[MUSIC PLAYING]

SPEAKER: Thank you, and good morning. So, when I was asked to speak about thyroid cytology update, this was a bit of a no-brainer, because in our world, the NIFTP has certainly caught our attention. But with the understanding that there are other moving stages in this theater, and cytology is just but one stage of the many other stages. So this is the paper that many of us are familiar with, in the landmark NIFTP paper. And the subtitle, as you can read here, states "a paradigm shift to reduce overtreatment of indolent tumors." So there's definitely a tendency trend toward more conservative diagnosis and management.

And this is what has certainly influenced our practice in cytopathology. So, just the diagrammatic scheme to illustrate NIFTP, as many of you know, it's usually a round neoplasm that is well-demarcated, oftentimes, encapsulated, and has features similar to follicular adenoma, but in contrast, has papillary carcinoma-like nuclear features, cytologically.

Molecularly speaking, it has usually RAS or RAS-like mutations. And the main issue that was discovered was that these tumors are rather indolent. And lobectomy, in general, is the treatment of choice.

So, regarding cytopathology, this is the new Bethesda classification atlas that was just published earlier this year. There are two main issues. One is, what are the influences of NIFTP on the Bethesda system? And then secondly, how has the Bethesda system addressed NIFTP? So, basically, I'd like to spend this 20 minutes or so to talk about these issues.

So this is the risk stratification for the thyroid cytology diagnoses, both before and after NIFTP inception. So the column on the right hand side would be equivalent to before NIFTP inception, so including NIFTP as cancer because many of these NIFTP neoplasms were called noninvasive follicular variant papillary carcinoma. But if we were to take NIFTP out of the cancer category, as you would expect, the risk of malignancy would drop.

Let's just focus on the central portion of this slide. And the main effect of the NIFTP being categorized out of the malignancy area influences the so-called indeterminate diagnoses-- atypia of undetermined significance, follicular neoplasm, and suspicious for malignancy. And as you can see, there is a degree of drop.

You could also ask, well, gee, these are a lot of numbers to memorize and learn. And what's really important? And after much discussions amongst cytopathologists, as well as other multi-disciplinary physicians, we have pretty much decided that it's still probably good to keep the risk along the side where we count NIFTP as a neoplasm. Although it is very indolent, we should still consider these numbers. Why? Because NIFTP is still considered to be a surgical disease-- something that should be treated by lobectomy.

So these are the distribution of the cytology diagnoses for eventual cases of NIFTP. Now, this is a review article garnered from a number of other studies. And you can see a wide range here, although many of the cases fall into the AUS/FLUS categories, there are still some numbers that fall into a suspicious category, and that has a wide range, depending on the institution.

So, having said that, we want to treat NIFTP by lobectomy from the cytopathologic point of view, what we want to do is to do our best to make the pre-operative diagnosis in this area-- AUS/FLUS, and follicular neoplasm. Because for these cytology diagnoses, usually, lobectomy is the treatment of choice if the patient goes to surgery. Whereas for suspicious for malignancy, not infrequently, the patient may get a total thyroidectomy.

So, this is the issue of differentiating between a AUS/FLUS and the suspicious diagnoses. But you could ask, well, what are we, as cytopathologists, seeing when we evaluate these cases? In the actual nitty-gritty parameters that we are evaluating are cytologic atypia and architectural atypia. And so, when we have cases with cytologic atypia, in a sense, if you have a little bit, then we would usually fall into the diagnosis of AUS/FLUS. And then, if we have more substantial cytologic nuclear atypia, we would go to the diagnosis of suspicious for malignancy.

Regarding the cases where architectural atypia is the predominant finding. Usually, we would fall under the category of follicular neoplasm. However, if there are concurrent atypia identified, then suspicious for malignancy comes into the differential diagnosis. So those are the issues that we contend with.

So we had mentioned earlier, the goal of NIFTP is to prevent overtreatment. And so, what the role of cytology becomes is to guide these eventual NIFTP cases toward lobectomy-- that is usually the AUS/FLUS diagnosis, or the follicular neoplasm diagnosis. And at the same time, keep the numbers of false negative and false positive cases to a minimum. And then, also, for places that have molecular testing on momentum, then we want to select the appropriate cases for ancillary testing.

