

[MUSIC PLAYING]

**RAJA R.** As your local ambassador for NIFTP, I'm going to talk about this for my update. I'm just joking. There's no such thing as an ambassador in NIFTP as far as I know. So let's go on. Next slide please.

**SEETHALA:**

Yeah, so we're going to talk about the history of what got us to NIFTP. And then we'll talk about some of the frequently asked questions that we as a group here have tackled over the past four years of living with this diagnosis. I guess you can play a beer game or a drinking game as to whenever a slide like this pops up. But this is the perennial classic thyroid cancer conundrum. The incidence is increasing over the past several decades with the stabilization of the mortality.

We conjecture that this is because we're making the diagnosis too readily, i.e. overdiagnosis. So this may be due to increased surveillance, as you heard before. But pathologists also have a role to play in this diagnosis.

How has pathologic diagnosis contributed to this phenomena? So in two ways. Basically, papillary thyroid microcarcinomas. So you have at least one or two generations of pathologists that have been conditioned to pick up not only sub-centimeter microcarcinomas but sub-millimeter microcarcinomas.

And then the other part of the equation is follicular variant of papillary thyroid carcinoma. So what is follicular variant of papillary thyroid carcinoma? Because it has increased-- advance please. There's an animation. Yeah, so if you see to the right of the dashed line, the more recent cohorts have a higher proportion of follicular variant of papillary thyroid carcinomas as compared to older cohorts.

Before 1960, follicular variant obviously did not exist. Thyroid carcinomas were categorized based on their growth pattern. If it was papillary, it was papillary thyroid carcinoma. If it was follicular pattern, it was a follicular thyroid carcinoma. About 1960 or so and ultimately in 1977 when Chen and Rosai officially described follicular variant of papillary thyroid carcinoma, the concept that a follicular pattern neoplasm with the same nuclear features as a papillary thyroid carcinoma arose.

This gives rise to basically an explosion of this diagnosis over the subsequent decades as well as an explosion in the controversy and disagreement about this entity. And a sub-categorization had evolved. You have invasive, or infiltrative, follicular variants in contrast with the non-invasive version of this tumor defined by nuclear features alone. This could be encapsulated, well demarcated, well circumscribed. Either way, the key thing was that this group of tumors was not invasive.

This was the basis for a lot of contention amongst pathologists and a lot of anxiety. So a lot of times these non-invasive tumors are actually very subtle. The nuclear features are not the classic textbook nuclear features that you would see in papillary thyroid carcinomas.

Yet at the same time, up until recently, these had not been historically treated any differently. They were treated in the same way. And pathologists had a lot of anxiety because a subtle subjective diagnosis was also subject to a pretty harsh penalty in many people's eyes.

And it turns out that when you look at the outcome on these nodules, they don't do particularly poorly. They have a very favorable outcome with a very low metastatic rate. Even the cases that are non-invasive that have a recurrence or metastases have questionable circumstances surrounding them.

So between 2015, 2016, a multi-institutional, multidisciplinary group was formed, led by Dr. Nikiforov. And we came up with this concoction which we now know as Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features, or NIFTP or NIFTP if you will. So we enumerated inclusion and exclusion criteria based on a study of several cases. And throughout the years, these criteria have evolved, been modified, or been added, as you see to the left. And we'll talk about these specific issues in the next couple of slides.

So this is a-- hopefully this animation works. Let's go through how a pathologist arrives at the diagnosis of NIFTP. You have this dominant nodule in the background of nodular hyperplasia and chronic lymphocytic thyroiditis. You can see it's well circumscribed, not invasive. It's not encapsulated, but it's not infiltrated at all. At this power, you can readily recognize that it's follicular patterned with microfollicles interspersed with macrofollicles, as is typical of this, and it's invasive counterpart, for that matter.

If you look at higher power, the nuclear features are subtle-- slight membrane irregularities, enlargement, chromatin alterations, and they're heterogeneous. You see a sprinkling over there. And often with these tumors, you see accentuation of this at the periphery.

So let's stabilize the image. Yeah, so peripheral accentuation of nuclear features, more so than in the center. For subtle things, we always like to compare with normal. And you can see the difference over here. So that seems pretty straightforward. The thing is this is a pretty easy case. And the other thing is that in a real case we not only have to do that with one side, we have to do that with several blocks to ensure that it is actually-- these features all remain consistent to establish the diagnosis of NIFTP.

So where do we stand with NIFTP right now? Well, despite the naysayers in early 2016, NIFTP is here to stay. It was accepted as an entity by WHO. There's an ICD code for it that registrars have adopted starting January 2017, even though they were coded even earlier. CAP protocol exists to allow for an optional limited data set for NIFTP, even though it's not a cancer technically speaking.

The ATA endorsed it. The current ATA link is a very nice summary. I have it listed over here. And the subsequent literature over the four years overall validates the indolent behavior of NIFTP but at the same time will highlight some of the flaws in application of initial criteria, as we'll discuss.

