoid surgery in almost 84% of these patients.

And so that's where we want to move this field forward. And this is very similar to the data with prostate cancer where we recognize now that operating on men with early stage relatively low volume disease of the prostate is unlikely to yield meaningful oncologic outcomes. But they will suffer the potential surgical sequelae from these interventions. And that's what we want to avoid in the patients with thyroid cancer as well.

So that was our data from Japan. And so one of the questions that comes up is, well, the Japanese have a different potential phenotype because of the exposure to radiation and maybe even the diet and ethnicity. So what happens in North American or European ancestry population? And so here is a recent study just published by Mike Tuttle from Memorial Sloan Kettering in JAMA Otolaryngology just this month in 2017.

And what Mike did was he actually reviewed his experience, the Memorial Sloan Kettering experience, observing patients with papillary thyroid carcinomas. So they themselves have been observing patients with PTC for the past about three or four years-- that they do have some patients who've been followed for much longer. And here you can see that they looked at 291 patients with PTC.

All of these patients actually had less than 1.5 centimeter cancers and not 10 millimeter cancers, like the Kuma Hospital data. But these are slightly bigger-- up to 15 millimeters. The median follow-up was just over 2 years but ranged from 6 months to 166 months. So you can tell they've been following some of these people for quite a long time. And tumor growth of 3 millimeters was once again used as a cut off. And so Mike decided to look at 3 millimeters as a standard, because that is what had been published by the Japanese group in the past.

However, Dr. Tuttle did something interesting, which is, not only did he look at a change of 3 millimeters in any one dimension as being a critical marker of growth, he also looked at volumetric measurements. And so when you take the volume of this tumor in a couple of dimensions, he asked the question, does volume predict tumor growth? Does volume change predict tumor growth? And which one is more sensitive?

So in short, here's some of the data that he found. So unlike the Kuma hospital data that showed a 7% increase-- 7% rate of growth in 5 years and 16% over 10 years, Dr. Tuttle only found a 3.8% growth over the median follow-up here of 25 months, suggesting once again that maybe the North American population has a slightly different propensity or different outcome for these patients. But this is something that was really quite interesting.

And here's the data from his paper. So he looked, as I said, both at a diameter increase of 3 millimeters-- a 3 millimeters increase in base dimension, or a volume increase of greater than 50%, measuring volume as a product of two measurements in orthogonal axes. And what he found was that the timed increase in tumor diameter of 3 millimeters or more, slowly happens over the course of about five years.

And the cumulative event index raises up all the way up to 10%. But really, it hovers somewhere around three years, in terms of a 50% effect. And we see once again a very similar trend but a much more striking trend with the volume increase. So to break this down. What this really means is that if you measure the volume of these tumors, and the volume is changing, that it's very likely that those tumors will then develop into and meet the criteria of a greater than 3 millimeter growth.

So what he's saying is that the volume change is more sensitive and is probably a better way to measure tumor growth than just a simple diameter change of 3 millimeters. When you put these data into a different format, this is called a waterfall plot. This is commonly used to report tumor volume data in clinical trials. This gives us a better snapshot of the kind of increases that we're seeing.

And what we can see is that there's actually a group of patients in whom the tumor regressed. It actually decreased by more than 50%, in terms of size, in terms of tumor volume. There are a lot of people in whom the tumor stayed the same or did not really change very much. So basically it's plus or minus 50%. So some grew a little bit-- some decreased a little bit.

There's a cohort that experienced some increase-- maybe up to 50% of an increase. And then here is the yellow or orange here demonstrates some patients who really had profound growth or profound change in tumor volume. Excuse me-- and this is a relatively really important group that we'd like to think that these are the people that probably really needed intervention earlier, as opposed to having intervention potentially later.

And so we can see in the legend that there are 284 patients were able to have this complete 3D volumetric dataset. The tumor size decreased by 50% or more in 19 patients and increased about 50% or more in 36 patients and we're stable in about 80% of patients, OK. And by 11 patients here, the tumor diameter increased by more than 3 millimeters, which led to a huge change in tumor volume.