So this is the overall view of a NIFTP neoplasm, well-demarcated, encapsulated, has follicular growth pattern predominantly and nuclear features of papillary carcinoma. There's a number of exclusion criteria, that I'm sure that Dr. Sittella will be talking about later today.

So this is a neoplasm. It's not considered to be malignant. However, it's not entirely benign-- emphasizing the point that, again, lobectomy is the treatment of choice. From a biologic/pathobiologic point of view, perhaps we could view this as something of like a dysplastic or in-situ-type neoplasm or process. In the pathology/cytology circles, there's been much discussion regarding the standardization of nuclear scoring.

And so, this has actually been something good that has come out of this exercise. Because before the inception of NIFTP, we really didn't have too much in terms of standardization of nuclear grading. So now we understand that if we have two out of these three nuclear features being detected-- that is, abnormalities in size and shape, membrane irregularities, and chromatin pattern-- then that would qualify a case that can potentially be NIFTP.

However, one can ask, why can't this be follicular variant papillary carcinoma? And the answer is, absolutely. You could have the same kind of nuclear features and infiltrative or invasive follicular variant papillary carcinoma. And on the other hand, why can't nuclei like this on the bottom right here-- the center column bottom-- be a part of thyroiditis? And the answer is, yes, absolutely. It can be. So that's what makes our world and cytology challenging.

So when we encounter a case like this, we're finding nuclear atypia. Why nuclear atypia? Because the nuclei-- some are round, but others are getting a bit elongated. And the membranes are getting a little bit irregular. So not perfectly round like some of these other nuclei. And also, we're finding that the cells are rather overlapping-- jumbled, in a sense. And so there is what we call cytologic atypia to this. So as long as these findings are rather focal and minor, we would put this into the AUS/FLUS category.

In this case, that was the right answer because this cytology turned out to be NIFTP. So, there are a number of other lesions that have similar nuclear features. And these are listed here, ranging from invasive follicular variant carcinoma, to benign neoplasms like at adenoma and adenomatous nodules.

Another reason why this whole exercise is challenging is because the so-called papillary-like nuclear feature can sometimes appear in a rather spotty pattern, in a sense. It's not diffusely present throughout the entire nodule. So these are the main reasons as to why we, in cytology, have this challenging issue and end up calling these in one of the indeterminate diagnosis.

Having said that, though, now with the inception of NIFTP, as we had talked about, the goal is to do the best we can, to put the eventual NIFTP cases into the AUS/FLUS or follicular neoplasm category. And then keep them, as best we can, away from the suspicious for malignancy category. And this has been addressed in the new Bethesda text. And this is what it states regarding the differential diagnosis of cytologic atypia. The distinction between AUS/FLUS and suspicious for malignancy is problematic in aspirates with focal features of papillary carcinoma. The first pattern has rare cells with enlarged, often overlapping, pale nuclei, pale chromatin, irregular nuclear outlines, and nuclear grooves.

The second pattern-- so the first pattern, we have rare cells, the second pattern is where the pattern is more diffuse with cytonuclear enlargement, focal irregularity, nuclear membrane irregularities, only occasional grooves, and often with a microfollicular architecture. So these are problematic areas. But the bottom line is, when we are on the fence now, this is a toss up. But we are tending now to be more conservative in calling these AUS/FLUS, rather than suspicious for malignancy.

So, what happens in real life in a case like this is, OK, it was diagnosed as AUS/FLUS because of cytologic atypia. In an institution like ours, we have the ability to provide molecular testing. And if it comes out as one of the RAS mutations, like it did here, then because RAS mutations are associated with follicular-patterned neoplasm, this patient would then go on to lobectomy, usually.

Here's another case that's interesting. We could say that, OK, these cells look rather similar to the previous ones right here. And they do. But in this case, this was also called AUS because this finding was focal. But it turned out to have BRAF V600E, which is a more significant mutation, oftentimes, associated with classic papillary carcinoma. It's also a variant papillary carcinoma. Or if it follicular variant, more the widely infiltrated follicular variant papillary carcinoma. And for these cases, a total thyroidectomy is perhaps the treatment of choice.

