

[MUSIC PLAYING]

**SPEAKER:** So this is just a quick rundown of pediatric thyroid nodule and cancer management. I have nothing to disclose. I plan to cover the prevalence rate, risk of malignancy, and evaluation of children with thyroid nodules, the role of a multi-disciplinary approach, then briefly address-- it'll be some repetition from what Dr. Joyce had said-- differences in management guidelines in children versus adults.

How common are thyroid nodules in children? Prevalence of thyroid nodules is reported as somewhere between 0.2% and 5%. This is definitely less than adults, but certainly not rare. Cystic lesions of thyroid were detected in more than half the children surveyed in Japan. This study was done following the nuclear accident there. But this was done immediately following the nuclear accident so this was not a result thereof.

Other groups of children at greater risk for developing thyroid nodules, children exposed to radiation are at high risk. Some of them are childhood cancer survivors who had radiation therapy. The study from Memorial Sloan Kettering looked at thyroid nodules that were picked up incidentally by CT and PET CT and they're cancer survivors, and followed them. About 30% of the nodules needed a close follow up evaluation and the malignancy rate was 7%.

At Nationwide Children's cancer survivors who received radiation versus no radiation were compared. About 35% of children who received radiation developed nodules. Study from Canada shows a single institution experience study included ultrasound surveillance in their cancer survivors. They found nodules in almost 60% of their long term cancer survivors after about 10 years. So there seems to be an increase in the risk of nodules usually after a delay of about 10 years of radiation exposure.

This diagram from a large multi-center cancer survivor cohort, children who got exposed to radiation therapy of about dose of 20 to 25 gray and who got exposed to radiation at a younger age were at greater risk. Current pediatric guidelines do not recommend routine ultrasound surveillance of this high risk group. But from these data, it looks like that might be a consideration, especially if they are over 10 years plus radiation.

Autoimmune thyroiditis. Are they at risk? There are a few studies. One study from Italy found thyroid nodules in a third of their patients with auto-immune thyroid disease. This might be an overestimation since this was done in an iodine deficient area and they included only symptomatic patients and not the ones we routinely screen or identify with this screening antibodies. Most of the nodules were found at the time of diagnosis. So this could be an overestimation of their incidence.

Study from Richmond, Virginia indicated an incidence of about 17%. And a study from Korea is reporting an increased risk of thyroid nodules as well as thyroid cancer in children with autoimmune thyroiditis. But this is a retrospective study looking at kids who had ultrasound for other clinical reasons. So overall, some association, no clear cut evidence. Routine ultrasound screening is not recommended for children with auto-immune thyroiditis unless indicated by physical exam.

However, other risk factors for development of thyroid nodules. Iodine deficiency is long known to be a risk factor. According to Enhance 3 data, about 10% of the US children are iodine deficient. As we heard earlier, there are genetic syndromes including PTEN hamartoma syndromes, familial adenomatous polyposis, Carney complex et cetera which predisposes children for development of thyroid nodules and thyroid cancer.

So overall, if we consider all these risk factors, thyroid nodules are more prevalent than thought earlier. So how likely are these nodules to be malignant? That's what we really care about. Well, overall the incidence of thyroid carcinoma in children was reported as 26% by comparing multiple studies over several decades. So roughly about one in four of the thyroid nodules in children are going to be thyroid cancer. Some studies are reporting a malignancy rate of 35% in children with Hashimoto's thyroiditis.

So in summary from this part of the talk, thyroid nodules are more common in children than previously appreciated. Compared to adults, thyroid nodules are rare in children. However, about 25% of the nodules in children are malignant compared to 5% to 10% in adults. So with increased malignancy risk, care for evaluation of the nodules becomes crucial. Incidence of thyroid cancer as we heard in children appear to be increasing as well. Incidents in children is up about two-fold over the last 40 years. And the incidence is increasing about 5% per year.

We've known for some time now that deduction is primarily in the adolescent age group. Young women are more likely to develop thyroid cancer than men. Different shaded thyroid cancer is the second most common malignant solid tumor in adolescent girls. So ability to predict the malignancy risk in the nodules then becomes very important. Ultrasound guided fine-needle aspiration has been shown to have a sensitivity of about 95%. But how to select as to which lesions warrant FNA. This is problematic in children.

