[MUSIC PLAYING]

**ELENA MORAIU:** I'm going to give you an overview of the 2015 ATA guidelines for management of thyroid nodules. Nodules may be detected either clinically by palpation or incidentally on imaging. The guiding clinical strategy behind these guidelines reflects an understanding that most thyroid nodules are low-risk, and many thyroid cancers pose minimal risk to health and can be effectively treated.

And only-- so in general, only nodules greater than a centimeter should be evaluated with FNA. And in the current guidelines, thresholds for FNA have changed, leading to fewer nodules meeting criteria for FNA. Occasionally nodules less than a centimeter may be appropriate for FNA evaluation. For instance, if they have associated lymphadenopathy.

So what is the appropriate evaluation for patients with clinically or incidentally discovered thyroid nodules? This is the algorithm that guides the management. So of course initially, history and physical exam to include questions regarding childhood head and neck radiation, family history of thyroid cancer, or regarding symptoms of rapid nodule growth or hoarseness.

And then first we check a TSH. If it's normal or elevated, we proceed to a thyroid ultrasound, if it has not yet already been done. And then the nodule may be evaluated by FNA based on thresholds according to their sonographic pattern.

To mention other studies discussed in the guidelines, a thyroglobulin measurement, routine measurement of serum thyroglobulin for initial evaluation of thyroid nodules is not recommended as it's insensitive and nonspecific for thyroid cancer. Regarding calcitonin measurement, which may detect sessile hyperplasia or medullary thyroid cancer at an earlier stage, due to unresolved issues of sensitivity, specificity, assay performance, and cost effectiveness, the panel did not recommend for or against routine measurements of serum calcitonin patients with thyroid nodules.

Regarding PET scan, so a focal PET uptick in a thyroid nodule does convey an increased risk of thyroid cancer. And FNA is recommended if the nodule is greater than a centimeter. Roughly a third of PET positive thyroid nodules are shown to be cancerous. For PET positive nodules that are less than a centimeter, that do not meet FNA criteria, they can be monitored similarly to nodules with high risk sonograph patterns that do not meet FNA criteria. Diffuse PET uptake, particularly in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis does not require further imaging or FNA, as it typically represents benign disease.

The new current guidelines include a section pertaining to the role of thyroid cancer screening, and people with familial differential thyroid cancer. So family members of patients with non-medullary differentiated thyroid cancer may be considered at risk based on epidemiological evidence showing that 5% to 10% of differentiated thyroid cancers have a familial occurrence. It's unclear whether two family members are sufficient to define a real familial disease. There's still a high probability that those could be sporadic, but three family members are more, indicates a predisposition for thyroid cancer.

The impact of screening at risk family members is not known, so the panel could not recommend for or against ultrasound screening as there is no evidence that this would lead to reduced morbidity or mortality. However, they recommend at-risk family members to have a history and neck exam as part of their routine health maintenance. And one should also keep in mind syndromes, tumor syndromes that are also associated with differentiated thyroid cancer, such as Cowden's disease, familial adenomatous polyposis, Carney complex.

We've seen this figure before. So once an ultrasound is obtained, we look at the sonograph patterns. So high suspicion nodules that exhibit features consistently shown to be associated with thyroid cancer, such as micro calcification, nodule hypoechogenicity, irregular margins, or shape taller than wide, these confer a high suspicion of malignancy greater than 70%, 90%.

And the FNA's highest cut off would be greater than-- one centimeter greater for these nodules. Nodule echogenicity is a less specific marker for malignancy. Up to 55% of benign nodules are hypoechoic. And so nodules that are hypoechoic but lack any of the other high suspicion features fall into an intermediate suspicion category, conferring an malignancy risk of 10% to 20%. And they should also be evaluated FNA at a centimeter or greater.

Low suspicion nodules that are isoechoic or hyperechoic or partially cystic with an eccentric solid area without the aforementioned high suspicion features, they're-- they carry a risk of 5% to 10%. And they should be considered for FNA at greater than one and a half centimeters. Very low suspicion nodules are spongiform or partially cystic nodules without any of the other features. Very low risk of malignancy.

They should be considered for biopsy at two centimeters or greater, or observation would also be a reasonable plan. And a benign cyst with no solid component should not be biopsied. This is a table depicting what we just talked about.