So we know basically that as all cancers, even if there's only a 2% rate of mortality or bad outcomes from thyroid cancer, that's still something that we don't want to face. And we want to avoid that. So while we know that many of these patients can probably be observed or not need to have aggressive surgery, we still struggle with identifying that cohort-- that subpopulation of patients that will do poorly from this disease.

And so we raised the hypothesis that those patients that do poorly from this disease-- those patients that end up having bad outcomes must have had a small tumor at some point in time. They didn't start off with, let's say, a T4 disease. It didn't start off with large volume nodal disease. So they started as small tumors. And then they spread. They developed-- they turned bad.

So what we wanted to do was to look at the genetic profile of these bad cancers and look at the genetic profile specifically of locally advanced well-differentiated cancer. So these are the T4 thyroid cancers. And this was part of a grant that was funded by the National Cancer Institute through the Head and Neck SPORE. And so this is some studies and some research that was funded through that mechanism.

And the way that we wanted to ascertain this-- the way that we wanted to see which cancers were the bad cancers was to perform a mutational analysis of these tumors and see if we could determine a specific genetic signature for these T4 thyroid cancers-- for these bad thyroid cancers. Here's a pie chart, generously share with me by Dr. Yuri Nikiforov, a world's expert in molecular pathology of the thyroid who has been blazing the trail in identifying mutations that drive or cause thyroid cancers.

And what Yuri has found is that the vast majority of thyroid cancers will harbor some genetic mutation that can be targeted or that can be assayed, I mean, not necessarily targeted or it can be assayed. And about 70% of thyroid cancers have mutations of this gene called BRAF-- B-R-A-F. A significant percentage will have mutations of other genes known as RAS or RET/PTC-- ones that we may have heard about in other sort of thyroid cancers, including the syndromic types.

And then there will be an assortment of other novel rearrangements or P53 or TERT and other such genes that are mutated in the remaining sets of cancer. So when we put this together based on the most up-to-date data we have now, we can basically identify some sort of mutation in 90%. So 9 plus 11 plus 70% of all thyroid cancers. So up to 90% of thyroid cancers will have some identifiable genetic mutation that we can then use, either to diagnose or maybe to predict the outcomes of these patients.

Now I told you that 70% of tumors have mutations of the gene called BRAF. So some data that was published in the past attempted to correlate BRAF status with disease outcomes in patients with thyroid cancer. And what Dr. Singh from Hopkins published in a couple of very nice papers was that BRAF did seem to correlate with aggressiveness in this cohort of patients.

However, these data have not necessarily been borne out and have not made themself really that useful from a clinical setting, because if 70% of patients have BRAF but not 70% of patients are dying from this disease. Disease-free survival should be much lower. It clearly tells us there's something other than just BRAF that is contributing to the outcomes of these patients. And that's really what we set out to identify.

We know that aggressive papillary thyroid carcinomas have multiple mutations and sometimes have mutations of the BRAF genes. Here's a model that's published by Dr. Nikiforov in 2/20/13 of 57 thyroid carcinomas. They underwent genetic testing. A significant percentage had mutations of BRAF. Some had mutations of this gene, NRAS and HRAS and other ISO forms.

But you see that there a couple of tumors that have multiple mutations. And if they have multiple mutations, then we think that those are the ones that are likely to behave in a more aggressive fashion. And in fact, when he looked at a series of patients that were poor actors with papillary thyroid carcinoma, here's a patient who was 56, male, and ended up having a chest wall metastasis from his papillary carcinoma. There's another patient with lung metastases. Another patient-- multiple bone metastases.

We saw that all of these patients had multiple mutations. A very few of them had only one mutation. They most commonly had multiple mutations of driver genes. In fact, when we look at the histology, we can actually show that some of these poorly differentiated areas within the tumors are the ones that harbor this phenotype-- this genotype, I should say, rather, of multiple mutations.

So what we asked was do locally aggressive well-differentiated thyroid carcinomas as a specific model for aggressive thyroid cancer-- for T4 thyroid cancer-- do they harbor a distinct genetic profile and mutational profile? So we went through the cases here at the University of Pittsburgh with that per stage as T4 thyroid carcinoma. We identified 80 such patients.