To begin with, a study from a tertiary care children's hospital in the United States evaluated about 283 children referred for evaluation of thyroid nodules. Of them, 99% of the referred children did not have any discrete nodules and this just created false alarm and panic for the families. So this calls out for radiologists with specific interest and expertise in reading pediatric thyroid ultrasounds. However, the nodule size in adults we had the clear-cut recommendations based on the nodular measurement on ultrasound. Since a thyroid gland itself is small in little children, size based stratification is difficult. Moreover, children grow rapidly so the size criteria cannot be used as a predictor for malignancy.

Differentiated thyroid cancer in children could primarily present with lymphadenopathy even without a nodule. So detection of just abnormal nodes in the neck is critical. TSH level is not very useful in children as a malignancy predictor. Heart nodules in adults have a low malignancy risk. In contrast in children, a much higher rate of malignancy has been reported.

So assuming that ultrasounds are done by radiologists with specific interest in pediatric thyroid disease, are we OK in predicting malignancy? There are other lesions in children which mimic a papillary thyroid carcinoma. Common one has ectopic thymic tissue.

So are there any combination of ultrasound characteristics that we could use? A few studies have come out, including a paper from our group looking at the ultrasound features and malignancy risk of thyroid nodules in children. If you look at these studies, fairly low numbers compared to adults. First study found irregular margins, abnormal nodes, and elevated TSH as predictive. Second study evaluated 184 children and teens with nodules. None of the ultrasound features had a diagnostic accuracy as high as fine-needle aspiration.

When we looked at our cohort, calcifications and intranodal vascularity was sensitive. But again, the interobservability among the radiologists was found to be limiting. So in effect, there is no single unifying feature in ultrasound that indicates increased probability of thyroid cancer, leaving us with fine-needle aspiration biopsy for confirmation of diagnosis.

Like in adults, fine-needle aspiration has a high sensitivity and specificity in children. But there are problems here as well. In adults, there are probably some malignancies assigned to each of these Bethesda categories. And they go up from 1% to 4% for non-diagnostic, up to highly likely to be malignant when the site a pathologist reads them as malignant. Remember, children, the pretest probability is higher. The risk for malignancy is about 25%. There are not many studies in children as a single risk stratification for the Bethesda system of reporting.

Combining two studies, including one from our group assessing the risk for malignancy for the Bethesda class in pediatric thyroid nodules, malignancy a risk for the AUS/FLUS lesions is about 28% and about 58% for the suspicious follicular lesions. So the pediatric risk for these categories are almost double compared to adults, based on the data so far.

What the pathologists currently report to us after FNA is the adult probability of malignancy and not a pediatric malignancy rate. And this is, again, due to lack of data. So this does not help the clinicians much.

With all these problems in pediatric thyroid cancer, the value of a regional center and as we heard before, a mighty multidisciplinary team approach is crucial. We have team members from various departments at University of Pittsburgh who work together at children's hospital. Children usually get referred to pediatric thyroid clinics for further evaluation. Occasionally they get referred to endocrinology from our surgeons' offices as well. Ultrasound guided FNA is done in lesions that are suspicious clinically and by ultrasound features. FNA is done under sedation. Adequacy of the sample is insured on site. Indeterminate samples are reflexed to molecular testing. Our surgeries are performed by our ENT surgeon, Dr. Jeff Simons and pediatric surgeon Dr. Kevin Mullin at children's hospital with our surgical colleagues at UPMC coming over for extensive lesions.

We have benefited greatly from our team approach. And the team's main interest is in the molecular diagnostics of pediatric thyroid cancer. In the ATA pediatric guidelines, no clear cut recommendations are made with regards to genetic testing. What we've learned from our practice is that genetic testing is very helpful in the treatment plan, especially for the indeterminate FNA pathology.

We are fortunate to have Yuri here in Pittsburgh. He has published about RET/PTC mutations in children with papillary thyroid carcinoma and mutations like RET/PTC 3 being more in children who got thyroid cancer following radiation fallout from Chernobyl accident. At children's hospital, samples are collected on all pediatric thyroid FNAs with reflex testing for indeterminate diagnosis to help us decide whether total or partial thyroidectomy versus just clinical follow up.

We currently have a broader study underway using ThyroSeq 3, which scans as you saw earlier for a lot more genetic variants. Our group initially reported lower BRAF mutations in children with PTC. We also found that RET/PTC and other fusion genes are more common than point mutations. When outside pathologist retested our previous samples, the 67% of the previous negative samples were found to have the [INAUDIBLE] NTRK fusion genes.

So with that in mind, what are the other major differences in the management guidelines in children compared to adults? We were concerned before in children that thyroid nodules tend to be more malignant. They have larger tumors, greater incidence of lymph node metastases. In the initial studies, younger children with PTC were also noted to have increased lung mets and also greater chance of recurrence. And because of all these, everyone was treated aggressively.