So one interesting thing to note is NIFTP may actually have already an impact on the incidence of papillary thyroid carcinoma. This is a recent publication demonstrating in the SEER database that from 2015 to 2017 the total incidence of papillary thyroid carcinoma had a slight dip.

A significant contributor to this is the decrease in the diagnosis of follicular variant of papillary thyroid carcinoma. And since for the first time in 2016 and 2017 NIFTP had been coded and recorded in the registries, it's estimated that this actually accounts for at least 20% of this decline.

So now we'll talk about some of the questions about NIFTP over the past couple of years that we've encountered as a group and myself individually as well. So is NIFTP benign then? Well, that's a common misconception and not exactly. It's important to reiterate that even though NIFTP is indolent, it is a pre-invasive neoplasm with the same morphologic and molecular spectrum as its invasive counterpart. The risk of recurrence is close to but not exactly 0%, assuming you adhere strictly to the enumerated criteria.

The important things to note are that if left untreated, NIFTP can progress to an invasive tumor-- invasive well-differentiated follicular variant of papillary carcinoma or even worse. But luckily complete resection is curative. Thus NIFTP is indeed a surgical disease. That's another common theme that you may hear throughout the day.

Just to summarize the molecular profile of NIFTP, if you look at the TCGA data which is arrayed in a spectrum where you have cumulative genetic events giving a RAS-like phenotype versus a BRAF V600E-like phenotype. The RAS-like phenotype-- this is basically where NIFTP sits. Just like other follicular pattern lesions, they tend to have RAS.

So most NIFTP, about 80% in the initial study and in subsequent literature, have clonal alterations with the majority being indeed RAS. PAX8/PPARGamma, THADA, rearrangements in BRAF K601E are also noted just like they're invasive counterparts. The important thing to note is that you don't see V600E or RET/PTC, which is on the other end of the spectrum.

This is a case that I use to illustrate exclusionary criteria for NIFTP. But it also highlights the danger of underestimating NIFTP as a simply benign disease. So this tumor has a follicular pattern in several areas is encapsulated and non-invasive. But it is not a NIFTP.

Indeed, some areas do have subtle nuclear features in a follicular pattern that are compatible with NIFTP. But there is a nodule within a nodule that actually shows a solid trabecular growth pattern and mitotic activity. So this is an indication these features exclude the diagnosis of NIFTP, number one.

It's also an indication of progression. So if you conceptualize that if this patient did not have this lesion resected, if this stayed in this patient, that nodule within a nodule may progress and blow out of its capsule. So now you're not only dealing with an invasive carcinoma, you're dealing with an invasive poorly differentiated carcinoma. So it's important to note that while NIFTP is indolent, it is a pre-invasive neoplasm. So interestingly, this has NRAS and TERT. And we'll talk about this shortly.

Another question I get a lot is-- Can NIFTP be diagnosed by molecular testing-- alone, that is anyway? And right now the answer is no. And in the foreseeable future, NIFTP will remain a morphologic diagnosis. It doesn't mean we should ignore molecular findings when they are present.

As we said before, NIFTP has a characteristic molecular set of alterations listed again over here. And in fact, now with new recommendations, you should think to exclude the diagnosis of NIFTP when you see mutations like BRAF V600E, RET/PTC, beta catenin mutations, when you see cumulative progressive mutations like P53 and TERT.

These all have morphologic correlates. BRAF, RET are along the conventional tall cell spectrum. beta catenin mutations are characteristic of the cribriform morular variant of PTC. And finally, when you have cumulative mutations like P53 and TERT, this is a harbinger of progression to poorly differentiated carcinoma.

I don't usually worry about these, because the morphological correlates are usually pretty obvious. And you're not really thinking about NIFTP, but NTRK and ALK represent kind of a new beast in our eyes, both from a management perspective and also from a diagnosis perspective.

This is a tumor that does a great impression of mimicking a NIFTP. It's an ETV6-NTRK translocated tumor. You see it's nice demarcation. The problem is when you look further-- and I tend to worry about tumors with clear cell vacuolated cytoplasm. I will get more levels to not only ensure that the entire lesional capsule is submitted.

And indeed, you see some infiltration over here. And you see that this is to highlight some of the more clear vacuolated cytoplasm that's characteristic of this group of tumors. Other areas, there was actually capillary vascular invasion. So it's very important to not underestimate ETV6 or NTRK translocated tumor, because they do mimic the appearance of NIFTP. And when you see the morphologic correlates, this will be a situation to worry.

Another question that we often encounter-- and this has been there since the inception of the diagnosis and the popular New York Times article. That question is my cancer no longer a cancer? So would it have been NIFTP by current standards? Patients and health care providers alike want an answer to this question sometimes.

Key issues in arriving at this question is feasibility. Can you do that for all nodules retrospectively? Well, at a busy center, no. It's not fair to anybody to do that. It may not even be relevant. So if you want to make this useful retroactive reclassification, you need to make sure that everybody, all the stakeholders are on the same page and have a process to do it.