So sonographic evaluation of the anterior cervical lymph node compartment, central and lateral, should be performed whenever thyroid nodules are detected. And if the ultrasound detects cervical lymph nodes that are sonographically suspicious for thyroid cancer, FNA of the suspicious lymph nodes should be performed for cytology, and watch out for thyroglobulin measurement. And at this table lists the ultrasound features for lymph nodes that are predictive of malignant involvement, including microcalcifications, the cystic aspect, peripheral vascularity, hyperechogenicity, or a round shape.

And with FNA, the nodules will be classified in one of six cytologic categories based on the Bethesda system. So now I'll go through each Bethesda category and the recommendations for each. So a non-diagnostic cytology where the specimen fails to meet the established quantitative or qualitative criteria for cytologic adequacy, or six groups of well visualized follicular cells, each group containing 10 well-presented-- preserved epithelial cells. In this situation, the FNA should be repeated with ultrasound guidance and onsite cytologic evaluation.

Previously it was suggested that repeat FNA should be performed no sooner than three months after the initial FNA to prevent false positive interpretation due to reactive changes. However, recent studies did not find a correlation between diagnostic yield or accuracy in waiting periods. So a three-month waiting period is likely not necessary. Repeat FNA with ultrasound guidance will yield a diagnostic cytology specimen in 60% to 80% of these nodules, particularly when the cystic component is less than 50%.

For nodules that are repeatedly non-diagnostic without a high suspicion sonograph pattern, close observation or surgical excision are acceptable based on the guidelines. Certainly consider surgery if there is a high suspicion sonographic pattern, if there's growth of the nodule, or if there are clinical risk factors for malignancy present. They recognize that most nodules with a non-diagnostic cytology interpretation are benign. In one study of 104 nodulars with non-diagnostic cytology results, thyroid cancer was found in 25% of those that had high suspicion features such as microcalcifications, irregular margins, or a taller than wide shape, but only in 4% lacking these features.

Mutational testing may be informative in samples that are considered inadequate based on qualitative criteria. But unlikely to be helpful if it's not diagnostic based on quantitative criteria. For benign cytology, if the nodule is benign, further immediate diagnostic studies or treatment are not required.

So what about larger nodules that are benign on initial FNA? So several surgical series have reported a higher malignancy rate in nodules greater than three to four centimeters. In a single-center study, actually at our institution, it suggested a higher false negative rates for nodules greater than four centimeters.

So thyroid cancer was found in 22% of nodules greater than four centimeters. And of 125 nodules that underwent preoperative FNA and were cytologically benign, 10.4% were malignant on final histopathology. And so due to a higher false negative rate, that has led to a practice of considering a patient for diagnostic lobectomy for four-centimeter nodule regardless of initial cytology result.

Other reports have suggested lower false negative rates. One study looked at nodules greater than three centimeters. So they had a lower threshold with initial benign cytology. They had a false negative rate of 1.5%.

And they noted that 66% of missed cancers were found in nodules with high suspicion sonographic patterns. So guidelines do not make a recommendation here. They state that it's unclear if patients with thyroid nodules greater than four centimeters and benign cytology should be managed differently than smaller nodules.

For malignant cytology, if cytology result is diagnostic for thyroid malignancy, surgery is generally recommended with some caveats. Active surveillance can be considered in patients with very low-risk tumors, patients at high risk, surgical risk because of co-morbid conditions, patients expected to have relatively short remaining time span, lifespan, and patients with concurrent medical surgical issues that need to be addressed.

Papillary thyroid microcarcinomas, so carcinomas smaller than a centimeter. Following thyroid surgery, these have disease-specific mortality rates that are less than 1%. Local regional recurrence rate 2% to 6%, and distal recurrent rates 1% to 2%.

So they have excellent outcomes, which may be due more to the indolent nature of disease rather than the effectiveness of treatment. So studies have suggested that observation may be safe. However, there are reports of some patients with microcarcinoma presenting with clinically significant regional or distal metastases. And so historically observation has not been offered to these patients.