Every child diagnosed with differentiated thyroid cancer used to receive thyroidectomy followed by remnant radioactive iodine ablation. So what created the need for specific pediatric guidelines? We heard earlier, we now know that the long term survival for children is excellent. There's also an apparent increase in the risk of second malignancy among childhood cancer survivors who were treated with radiation. So the goal here is to prevent long term complications from extensive surgeries and radioactive iodine therapy. But even children who have extensive disease at presentation are less likely to die from the disease. 2% or less long term cost specific mortality. Primary mets are usually microscopic and many children with primary mets developed persistent but stable disease following I1-31 therapy. So a more favorable progression-free survival in children compared to adults with persistent DTC.

And also important molecular differences and pathological differences among children who when compared to adults, children have a better response to radioactive iodine. And poorly differentiated tumors are uncommon. So better knowledge of all these factors has led to rethinking of the earlier concepts. So guidelines provide us an opportunity to consider aggressive therapy when warranted and to limit overtreatment of those children who are unlikely to benefit.

So pediatric guidelines, we heard was published for the first time in 2015. Again, the age group referred here is 18 years and under. Guidelines provide recommendations regarding management of thyroid nodules, the role of ultrasound and ultrasound guided FNA. Two major points emphasized are the pre and post-operative staging and the selective use of radioactive iodine.

Let's compare thyroid nodules. In adult guidelines, recommendation is to do FNA if the nodule is greater than 1 centimeter and has suspicious ultrasound features. If the ultrasound does not look that suspicious, to continue to watch until about one and a half centimeter. And if it's not suspicious, may follow up to two centimeters before FNA. In pediatrics, size is a problem for us. As discussed earlier, in a young child, one centimeter might take up a significant portion of the thyroid gland. So in a young child, one centimeter rule does not help us very much.

In the pediatric studies done so far, the size does not correlate with the risk of malignancy. So the current pediatric guidelines recommend FNA for all nodules greater than one centimeter unless they are purely cystic. Or if it's greater than half a centimeter, if a suspicious ultrasound FNA is recommended. So we are a little more anxious about these lesions in kids since the probability of malignancy is higher. Also, small differentiated thyroid cancer and follicular thyroid carcinoma often look benign on ultrasound.

How about the follow up of benign nodules? As for adult guidelines, if it's a highly suspicious ultrasound but a benign FNA, ultrasound can be repeated in a year or so. If it is an intermediate suspicion, repeat ultrasound in a year or two. If it's a very low suspicion, no need to repeat it. And if lesion has been FNAed twice, don't have to follow it.

How does that compare to the pediatric guidelines? We are more cautious with children. High suspicion ultrasound, FNA is recommended regardless of size. Even if the FNA is benign but highly suspicious features, recommendation is to remove the lesion. Low, intermediate suspicion, repeat ultrasound. And if suspicious ultrasound, then recommend removal. We don't have the very low suspicion or low suspicion categories. We're probably going to end up following them for a long time. So this is kind of problematic in terms of cost effectiveness, which indicates more long term studies.

In the current pediatric guidelines, strong recommendation for preoperative staging for thyroid cancer is recommended. This includes ultrasound of the neck including lymph node mapping. This is a very informative study from 2010. You can see that on the left, that multi-focal disease is very common in pediatrics. And 80% to 85% of patients have lymph node involvement. It seems to be true at all ages, including the 18-year-olds.

Another thing to note from the study is the probability of extra thyroidal extension as well as distant metastases that goes up with the number of lymph nodes. If you have less than five nodes, you are not likely to have recurring disease. But by the times 10 to 20 lymph nodes were involved, probability of extension and distant metastases is quite high. Total thyroidectomy reduced recurrence by about 10-fold. So the current recommendation for thyroid cancer in children is still total thyroidectomy.

The same group from Germany recently published the post-op complications from center compartment sections and do not recommend routine center neck dissections due to increased surgical complications. So prophylactic centered neck dissection is for very selective cases with severe extension or significant lateral mets.

Goals of therapy in children is thus. To maintain the low disease specific mortality and to reduce the potential complications from therapy. Recently published paper from Mayo Clinic compares children and adults with differentiated thyroid cancer treated between 1936 to 2015. The panel on the left shows that the tumors in children at presentation are larger, more often with extra thyroid [INAUDIBLE], and more likely to be incompletely resected. Also, children are more likely to have regional and distant metastasis. But despite all these features, the prognostic scores are better and low cost specific mortality.

