


# Pediatric Thyroid Nodules: Ultrasound Characteristics as Indicators of Malignancy

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OTO Open  
 2022, Vol. 6(1) 1–5  
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 DOI: 10.1177/2473974X211073702  
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## Abstract

**Objective.** Pediatric thyroid nodules are uncommon but carry a 25% malignancy risk. Adult patients have well-established ultrasound characteristics that are predictive of malignancy, but these are not clearly defined in pediatric patients. We reviewed a case series of pediatric thyroid nodules.

**Study Design.** Retrospective chart review.

**Setting.** Tertiary children's hospital.

**Method.** Institutional review board approval was obtained. This case series with chart review includes all pediatric thyroid nodules with ultrasounds from 2006 to 2016 at 2 pediatric tertiary care centers.

**Results.** An overall 112 pediatric thyroid nodules were analyzed. The mean patient age was 14.3 years; there was a female:male ratio of 4:1; and 94% were Caucasian. Seventeen percent (20/112) of nodules were malignant. In patients with malignant nodules, the average presenting age was 15.5 years, with a female:male ratio of 5.6:1. Seventy percent of malignant nodules had accompanying microcalcifications, 55% had abnormal lymph nodes, and 45% had irregular margins. In the benign nodules, 11% had microcalcifications, 12% had abnormal lymph nodes, and 26% had irregular margins. The presence of microcalcifications (odds ratio, 19.1 [95% CI, 6.0–61.0];  $P < .0001$ ), abnormal lymph nodes (odds ratio, 9.0 [95% CI, 3.0–26.6];  $P = .0001$ ), and size  $>3.5$  cm (odds ratio, 5.8 [95% CI, 1.5–22.5];  $P = .01$ ) was associated with thyroid cancer. Irregular margins were not statistically significant (odds ratio, 2.3 [95% CI, 0.86–6.3];  $P = .9$ ).

**Conclusions.** Our data suggest that abnormal lymph nodes, microcalcifications, and size  $>3.5$  cm could be predictors of malignancy in the pediatric population and influence clinical decision making.

## Keywords

pediatric thyroid nodules, ultrasound-guided fine-needle aspiration, thyroid cancer

Received September 14, 2021; accepted December 19, 2021.

Thyroid nodules in children have an incidence of only 0.1% to 5%, as opposed to 68% in adults. However, the rate of pediatric malignancy is 22% to 26%, as compared with 5% to 10% in adults.<sup>1–3</sup> The literature has demonstrated that pediatric thyroid cancer is more advanced upon presentation, holds a greater risk of recurrence, and is more likely to metastasize to the lymph nodes and lungs.<sup>3</sup> In addition to a detailed history and physical examination, diagnostic interventions such as ultrasound-guided fine-needle aspiration biopsy (US FNAB) help delineate benign vs malignant disease and dictate the course of disease management. The American Thyroid Association (ATA) and TI-RADS (Thyroid Imaging, Reporting and Data System) standardized the description of thyroid nodules and stratified the risk of characteristics in adults.<sup>4</sup> The standardization was extended to thyroid nodules in children with a greater emphasis on US characteristics rather than size.<sup>5,6</sup> The predictive value of these characteristics is varied in children, and few studies have identified US characteristics most predictive of malignancy among pediatric thyroid nodules.

Abnormal-appearing lymph nodes, microcalcifications, and irregular margins are the most agreed-on US characteristics predictive of malignancy in children. A rounded lymph node with mass effects, diffusely increased vascularity, or a small/absent hilum is considered abnormal.<sup>3</sup> A microcalcification is seen on US as punctate foci  $<1$  cm with no posterior acoustic shadowing. Nodules with jagged or spiculated edges are defined as irregular, while margins difficult to distinguish from background are ill-defined nodules. Despite high specificity, these characteristics rarely occur, leading to a lower

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This article was presented at the 2021 AAO-HNSF Annual Meeting & OTO Experience; October 3–6, 2021; Los Angeles, California.

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rate of sensitivity.<sup>6,7</sup> Additional, less universally accepted features include larger size, solid parenchyma, and taller-than-wide shape.<sup>8</sup> Indeterminate results on US FNAB have variable treatment options, such as repeat US FNAB or biopsy/lobectomy.

A greater consensus on the predictive ability of US findings to differentiate benign vs malignant on initial US FNAB will minimize repeat or potentially unnecessary US FNAB or surgery. Our study objective is to further identify US characteristics of pediatric thyroid nodules that are most predictive of malignancy.