There aren't clinical features that can reliably differentiate the small number of microcarcinoma patients that are destined to develop clinically significant disease, but specific molecular profiles may serve as markers for a less favorable outcome of papillary thyroid carcinoma. And so finding these molecular profiles in a small tumor likely represents an early stage of clinically relevant PTC. So studies in this area could establish a role for molecular testing on clinical management of a patient with PTC with microcarcinoma.

So for indeterminate cytology, which encompasses atypia, undetermined significance, follicular neoplasm, and suspicious for malignancy cytology results, molecular testing can be used for diagnosis and to inform decision making on primary surgical management. Molecular testing can refine the risk stratification and reduces the need for diagnostic thyroid surgery. The molecular testing assays that are more extensively studied and discussed in the guidelines include the next generation sequencing panel known as Thyroid Seek.

That was developed at our institution. Currently, we have version three that analyzes 112 genes for a variety of genetic alterations that are known to be associated with thyroid cancer. And they also discussed the gene expression classifier, known as AFIRMA.

So if molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing, and about the possible uncertainties and therapeutic and long-term clinical implication of the results, as long-term outcome data is still lacking. So for AUS evaluative cytology, these are specimens that contain cells with architectural or nuclear atypia that is more pronounced than expected for benign changes, but not sufficient to be placed in one of the higher risk diagnostic categories with an estimated risk of malignancy for 5% to 15%. Repeat FNA can yield more definitive diagnosis, and tend to in some nodules, but a substantial amount, 10% to 30% of nodules, are repeatedly AUS on repeat FNA.

Molecular testing, interpretation of molecular testing, is complex. And its utility is strongly influenced by the prevalence of cancer in the tested population of nodules. So using Thyroid Seek version 2.1, finding positive molecular testing conferred a sensitivity of 90% specificity of 92% the positive predictive value of 76%, and a negative predictive value of 97%. Using AFIRMA, there's a sensitivity of 90% to negative predictive value of 95%. But the specificity and positive predictive values were low, so this is more useful as a rule out test.

After consideration for worrisome and clinical sonographic features, repeat FNA or molecular testing may be used to supplement malignancy risk assessment, which can lead to either surveillance or diagnostic surgery. If repeat FNA, molecular testing, or both are not performed or conclusive, the guidelines leave room for either surveillance or diagnostic surgical excision, depending on clinical risk factors, sonographic pattern, patient preference.

For the follicular neoplasm category, these are cellular aspirates comprised of follicular cells arranged in an altered architectural pattern characterized by cell crowding and or micro follicle formation, and lacking nuclear features of papillary carcinoma, or comprised almost exclusively of hurthle cells carrying an estimated risk of 15% to 30%. Many of these are follicular adenomas driven by oncogenic RAS mutation with uncertain malignant potential. So molecular testing in this category, Thyroid Seek version two.

Sensitivity in this category was 90%. Specificity of 93%. Positive predictive value of 83%. Negative predictive value of 96%. Using the AFIRMA assay had a negative predictive value of 94%, and again a low positive prediction value of 37%.

Diagnostic surgical excision was the long-established standard of care for the management of follicular neoplasm nodules. However, after consideration of clinical sonographic features, molecular testing can be used to supplement malignancy risk assessment instead of proceeding directly to surgery. And if molecular testing is not performed during conclusive, surgical excision should be considered for removal and definitive diagnosis.

For nodule suspicions for malignancy, aspirates with cytologic features that raise a strong suspicion for malignancy, mainly for PTC, but are not sufficient for conclusive diagnosis, the estimated risk is 60% to 75%. Due to the high risk of cancer, the diagnosis of suspicious for papillary carcinoma is an indication for surgery. However, again molecular testing can be used to further risk stratify. So if the cytology is reported as suspicion for papillary carcinoma, surgical management should be similar to that of malignant cytology, depending on clinical risk factors, sonographic features, patient preference, and possibly results in mutational testing.

So what is the appropriate operation for cytologically indeterminate thyroid nodules? When surgery is considered for patients with a solitary cytologically indeterminate nodule, thyroid lobectomy is the recommended initial surgical approach. This approach may be modified based on sonographic characteristic, molecular testing, patient preference. Because of the increased risk of malignancy, total thyroidectomy may be preferred in cytologically suspicious for malignancy nodules. Those that are positive for known mutations specific for carcinoma, those that are sonigraphically suspicious, that are greater than four centimeters, or in patients with familial thyroid carcinoma or a history of radiation exposure.