Once again, these patients had to be restaged, because T4 thyroid cancer staging was changed in the AJCC 7th edition. We therefore, had to exclude some patients, especially those with poorly differentiated histology, such as anaplastic histology or patients that had minimal [INAUDIBLE] thyroid extension. We found, therefore, 29 cases that met our inclusion criteria, which means that we had tissue. And we had good outcomes and follow-up on these patients.

We subsequently were able to obtain tissue on 26 of these patients, because some of them didn't have tissue that was available. And then 25 patients had successful molecular profiles performed of their differentiated T4 thyroid carcinoma. This is a brief table demonstrating the demographics. And this is really pretty standard for this patient cohort. Most of them were older. Male-- female distribution was as expected.

And what we found was that in the mutation of profiles of these 25 T4 thyroid cancers, the vast majority of them, once again, had BRAF mutations, not unexpectedly. What was interesting, however, is that a significant percentage of these patients also had mutations in the promoter region of a gene called TERT.

So TERT is a telomerase gene. This is the gene that helps keep cells viable and healthy. And as telomeres get longer, the genetic material is able to replicate. And this is an essential component of cell viability and cell growth. And so mutations of the TERT promotor region with having associated malignancies in several different subtypes.

And interestingly what we found was a full 50% of these advanced thyroid cancers had co-mutations of BRAF and TERT, suggesting that they may, in fact, be a signature for the patients that are bad players or bad actors by having this co-mutations of BRAF and TERT. When we looked at another cohort and independent cohort of 102 small thyroid cancers that we sequenced, we saw that only 5 of the 102 had BRAF and TERT mutation. It's only 5%.

So you have 50% on one hand for the bad cancers and only 5% co-mutations in the supposedly small cancers. Now these were all surgically treated. But this leads us to think that maybe this 5% or these 5 out of 102 cancers that had BRAF and co-mutations, maybe those guys that turn into the bad cancers down the road. All right, so maybe this is the signature of how we can predict who is going to be a bad player in the thyroid field versus those that are not.

And so what this tells us-- also, we did some additional analysis to show that BRAF and TERT correlates with recurrence and poor outcomes in these patients with advanced thyroid cancer. And so what this really tells us is that people with advanced thyroid cancer suffer from a higher recurrence rate. We know that. They are more likely to die. We know that as well. And these are the patients that seem to have a unique molecular profile with co-mutations, BRAF and TERT.

Now we can't conclude that this is the only combination that is present in these advanced thyroid cancers is because we only did 25. So this is not, by any means, an exhaustive analysis of this topic. But it does provide some really, really fascinating and interesting data that we're following up on now with a large cohort of patients.

So the real question is can we use this data now in former prospective trial? And so this is what I wanted to present today to the audience that we now actually have a National Cancer Institute approved and funded prospective trial that seeks to avoid operating on patients with small thyroid carcinomas. So we propose a trial to observe what we define as low-risk thyroid cancers instead of surgical intervention. And we define low risk by the basis of the molecular signature that we gather from doing molecular testing in addition to clinical parameters.

What this means is that people that have papillary thyroid carcinoma or suspected PTC should have a sample from the FNA saved. And the pathologist at the University of Pittsburgh do this routinely. They save a small [INAUDIBLE] of the cells in a special container with a special reagent that preserves the nucleic acids from these cells.

And so if the patient has a thyroid cancer, we can now go back and analyze that thyroid cancer sample. And this is paid for under the trial by the National Cancer Institute. So this is no charge to the patient. And this genetic information can then be used to stratify the patient or to guide the patient and see whether they're a candidate for observation instead of having surgery.

So what we want to do is observe people, not with just 10 millimeters or 15 millimeters, but we actually got permission to purchase up to 2 centimeters based on the data from Memorial Sloan Kettering. We now feel more comfortable expanding the indications and observing patients with these T1 or less than 2 centuries thyroid cancers.

And so there are a couple of questions that we need to address, and that we would like to get information from this trial concept. Number 1 is can we enroll patients into such a trial? So if we were to tell people that we can do molecular tests and tell you with a decent probability chance that you have a low-risk thyroid cancer and that we will observe you and hopefully not have to intervene or not have to do surgery.

Will patients agree to such a trial? This is an important question. We don't know the answer to this question. We think that they will. But it is still something that requires careful consideration-- observation. And clearly, the risk associated with observing a 20-year-old with thyroid carcinoma, who has a very, very long life ahead of him or her, is different than observing a patient, maybe, who is in their 70s or 80s and may have medical co-morbidities which might make surgery less attractive for that patient.

