Predictors of Malignancy in Children with Thyroid Nodules

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Objective To evaluate the diagnostic accuracy of clinical, laboratory, and ultrasound (US) imaging characteristics of thyroid nodules in assessing the likelihood of malignancy.

Study design Data from 184 children and adolescents with thyroid nodules were evaluated and compared with respective cytologic/histologic outcomes. A regression model was designed to assess the predictors associated with malignancy and to calculate ORs.

Results Twenty-nine malignant neoplasms (25 papillary, 1 medullary, 3 Hurtle-cell carcinomas), 8 follicular adenomas, and 147 goitrous nodules (92 based on cytology, 55 on follow-up) were diagnosed. Fine-needle aspiration biopsy diagnostic accuracy, sensitivity, and specificity were 91%, 100%, and 88%, respectively. Male sex, compression symptoms, palpable lymphopathy, thyroid stimulating hormone concentration, microcalcifications, indistinct margins, hypoechoic US pattern, pathologic lymph node alterations, and increased intranodular vascularization were associated with malignancy. Regular margins, mixed echoic pattern, and peripheral-only vascularization were associated with benignity. During follow-up, nodule growth was associated with malignant disease, especially with levothyroxine therapy. A multivariate analysis confirmed that microcalcifications, hypoechoic pattern, intranodular vascularization, lymph node alterations, and thyroid stimulating hormone concentration were independent predictors of malignant outcome. For each predictor, we provide sensitivity, specificity, and positive/negative predictive values.

Conclusions Clinical, laboratory, and US features of nodules can be used as predictors of malignancy in children. Although none has diagnostic accuracy as high as that of fine-needle aspiration biopsy, these predictors should be considered in deciding the diagnostic approach of children with thyroid nodules. *(J Pediatr 2015; ■: ■-■).*

See editorial, p •••

Both thyroid nodules and cancer are less common in children than adults. Nodule prevalence is estimated to be 0.2%-5% in children[1-3] vs 19%-35% in adults.[3,4] However, pediatric thyroid nodules have a higher likelihood of malignancy compared with those in adults,[5-7] with cancer diagnosed in approximately 10% of thyroid nodules in adults and up to 25% of those in children.[8-10] Besides its epidemiology, childhood thyroid cancer has other relevant peculiarities: it is almost always well-differentiated, shows frequent and precocious lymph node metastases, and harbors specific molecular anomalies.[7,10] These differences raise the issue as to whether pediatric thyroid cancer should be considered a distinct clinical entity with specific diagnostic and therapeutic recommendations.[5,7,9,10]

In both adults and children with thyroid nodules, the diagnostic approach aims at estimating cancer risk. Initial diagnostic assessment is based on clinical, laboratory, and ultrasound (US) evaluation, followed by fine-needle aspiration biopsy (FNAB) cytology, if indicated. Several studies have documented high sensitivity and specificity of FNAB in pediatric thyroid nodules (94% and 81%, respectively),[11] and there is general agreement on its crucial role in selecting nodules for surgery.[2,12-17] However, the decision whether or not to submit a patient with a thyroid nodule to FNAB is based on an estimate of malignancy likelihood that takes into consideration a number of characteristics suggestive of benignity or malignancy. Most of these features are inferred from observational studies in adults.[18-20] The American Thyroid Association guidelines provide[21,22] a list of indications to perform a FNAB in nodules in adults and states that the diagnostic approach to childhood nodules should be the same as in adults. However, data concerning the predictors of malignancy specific for the pediatric setting are limited by the rarity of thyroid nodules in this population, the small cohorts described so far, or the retrospective design of the majority of studies.

In this study, we performed an analysis of a large cohort of children and adolescents with thyroid nodules diagnosed at our institution to determine the diagnostic value of these factors in predicting the likelihood of pediatric nodules malignancy.