Other things to consider are that the risks of total thyroidectomy are greater than that for lobectomy regarding recurrent laryngeal nerve injury, hypocalcemia, hemorrhage. And post-operative hypothyroidism is certain in after thyroid-- a total thyroidectomy. In lobectomy, it's estimated at 22%. Lobectomy may be sufficient for smaller, inter-thyroidal nodules that ultimately prove malignant. And one must weigh the advantages and disadvantages of thyroid lobectomy with possible-- with total thyroidectomy, and also consider the possibility of needing a subsequent completion thyroidectomy if the initial surgery is a lobectomy.

So how should multi-nodular thyroid glands be evaluated? Multiple thyroid nodules greater than a centimeter should be evaluated similarly to those with solitary nodules, as each nodule carries an independent risk of malignancy. Some multiple nodules may require FNA. FNA should be performed preferentially based on nodules, sonographic pattern, and size cut off.

If none of the nodules has a high or intermediate suspicion sonographic pattern and multiple sonographically similar, very low, or low suspicion pattern nodules coalesce with no intervening normal parankima, the risk of malignancy is low, and one should aspirate the largest nodules greater than two centimeters. Or there is also the option to continue surveillance without FNA. A low TSH in patients with multiple nodules may suggest that some nodules may be autonomous. So an I123 optic scan should be done to compare to the ultrasound images to determine functionality of each nodules. And isofunctioning nodules, or non-functioning nodules, should be assessed with FNA.

So what is the follow-up strategy for nodules that are benign on FNA? The follow up should be determined by risk stratification based on ultrasound pattern. So high suspicion nodules on ultrasound, repeat ultrasound and ultrasound guided FNA should be repeated within 12 months.

Low to intermediate suspicion, repeat an ultrasound at 12 to 24 months. And if growth, defined as an increase in volume by 50% or growth in two dimensions by 20%, or if new suspicious sonographic features appear, one should repeat the FNA. Continued observation with repeat FNA in case of continued growth is also an option.

Very low suspicion nodules, such as spongiform nodules, the utility of surveillance, of ultrasound assessment, of nodule growth as an indicator for repeat FNA is not known. If an ultrasound is repeated, it should be done at greater than 24 months. And these recommendations are based on the findings that there is a higher yield of missed malignancies based on nodule sonographic pattern rather than based on nodule growth.

Follow up of nodules with two benign FNA cytology results. If a nodule has undergone repeat ultrasound guided FNA with a second benign cytology result, ultrasound surveillance for this nodule for continued at-risk of malignancy is no longer indicated. The risk is virtually zero.

How do we follow up nodules that do not meet FNA criteria? Again, based on the nodule sonographic pattern. So high suspicion nodules should be reassessed with an ultrasound in 6 to 12 months. Low to intermediate suspicion nodules, repeat an ultrasound at 12 to 24 months.

Nodules greater than a centimeter with a very low suspicion, such as a spongiform nodule, the utility and time interval of surveillance ultrasound for risk of malignancy is not known. If an ultrasound is repeated, it should be at greater than 24 months. And nodules that are less than a centimeter with very low suspicion pattern do not require further ultrasound follow up.

The guidelines also addressed the role of medical or surgical therapy for benign thyroid nodules. So TSA suppression, routine suppression for benign thyroid nodules is not recommended. Levothyroxine suppressant therapy demonstrates only modest efficacy in nodular volume reduction of about 5% to 15%, which is usually clinically insignificant. But it does increase the risk of adverse consequences due to the iatrogenic thyrotoxicosis.

There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign on cytology. They give recommendations on adequate iodine intake. Surgery for benign nodules can be considered for growing nodules if they are greater than four centimeters, if they are causing compressive or structural symptoms, or based upon clinical concern.

Patients with growing nodules that are benign after FNA should be regularly monitored. And most asymptomatic nodules demonstrate modest growth that can be followed without intervention. And a note on recurrent cystic nodules, recurrent cystic nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules can be followed conservatively. And thank you.

[APPLAUSE]