Also shown in the right panel, the tumor recurrences are also more common in the neck in children compared to adults. So Mayo Clinic data also shows the importance of surgical treatment as the single most important factor in determining long term disease free survival in children. So questions looked at pediatric guidelines included as to who gets radio iodine treatment, along with total thyroidectomy and lymph node dissection and who can do with less.

Using the AJCC TNM classification, patients were classified into low risk, intermediate, and high risk. Low risk is when the disease is confined to thyroid and minimal central neck nodes. Intermediate risk was extensive central neck or minimal extension to lateral. So these are the children who are at an increased risk for incomplete lymph node dissection and persistent cervical disease. Any extensive lateral neck or locally invasive thyroid disease is [INAUDIBLE] high risk group.

Again, this classification into low, intermediate, and high risk is based on records in pediatrics and not mortality. This identifies patients at risk for persistent cervical disease and helps to determine which patients should undergo detailed post-operative staging to screen for the presence of distant metastasis.

As Judy said, low risk patients can be followed with thyroglobulin post-operatively and serial neck ultrasounds. Intermediate risk post-op recommendations is to consider diagnostic radio iodine scan and TSH stimulated thyroglobulin. But for high risk patients, definitely to include the diagnostic scan and stimulated PG levels.

So in the post-operative staging, if the whole body scans shows cervical uptake, then consideration to be given for any possible resectable disease in the neck and consider surgery. If remnant is not amenable to surgery, then radio iodine therapy and surveillance.

We already heard about radioactive iodine therapy in detail. So I would just emphasize three points. Radio iodine therapy in children is limited to selective high risk group with extensive disease. There is no consensus regarding dosing. The goal here is to prevent second malignancies from the treatment. So aim in extensive pediatric disease is now not to achieve no evidence of disease status, but to avoid repeated radiation.

So children with thyroid cancer following the Chernobyl accident were followed with serial radioactive iodine treatments. All of a sudden, the treatments had to be stopped for various reasons. So what we learned from that was that disease progression remained stable even when they did not get additional radio iodine treatment. And also, majority of children with primary mets demonstrated excellent radio iodine uptake. Maximal response from the radio iodine treatment may not be reached up to 15 to 18 months. So it's suggested to wait for at least year after the previous treatment.

In a long term follow up study, we see that in patients with primary mets who recurred, they still tend to recur in the cervical nodes. So it is a surgical disease in the neck that tends to be the recurrence. For the high risk group, after the initial radio iodine therapy, surveillances with thyroglobulin levels on levothyroxine. If TG starts to be detectable, look for the disease with ultrasound. Locate whether the remnant is in the neck or chest. The goal is to identify the surgically removable disease.

We want to look not only for persistent disease but increasing TG levels. If thyroglobulin levels are increasing and if disease is in locations inoperable, then consider repeat radio iodine treatment. Repeat I1-31 therapy in children should be considered only if iodine [INAUDIBLE] disease is suspected and a response to previous therapy was observed.

So is there iodine refractory disease in pediatrics? There are no current definition in the pediatric guidelines. Since the pediatric disease remains stable over several years, it's hard to define radio iodine refractory disease. Like in adults, there might be lesions in children which do not take up iodine equally. So we might not eradicate all disease. So for the disease that progresses despite radioactive iodine, kinase inhibitors are being trialed in a very few cases.

So finally, a few points on follicular thyroid cancer. It's a rare malignancy in children. Pediatric follicular thyroid cancer is less aggressive and spreads by vascular root. Patients with clear evidence of vascular invasion with more than three vessel involvement should receive total thyroidectomy and radio iodine treatment. Since FNA is inconclusive for follicular lesions, current recommendation for any follicular neoplasm is lobectomy. Follow up is similar to PTC but with lesser importance to the neck ultrasounds. And we heard a lot about NIFTP today. There is no long term data on NIFTP in children.

So to conclude, I would like to point out that incidence of pediatric thyroid cancer is increasing. Thyroid nodules in children are more likely to be malignant than thyroid nodules in adults. Early detection and treatment of thyroid cancer is associated with a very favorable outcome. So what is the goal? Limiting morbidity from interventions and selective treatment to the few children who deserve that. Proper management requires a multi-disciplinary approach. I can say for sure that the presence of a multi-disciplinary pediatric center has lead to improved communication, enhanced research in identifying molecular markers, and optimized patient care. And thank you for staying back.