The other question is if we do identify a cohort of 3 or 7% of people who progress, can we subscribe some sort of molecular signature to those patients. Can we identify the samples of the patients who progressed? And can we do molecular testing on those tumors?

And finally, how good are we at defining low risk versus high risk molecular features on the basis of this testing. So the inclusion criteria for this trial is to have patients with well-differentiated thyroid carcinoma that is 2 centimeters or less in greatest dimension. We want them to have no evidence of nodal metastasis. We want them to have no evidence, of course, of local invasion, such as tracheal invasion or esophageal invasion.

And, of course, good clinical judgment's required to ensure compliance with the surveillance. We're not just telling these people that we're going to do a biopsy and then just not do anything and let you go. These people need to be enrolled in a watchful observation program, which means that they will have serial ultrasounds, be seen by a physician, and have blood tests about every six months to ensure that they're not developing a disease that goes unchecked.

An endpoint is a nonrandomized prospective study. It's considered a crossover, because the patients can have surgical intervention at any point in time if they feel uncomfortable with observation that's allowed by the study and that still considered acceptable. The primary endpoint is progression to surgery. And we estimate that 10% of patients will be at high risk at the initiation of the trial. And these patients will not be observed. They will go on to have surgery.

So this is the schema. So patients get seen. They get assessed for eligibility based on imaging and biopsies of these all [INAUDIBLE] to patients diagnosed with papillary thyroid carcinoma. They will have a molecular signature analysis performed. If they're high risk, they go on to have surgery. So they're not observed if we think they have high-risk disease.

If we think of low-risk disease-- that is they don't have any mutations or only one mutation-- then these patients will be offered observation with an office visit and ultrasound every six months and thyroid function test every 12 months. And these patients can undergo TSH suppression with centroid, as per the discretion of their treating physician. If they have stable disease, then they continue with observation.

If, however, at any point in time they progress, meaning they have tumor growth-- they develop any sort of nodal metastases or identification of [INAUDIBLE], which I think is extremely unlikely. But we put it in there as a possibility. Then these patients, of course, would progress to surgery and then be treated with standard of care with radioactive iodine or other such measures.

But we really expect, based on the data that I showed you before from Kuma Hospital and Memorial Sloan Kettering, that we should only have about 4% of people that progress that should need to go onto to have surgery. So we suspected that a full 90% of people will not have progressive disease. And we'll do just fine.

So with that, I'd like to thank all of our collaborators from pathology, head and neck surgery, endocrine surgery, and statistics. This is a very, very important program which cannot be completed without many, many physicians involved. So thank you for your attention.

SPEAKER 2: So thank you. Thank you, Omar. So I know that the word, "cancer," is frightening to patients. And currently we make that determination based on light microscopy. Do you see a future where the definition of cancer will change based on the genetic testing?

SPEAKER 1: That's an excellent question, David. I think the answer is yes. In fact, and we're already getting there. And I didn't have time to address the more diagnostic aspects molecular testing. But we know that [INAUDIBLE] biopsies can be classified into six different criteria based on the Bethesda criteria scale. 0 means it's inadequate. 1 means it's benign. And 6 means it's cancer. And 2 through 5 are shades of gray. 5 is suspicious for cancer. 2 is atypical cells.

Low risk of cancer-- much higher risk of cancer. But there's this gradation. What we're doing now, the University of Pittsburgh, is actually subjecting patients who have these what we call indeterminate nodules or indeterminate criteria. So they're not clearly benign. They're not clearly cancer. They actually have molecular testing. And with the latest version molecular testing that Dr. Nikiforov has perfected, we're now able to give up to a 95% probability that the patient actually has cancer if they have one of these mutations.

Or a 95% chance that they do not have cancer if they don't have any of these mutations. So the short answer to your question is yes. We're already, in some ways, trumping the light microscopy cytology aspect with the genetic testing so that even though the light microscopy was not saying cancer, if the genetics say cancer, we're calling it cancer. Now, whether that cancer is actually really bad cancer or not so bad cancer, that's what we're trying to figure out with this next phase.