## Materials and Methods

Approval was obtained from the Akron Children's Hospital institutional review board. All patients who underwent an US FNAB of the thyroid or thyroid nodules between 2006 and 2016 at a tertiary children's hospital were included with *ICD-9* and *ICD-10* code E041 (thyroid nodule; *International Classification of Diseases, Ninth Revision and Tenth Revision*). Patients lacking US records, pathologic information, or operative reports were excluded. Patients with no nodules who underwent FNAB were also excluded. Information regarding patient demographics, clinical information (eg, imaging, cytopathologic, and histopathologic results of US FNAB), and surgical specimens was attained from the electronic medical records. All cases were reviewed by a pathologist and interventional radiologist.

### Nodule Characterization

The location of nodules was determined from the US. Location was described as in the anterior or posterior portion within the lobe, in the mid, superior, or inferior pole. Size dimensions were described as the diameter of the anteroposterior, transverse, and sagittal length. The composition of each nodule was noted as homogeneously solid, homogeneous cystic, or heterogeneous. Echogenicity of the nodule was compared with the surrounding thyroid gland: isoechoic represented a similar echogenicity between nodule and surrounding gland; hyper- and hypoechoic indicated more and less echogenicity between the nodule and thyroid, respectively. If available, calcifications were differentiated as microcalcifications, macrocalcifications, and/or artifact. The margins of each nodule were defined as smooth, irregular, ill-defined or well defined, and lobulated. The presence of calcifications, abnormally round shape, and unusual echotexture in lymph nodes was also considered abnormal.<sup>7,9</sup> Specifically, hyperechogenicity, peripheral vascularity, and cystic lymph nodes with no echogenic hilum were noted as abnormal echotexture.<sup>10</sup> Lymph node location and number of prominent or enlarged lymph nodes were included. Color Doppler US images were used to assess vascularity. We defined each nodule as hypervascular, hypovascular, or avascular and, if available, defined the location of nodule vascularity as central, peripheral, or both. Elastography was rarely found in patient charts. Total thyroid composition, echogenicity, septations, and foci were recorded when abnormal or significant.

Fine-needle aspiration pathology was classified per the Bethesda System for Reporting Thyroid Cytopathology as follows: benign, Hashimoto thyroiditis, atypical or cells of undetermined significance, papillary carcinoma, follicular neoplasm, or nondiagnostic due to insufficient cellular material.

### Statistical Analysis

The results were analyzed per patient. The presence of US characteristics for the prediction of malignancy was assessed by sensitivity, specificity, negative predictive value, positive predictive value, and odds ratio (OR). To determine which demographic and sonographic features were associated with thyroid cancer, Fisher exact and  $\chi^2$  analyses were used for categorical variables. For continuous variables, the Student *t* test and logistic regression analyses were used. The results with *P* values  $\leq .05$  were considered statistically significant. Software programs were used for statistical analyses (www.vassarstats.net; Systat version 9, IBM SPSS Statistics).

## Results

An overall 112 pediatric patients were found to have thyroid nodules, of which 20 were malignant. The mean patient age was 14.3 years (range, 2-18). The female:male ratio was 4:1. Ninety-one patients were female and 105 were Caucasian. Forty-two patients had preexisting thyroid disease (Hashimoto, Graves, congenital hypothyroidism, hypothyroidism) and were taking thyroid replacement therapy (methimazole and levothyroxine sodium). More than half of patients presented with symptoms in an appointment outside of a well child visit. The demographic information is summarized in **Table 1**.

Among patients with malignant nodules, the average presenting age was 15.5 years, with a female:male ratio of 5.6:1. Seventeen patients were female and all were Caucasian. Papillary carcinoma was found in 18 patients and follicular cancer in 2. The presence of microcalcifications increased with malignancy (14 of 20 vs 10 of 92; OR, 19.1 [95% CI, 5.9-61.0]; *P* < .0001). Abnormal lymph nodes also increased with malignancy (11 of 20 vs 11 of 92; OR, 9.0 [95% CI, 3.0-26.6]; *P* = .0001). Irregular margins were not more prevalent in malignant nodules (9 of 20 vs 24 of 92; OR, 2.3 [95% CI, 0.9-6.3]; *P* = .0981).

Size >3.5 cm was nearly 5 times more common in malignant nodules (5 of 20 vs 5 of 92; OR, 5.8 [95% CI, 1.5-22.5]; *P* = .0110). Five patients had nodules >3.5 cm. Two patients had nodules between 2 and 3.5 cm. Clinical characteristics are presented in **Table 1**.

Fifty-five percent of malignant nodules were solitary; 7 patients had multiple nodules; and 2 patients had no nodule at presentation. Five patients with no nodules who underwent FNAB were excluded. Composition, vascularity, echogenicity, and family history were not associated with greater malignancy. Heterogeneous nodules were not associated with a statistically higher risk of malignancy. The test characteristics, ORs, and 95% CIs are shown in **Table 2** and **3**.