FNAB	Fine-needle aspiration biopsy
LT4	Levothyroxine
TSH	Thyroid stimulating hormone
US	Ultrasound

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Methods

A retrospective analysis was conducted on 241 consecutive pediatric patients with thyroid nodules ≥5 mm maximum diameter at the Division of Pediatric Endocrinology of the Department of Public Health and Pediatric Sciences of the University of Torino, Italy between 1999 and 2011. The patients were referred for evaluation of thyroid nodule and/or goiter (n = 83, 53 palpable nodules and 30 goiters), for autoimmune thyroiditis (n = 68, 14 palpable nodules and 54 nodules incidentally detected at US) or because the endocrine evaluation was part of follow-up for a previous oncologic disease (n = 33, 6 palpable nodules and 27 detected at US screening). Overall, 57 patients were excluded because of incomplete data (n = 21) or because they were lost to follow-up (n = 29). Excluded patients did not differ from those analyzed in the study in clinical, laboratory, and sonographic features. Patients with hyperthyroidism were excluded (n = 7) because different diagnostic procedures are usually employed in hyperthyroidism.[13] The remaining 184 patients underwent a clinical examination, laboratory tests, and thyroid US at nodule diagnosis and every 6 months during the follow-up period (12 months in case of benign cytology). Laboratory tests included serum thyroid stimulating hormone (TSH), fT4, calcitonin, and antithyroperoxydase and antithyroglobulin antibody measurement. All clinical examinations were performed in a similar manner by the same pediatric endocrinologist, whereas US imaging and FNAB data were gathered by 2 endocrinologists with extensive experience. All cytologic samples were processed in the same center. FNAB was performed in almost all nodules with a diameter ≥1 cm, with the exception of a few cases (n = 20). Of the latter, 11 had reassuring nodule characteristics, and 9 decided to defer FNAB: all were submitted to a clinical evaluation and US twice yearly. FNABs performed in mixed cystic–solid nodules were evaluated by biopsy of the solid component. All cases with FNAB indicative of suspicious/malignant or indeterminate cytology were submitted to surgery (N.P.).

Clinical, laboratory, and US data were compared with the final outcome based on histopathology (for patients submitted to surgery), cytology (for those submitted to FNAB only), or follow-up (for those submitted to neither surgery nor FNAB).

Several clinical, laboratory, and US factors were examined based on previously reported risk factors for malignancy.[1,2,15,21] Sex, family history of thyroid nodule and cancer, age at nodule diagnosis, pubertal status, compressive symptoms (local discomfort or pain, voice changes, cough, breathing, or swallowing difficulties), history of head/neck irradiation, and nodule or lymph node palpability were recorded. Laboratory assays included TSH, fT4, thyroid antibodies, and calcitonin. US data collected were focality (solitary vs multiple), nodule maximum diameter, echoic pattern (anechoic, hypoechoic, mixed, isoechoic, hyperechoic), presence of micro/macrocalcifications, margins (regular/translucent halo vs irregular/infiltrative borders), vascularization pattern by color Doppler (poor, increased flow with intranodal or peripheral pattern), sonographic lymph node alterations (bulging shape, irregular margins, increased size, absence of echogenic hilum, mixed/cystic pattern, calcifications, or peripheral or disorganized intranodal vascular flow at Doppler) at the satellite lymph node/sites most commonly involved in thyroid carcinoma (prelaryngeal, pretracheal, and the right and left paratracheal nodes).[23-25] Cytology results were categorized as: (1) benign; (2) indeterminate; or (3) suspicious for malignancy/malignant.[21] The category indeterminate encompassed all follicular-patterned lesions: adenomatoid hyperplasia, adenoma, microinvasive follicular carcinoma, oxyphilic cell lesions, and some cases of follicular variants of papillary thyroid carcinoma, according to the more recent classification criteria.[26] In all cases with insufficient or nondiagnostic results (n = 8), FNAB was repeated. Therefore, all patients had an unambiguous cytological diagnosis.

Patients not submitted to surgery were followed-up clinically and sonographically for 2.6 ± 1.9 years. Nodule diameter modifications during follow-up were registered and classified as increased/unmodified/decreased based on ≥20% change of the largest diameter. After the largest diameter was <5 mm, it was classified as having disappeared. Patients were categorized by treatment status with levothyroxine (LT4).

Statistical Analyses

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess ~~variables distribution of the variables~~. The Student *t* test or Wilcoxon-Mann-Whitney tests were used to check differences between groups. Pearson correlation coefficients were applied to check associations. The χ^2/Fisher exact tests were employed to assess variables distribution. A stepwise binary logistic regression analysis was used to evaluate the influence of factors on the final outcome (benign vs malignant), including all variables with significant differences evidenced at the first step analysis. SPSS software v 15.0 (IBM, Chicago, Illinois) was used.