How can we explain this phenomena? And I use this image to do that. For the cytopathologists, when we see an image like this, our mind's eye immediately focuses on areas like this where you have nice beautiful pseudo-inclusions, enlarged nuclei with grooves. That's saying, OK, this is a no-brainer. This is papillary carcinoma. But if you pay close attention, if you look at this area in this upper right hand box, you find that the nuclear features seen in the lower box are missing. And so, if we were to just sample these types of cells, you end up in a situation like we had here, where the cytologic atypia are more indeterminate.

How about the and the other issue regarding more of a follicular pattern cytologic finding, where oftentimes, follicular neoplasm is certainly in the running. And perhaps with degrees of cytologic atypia placed in a follicular pattern process, then suspicious for malignancy may come into the differential diagnosis. And for this, the Bethesda text now states that for lesions deemed borderline between follicular neoplasm and suspicious for malignancy, it may be more prudent to opt for the follicular neoplasm designation, because that diagnosis is more likely to prompt a limited surgical approach-- that is, lobectomy.

So here's an illustration of this, what we call micro-follicular pattern, where we have these small circles of cells with nuclei that are overlapping, slightly enlarged. Actually, some of them are getting a little bit more than being comfortably enlarged. And we start getting concerned that there are some degree of atypia here. And there's another one right here, where the nucleus is getting a bit elongated, perhaps with a groove formation.

So these features start getting us concerned that, gee, should we keep this in the follicular neoplasm category? Or, shall we bump it up to the suspicious for malignancy category? Here's another one right here. Some of the nucleis, you can see, are getting somewhat large with paler chromatin, and start wondering then, is this possibly like a follicular variant papillary carcinoma? So here again, molecular testing does help in this case. This was also another case with HRAS mutation. And so, HRAS being associated with follicular pattern neoplasm, the treatment of choice would be more toward lobectomy.

And finally, the last issue to talk about is the malignant category. Although the drop in the risk of malignancy is not perhaps as significant as that seen for the indeterminate diagnoses, you can notice that if you're going from somewhere from, like, 97% to 99%-- which is the case in most institutions-- and dropping down to about, let's say, 95%, even though that's a relatively small drop, if you're dropping down to 95%, that means that 1 out of 20 cases or so are falsely positive. And this may get us into a situation where how trustworthy is that positive diagnosis?

So this has been addressed amongst cytopathologists, and nicely stated in the new Bethesda classification as such. And mainly because for the positive for malignancy category, oftentimes, the treatment of choice is upfront total thyroidectomy. So what the Bethesda classification now states is to avoid overtreatment, it is highly desirable to exclude potential NIFTP cases from malignant category. Preliminary data suggests that a definitive diagnosis of PTC should be reserved for cases with at least one of the following-- and they list three-- papillary architecture, psammoma bodies, or inter-nuclear pseudo-inclusions.

Now, while this is true in our practice, I personally find that the first two are relatively rare to find in cytology specimens. So, the pseudo-inclusions are perhaps the most important feature to pay attention to. And what we have found in our experience is that because we have been practicing in a rather conservative manner, even before the inception of NIFTP, that the oncoming of NIFTP did not really influence our positive for malignancy category. So whether it be before or after NIFTP reclassification, our risk of malignancy was 99%.

So other institutions have experienced a drop. So what does that mean? That means that in general, for those institutions that have experienced a drop in the risk of malignancy from, like, let's say, 99%, to 94%, 95%, well, that generally means that prior to NIFTP inception, they were probably attempting to diagnose follicular variant papillary carcinoma by cytology. So it comes down to that. If they were attempting to do that, yes, the risk of malignancy will drop. But if you had not been doing that, then it probably won't affect you.

So, your bottom line is apply your criteria carefully, look for inter-nuclear pseudo-inclusions. And this is my last slide. So in summary, regarding NIFTP and the new Bethesda classification, there are three main issues regarding AUS/FLUS. The risk of malignancy will drop, but still, it's probably good to talk about including NIFTP as a malignancy category. So 10% to 30% is what we expect.

In borderline cases, many of us in cytology circles are leaning more toward AUS/FLUS. Similarly, for the follicular neoplasm category, again, the risk will drop If you take NIFTP out of the malignancy category. But if you don't, we're still in the range of 25% to 40%. And then borderline cases lean toward follicular neoplasm. And for the positive for malignancy cases, the important thing is to use strict criteria, especially the identification of inter-nuclear pseudo-inclusions. So with that, I conclude my talk. Thank you for your attention.