In patients with benign nodules, 10 patients had microcalcifications, 11 had abnormal lymph nodes, 24 had irregular margins, and 5 had nodules >3.5 cm. The presence of

**Table 1.** Nodule Characteristics.

	Patients with nodules, No. (%)		
	All	Benign	Malignant
All	112	92/112 (82.14)	20/112 (17.86)
Male	21 (18.75)	18/21 (85.71)	3/21 (14.29)
Female	91 (81.25)	74/91 (81.31)	17/91 (18.68)
Caucasian	105 (93.75)	85/105 (80.95)	20/105 (19.05)
Abnormal lymph nodes	22 (19.64)	11 (11.96)	11 (55)
Microcalcifications	24 (21.42)	10 (10.87)	14 (70)
Irregular margins	33 (29.46)	24 (26.09)	9 (45)
Size, cm			
<2	65 (58.04)	55 (59.78)	10 (50)
2-3.5	27 (24.11)	25 (27.17)	2 (10)
>3.5	10 (8.93)	5 (5.43)	5 (25)
Age ≥ 10 y	105 (93.75)	85 (92.39)	20 (100)
Preexisting thyroid disease	42 (37.50)	35 (38.04)	7 (35)
Thyroid replacement	42 (37.50)	35 <sup>a</sup> (38.04)	7 (35)
Symptoms	64 (57.14)	53 (57.60)	11 (55)

<sup>a</sup>Methimazole, n = 3; levothyroxine sodium (Synthroid), n = 32.

**Table 2.** Odds Ratio for Thyroid Nodule Characteristics.

	Odds ratio (95% CI)	P value
Abnormal lymph nodes	9.00 (3.0474-26.5800)	.0001
Microcalcifications	19.13 (5.9978-61.0360)	<.0001
Irregular margins	2.32 (0.8560-6.2783)	.0981
Size, cm		
<2	0.67 (0.2549-1.7756)	.4234
2-3.5	0.30 (0.0644-1.3771)	.1210
>3.5	5.80 (1.4956-22.4925)	.0110
Composition		
Homogeneously solid	0.27	.2187
Heterogeneously solid and cystic	0.78 (0.2966-2.0689)	.4028
Cystic	1.17 (0.2284-5.9605)	.5656
Vascularity		
Hypervascular	1.24 (0.4724-3.2753)	.4212
Hypovascular	1.47 (0.4699-4.6023)	.3484
Echogenicity		
Hyperechoic	2.03 (0.6288-6.5257)	.1901
Hypoechoic	1.56 (0.5889-4.1092)	.25805
Family history		
Thyroid disease	1.37 (0.4402-4.2663)	.39117
Cancer or nodules	0.90 (0.2704-2.9955)	.5658
No. of nodules		
>1	0.43 (0.1582-1.1845)	.078896
1	1.52 (0.5751-4.0192)	.2735

microcalcifications (OR, 19.1 [95% CI, 5.9-61.0];  $P < .0001$ ), abnormal lymph nodes (OR, 9.0 [95% CI, 3.0-26.6];  $P = .0001$ ), and size >3.5 cm (OR, 5.8 [95% CI, 1.5-22.5];

$P = .0110$ ) was associated with thyroid cancer. Irregular margins did not prove statistically significant (OR, 2.3 [95% CI, 0.9-6.3];  $P = .0981$ ).

**Table 3.** Test Characteristics.<sup>a</sup>

	Specificity	Sensitivity	PPV	NPV
Abnormal lymph nodes	88	55	50	90
Microcalcifications	89.8	70	58.3	93.2
Irregular margins	73.9	45	27.3	86.1
Size, cm				
<2	40.2	50	58	41.9
2-3.5	72.8	10	7.4	78.8
>3.5	94.6	25	50	85.3
Composition				
Homogeneously solid	83.7	5	6.3	80.2
Heterogeneously solid and cystic	48.9	45	16.1	80.4
Cystic	91.3	10	20	82.4
Vascularity				
Hypervascular	55.4	50	19.6	83.6
Hypovascular	81.5	25	22.7	83.3
Echogenicity				
Hyperechoic	85.9	25	27.8	84
Hypoechoic	60.9	50	21.74 <sup>b</sup>	84.9

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

<sup>a</sup>Values are presented as percentages.

<sup>b</sup>Range: 14.33% to 31.56%.

## Discussion

US is widely accepted as the most sensitive imaging modality for nodule detection and routine interval monitoring. US FNAB is the gold standard in identifying malignant nodules according to the ATA. According to the 2015 guidelines proposed by the ATA Guidelines Task Force on Pediatric Thyroid Cancer, pediatric cases should be classified on the extent of disease and stratified into risk levels according to the AJCC TNM system.