Results

The **Figure** (available at www.jpeds.com) synthesizes the diagnostic procedures and outcomes of the 184 patients included; FNAB was performed in 111 patients shortly after the diagnosis. The initial approach was based on clinical and US follow-up in 73 cases with nodules having features suggestive of benignity. Of those, 18 were subsequently submitted to FNAB (5.9 ± 2.9 months later) because nodule features changed during follow-up; in 10 cases, the nodules were <1 cm diameter but grew rapidly, and in 6 cases the nodules developed some sign of malignancy during observation. Two patients opted for a wait-and-see approach. The remaining 55 patients were followed up clinically and sonographically for 2.7 ± 1.8 years (range

1.1-11.0 years, median 2.9 years) displaying no features suggestive of malignancy. Two subcentimetric nodules ultimately were diagnosed with papillary carcinoma: one underwent FNAB at diagnosis because of malignancy features (hypoechogenicity, history of irradiation, irregular margins), and one after 6 months follow-up as size increased >1 cm. Overall, FNAB revealed 25 lesions that were malignant or suspicious for malignancy and 88 with benign cytology; 16 were indeterminate. Among the 129 patients who underwent FNAB, thyroidectomy was performed in 54. No patient had surgery without previous evaluation by FNAB. Overall, we diagnosed 29 malignant neoplasms (group A): 25 papillary cancers (7 with follicular variant, 1 diffuse sclerosing), 1 medullary cancer, and 3 Hurtle-cell neoplasms (2 adenomas, 1 carcinoma). Twenty-five patients submitted to surgery had benign nodules: 8 had a follicular adenoma (group B) and 17 a goitrous nodule. As 2 papillary carcinomas were diagnosed in 48 nodules with maximum diameter <1 cm, and the remaining cases (n = 28) in those with nodules ≥1 cm (n = 136), the malignancy rates were 4.2% and 20.6%, respectively. Overall, 147 patients were diagnosed with goitrous nodules (group C). Of these 147 patients, 17 cases submitted to surgery, 75 based on cytology only (referred to as patients' group C1), and 55 based on clinical and US follow-up (group C2). All cases with a malignant or benign cytology were confirmed histologically and diagnosed with thyroid cancer and goitrous nodules, respectively. The diagnostic accuracy ~~for suspicious/malignant or indeterminate/benign cytology vs malignant/benign histology and~~ 90.7%, with 100% sensitivity and 88% specificity, respectively. Discordance between cytology and histology was observed only among the 16 cases with indeterminate cytology: histology revealed 8 follicular adenomas, 4 goitrous nodules, 3 Hürtle-cell neoplasms, and 1 papillary carcinoma.

Nodule Features at Diagnosis

Table I compares the clinical and US features of malignant and benign nodules in the groups. Malignant nodules were significantly more frequent in males, more commonly had compression symptoms, were more likely palpable and [T1]