So basically, this is what we did. The important thing to note is that these are patient, clinician driven requests with a specific protocol. We looked at the reports and glass slides to evaluate for reclassification. And importantly, these are reported in an addendum rather than amendment. So in other words, pathologists were not held to a standard that didn't exist back when the original diagnosis was made. We were just basically saying that this would have qualified as a NIFTP. And that's enough information to potentially alter management.

So we're just basically going to go through this very quickly because we're short on time. But the bottom line is if you did this exercise at your institution you can estimate that about a quarter of your cases can be successfully reclassified. And another quarter of patients can be excluded from reclassification by reviewing the reports alone.

So if you look at the reclassification rates by year, you'll see that the most cases that were successfully reclassified were actually rather recent. And we'll talk about the reason really quickly. So the top two reasons for not reclassifying a tumor are presence of papillae and incomplete lesional capsular submission.

So some cases, like the one on your left, is pretty obvious. A conventional papillary thyroid carcinoma probably shouldn't have been categorized as follicular variant to begin with. Other cases are a little more subtle. You see some aborted papillae and psammomatoid calcifications.

Next slide please. But the other important thing is that some cases you can exclude on report alone because you don't have the entire lesional capsule submitted. And that's very important for establishing the diagnosis of NIFTP. If this does not occur, you're disqualified from NIFTP. And this is why the older cases were only rarely classified as NIFTP because this was not standardized until about 2005, 2006 at our institution.

NIFTP is no longer new. Why do we care? This is a question that my colleagues that practice other pathologic subspecialties often ask me. Then if a GI pathologist asked me that, I'd tell them well, serrated neoplasia is no longer new. Why do we care about this? Why are you giving talks about this like I'm giving a talk about NIFTP? It's because we still have room for improvement.

Application of criteria vary a lot. If you're strict with your criteria, you have a lower incidence than originally projected. If you're less strict with the criteria, you have more adverse outcomes and aggressive molecular phenotypes than are acceptable for this. What I want to emphasize is that there's no such thing as an easy NIFTP. There are several aspects to deal with that are complicated still. And if anybody says this is an easy NIFTP, they may not know what they're doing or talking about.

Again, to reiterate, you have to have the entire tumor normal interface. This is no longer an option. Cases need to be mapped very methodically. This is a sample grossing template that RPAs and residents use when they gross their specimens. So everybody at UPMC, all hospitals within the system should be using this.

If they're not, number one, shame on you. Number two, email me and I'll connect you to the lead PA that will give you this voice recognition friendly template. The goal is to take something like this and make it into something like this. So you want to maximize surface area and minimize the number of cassettes or blocks.

A little bit about nuclear features, because they are still defining in NIFTP. They have been a main point of contention with moderate reproducibility at best. Some geographic variation-- this would be where I'd usually joke about political variation. But politics, I mean, they're funny enough or sad enough in real life. So we can skip that.

So this is the scoring scheme that we came up with. What you need to acknowledge is the happy medium in the middle column here where the nuclear features-- the enlargement, membrane irregularity, and chromatin characteristics-- are subtle but not overt. While the column to the right would qualify as a NIFTP, it's too easy. So if it's too easy, it's probably not NIFTP. And this is something to take home as well. If the nuclear features are readily visible, you've got to think about a more aggressive variant.

We devised this point scoring scheme and tested it against molecular endpoints and found that at least among the multidisciplinary group it is very accurate. 85% accuracy in the test set-- validation set about 94% accuracy. When you give it to general pathologists-- this scoring scheme-- and use the same test set, accuracy still remains up to 75%, which is pretty good.

The issue at large right now is papillae. So nobody agrees at this point on what constitutes an exclusionary papillae and how much is adequate. Initial criteria allowed for 1%, but this led to adverse events. So the new recommendations are to have no papillae. But the Memorial group has pushed back and shown that even with up to 1% nodal metastases were not seen. What that tells me is not only that the quantity's an issue but the papillae themselves are not well defined.

To the left is a true papillae with fibrovascular core and obvious nuclear features. To the right is a more of a hyperplastic polster-like papilla that's acceptable in NIFTP. Now, these examples are pretty distinct. But what about cases like these? Are these abortive papillae or papillae cut in cross section? These are things that pathologists would wrestle with? You may agree or disagree with whether or not these are papillae. But this is a case that had nodal metastasis. So obviously, there needs to be a better definition of papillae.

NIFTP and variants. We're still evolving in terms of categorizing variant morphologies. Now, can we apply NIFTP to multiple tumors? Possibly. Up to 15% are multifocal. Follow-ups for these nodules is not well documented. Small tumors, kind of an obvious thing. But the Memorial group and the UPM group have validated use of NIFTP in sub-centimeter tumors.

And now the thing to move forward with is heavily oncocytic tumors, because these, again from the Memorial group, seem to actually justify use of NIFTP. The Royal College in London actually uses oncocytic features to exclude the diagnosis of NIFTP. So this is something to work around or work with in the future to validate whether or not you can have oncocytic NIFTP.

So basically NIFTP was a response to the problem of non-invasive follicular thyroid for papillary thyroid carcinoma. Evidence to date has highlighted its validity but also has illustrated some misconceptions and also ongoing dilemmas and challenges. Thank you very much.