Abnormal-appearing lymph nodes, microcalcifications, irregular margins, larger size, solid composition, increased blood flow, and hypoechogenicity are commonly recognized US characteristics most predictive of malignancy in adults.<sup>3,5,6</sup> However, there are varying reports of the predictability in US characteristics in pediatric patients.<sup>11</sup>

In a study evaluating 404 thyroid nodules (314 patients), Richman et al determined the criteria of the American College of Radiology's TI-RADS to be inadequate in assessing the risk of pediatric thyroid nodules, as it would have missed 21% of malignant cases.<sup>4</sup> A size criterion for the pediatric population, in which the thyroid volume changes as children grow, can be problematic.<sup>2</sup> Varying accounts of predictability require a large study to understand and help standardize the most important guidelines for indeterminate nodules after US FNAB.<sup>12</sup>

Our study supports accepted literature on the higher rate of malignant nodules in children (18%) than adults (5%-10%). It also supports literature on the predictive value of microcalcifications, abnormal lymph nodes, and size. However, irregular margins, hypoechoic nodules, and vascularization did not prove to be statistically significant predictors in our study. A nodule with microcalcifications was 19 times more likely to be

malignant than a nodule without microcalcifications. The presence of microcalcifications is the strongest predictor of malignancy and shows a specificity of 90% and a sensitivity of 70%.

Patients with abnormal lymph nodes are 9 times more likely to have malignant nodules. Nodules that were >3.5 cm in diameter were highly specific (95%) but not sensitive (25%) in predicting malignancy. Larger nodules were 5.8 times more likely to be malignant. Irregular borders were not statistically significant.

Ninety-four percent of the children in our study were Caucasian, and all malignant nodules were found in Caucasian children. Females are generally more likely to present with nodules.<sup>13</sup> In our study 6 times as many females were likely to have malignant nodules when compared with their male counterparts. The incidence of thyroid nodules rises after females go through puberty; this is hypothesized to be an effect of estrogen.<sup>14</sup> All our patients with malignant nodules were  $\geq 10$  years old. The predilection for females to develop benign nodules proved significant, with a female:male ratio of 3.8:1. These demographic characteristics are consistent with previous literature.<sup>6</sup>

Most patients who underwent US FNAB proved to have benign nodules (96/116, 82%). The abnormal characteristics found in malignant nodules—irregular margins, abnormal lymph nodes, and microcalcifications—were much less common with prevalences of 26%, 12%, and 11%, respectively. Over 95% of benign nodules were <3.5 cm in diameter.

With improvements in US technology, additional characteristics have been hypothesized and studied in pediatric thyroid nodules and lymph nodes. Ríos et al analyzed 221 pediatric thyroid nodules with US and elastography and reported 100% specificity in determining benign nodules. Elastography has recently risen as a noninvasive imaging

modality to increase the specificity of US.<sup>15</sup> Additionally, oncogene testing may prove useful in ruling out malignancy in nodules with indeterminate cytology. Oncogene testing has become popular and reliable in adult thyroid nodules that are indeterminate and have the potential to dramatically dictate treatment.<sup>16</sup>

### Limitations

Limitations of the study include bias inherent in case series with chart review. The study assessed patient nodules instead of simply total nodules. The overall sample size, as well as that of the malignant nodule group, was small. This diminished the power of the study and resulted in large confidence intervals. There was prominent interobserver variability between the radiologists who read the US as well as the multiple radiologists who performed each FNAB.

A subset of characteristics, such as vascularity, elastography, and echogenicity, was not always documented or was completely missing from US reports. Almost 95% of the participants were Caucasian at a single hospital system, thereby limiting the generalizability of the study to the general population. Although we aimed to look at the pathology of each nodule, the ability to sample all nodules in patients with multiple nodules may have been limited to those with dominant and incidental nodules.

Multiple nodules in a single patient were evaluated together. The most prominent nodule characteristics were taken, which may have skewed more positive findings among the patient population rather than true nodule findings. However, advantages include not associating all accompanying factors to all nodules when one may have been malignant while the others may have been benign.

### Conclusion

Our data suggest that abnormal lymph nodes (as defined by the presence of calcifications, abnormally round shape, hyperechogenicity, and peripheral vascularity), microcalcifications, and size >3.5 cm could be predictors of malignancy in the pediatric population and influence clinical decision making. Future directions include collecting more data on pediatric malignant thyroid nodules, thereby increasing the power of the study.

### Author Contributions

**Brandon Fornwalt**, study design, data collection, manuscript preparation (all portions), revisions; **Manasa Melachuri**, data collection, manuscript preparation (discussion), **Matthew Kubina**, data collection, statistics, manuscript preparation (results); **Janice McDaniel**, study design, manuscript review, ultrasound review; **Anita Jeyakumar**, study design, manuscript review, revisions, submission.


### Disclosures

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.

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