Table I. Comparison of the features of malignant and benign nodules at diagnosis

	Malignant nodules		Follicular adenoma		Goitrous nodules (group C)			
					Based on cytology		Based on follow-up	
	Group A		Group B		Group C1		Group C2	
	n	%	n	%	n	%	n	%
Patients	29		8		92		55	
Clinical and laboratory features								
Males	15	51.7%^{C}	6	75.0%^{C}	19	20.7%^{A,B}	14	25.5%^{A,B}
Family history of nodule	4	13.8%	2	25.0%	19	20.7%	11	20.0%
Family history of thyroid cancer	2	6.9%	0	0.0%	5	5.4%	1	1.8%
Radiotherapy	7	24.1%	3	37.5%	12	13.0%	5	9.1%
Pubertal	25	86.2%	5	62.5%	63	68.5%	44	80.0%
Goiter	12	41.4%	3	37.5%	35	38.0%	22	40.0%
Palpable nodule	19	65.5%^{C}	5	62.5%	48	52.2%^{A,C2}	1	1.8%^{A,C1}
Palpable lymph nodes	20	69.0%^{C}	5	62.5%	33	35.9%^{A,C2}	10	18.2%^{A,C1}
Compression symptoms	8	27.6%^{C2}	1	12.5%	13	14.1%^{C2}	1	1.8%^{A,C1}
Positive thyroid antibodies	9	31.0%^{C2}	0	0.0%	18	19.6%^{C2}	41	74.5%^{A,C1}
Age at diagnosis (y)	13.0 ± 3.0		12.5 ± 3.9		12.5 ± 3.5		13.3 ± 2.76	
Age at FNAB (y)	13.4 ± 3.2		12.5 ± 3.9		12.8 ± 3.6		-	
Follow-up duration (y)	0.9 ± 1.1^{C2}		-		2.4 ± 1.7^{C2}		3.1 ± 2.0^{A,C1}	
TSH (mU/L)	2.86 ± 1.48^{C}		2.00 ± 1.22		1.89 ± 1.30^{A}		2.20 ± 0.91^{A}	
Nodule diameter (cm)	1.71 ± 0.80^{C2}		2.28 ± 0.95^{C}		1.76 ± 0.84^{B,C2}		0.85 ± 0.37^{A,B,C1}	
Subcentimetric nodules	2 (6.9%)^{C}		0 (0%)		11 (12.0%)		35 (63.6%)	
US								
Uninodularity	20	69.0%	5	62.5%	59	64.1%	31	56.4%
Microcalcifications	13	44.8%^{B,C}	0	0.0%^{A}	3	3.3%^{A}	1	1.8%^{A}
Macrocalcifications	1	3.4%	0	0.0%	4	4.3%	1	1.8%
Indistinct margins	14	48.3%^{C}	1	12.5%	23	25.0%^{A}	12	21.8%^{A}
Regular margins	4	13.8%^{B,C}	7	87.5%^{A,C}	35	38.0%^{A,B}	16	29.1%^{A,B}
Isoechoic pattern	1	3.4%^{B}	3	37.5%^{A}	10	10.9%	10	18.2%
Hypoechoic pattern	22	75.9%^{C}	5	62.5%	41	44.6%^{A}	24	43.6%^{A}
Mixed echoic pattern	5	17.2%^{C}	0	0.0%^{C}	37	40.2%^{A,B}	17	30.9%^{A,B}
Hyperechoic pattern	1	3.4%	0	0.0%	4	4.3%	4	7.3%
Lymph node alterations	14	48.3%^{C}	0	0.0%	3	3.3%^{A}	3	5.5%^{A}
Vascular flow at Doppler								
Not performed	4	13.8%^{C}	2	25.0%	34	37.0%^{A}	25	45.5%^{A}
Peripheral increased flow only	3	10.3%^{C}	1	12.5%	35	38.0%^{A}	14	25.5%^{A}
Central ± peripheral increased flow	20	69.0%^{C}	4	50.0%^{C}	9	9.8%^{A,B}	3	5.5%^{A,B}
Poor vascularization	2	6.9%^{C}	1	12.5%	14	15.2%^{A}	13	23.6%^{A}

Nodules have been classified as malignant (group A), follicular adenoma (group B), and goitrous (group C) based on cytology (group C1) or follow-up only (group C2). Significant differences between groups have been marked in superscript.

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with lymphopathy, and were associated with higher TSH concentrations. On US, they had more commonly microcalcifications, indistinct margins, a hypoechoic pattern, and relevant pathologic alterations of the satellite lymph nodes. Increased vascular flow with intranodular pattern on color Doppler US was significantly associated with malignancy. On the other hand, benign nodules were significantly associated with regular margins, mixed echoic pattern, and a peripheral-only blood flow pattern. Cases with follicular adenoma were more commonly associated with predominance of male sex, larger diameter, and increased flow with intranodular pattern than goitrous nodules. As opposed to malignant nodules, follicular adenoma cases had no microcalcifications, almost always regular margins, and more commonly isoechoic US pattern.

The features of the 7 cases of follicular variant papillary thyroid carcinoma were not substantially different than the classic papillary cancer cases. The subgroup of patients with exposure to ionizing radiations had almost double the likelihood of malignancy (25.9% vs 13.8%) and smaller nodule diameters (1.2 vs 1.9 cm). Males were overrepresented among exposed patients (66.7% vs 26.7%, $P < .001$) and all cancer patients were males (vs 36.3% in the nonirradiated groups, $P = .006$).

Follow-Up and Medical Treatment of Cases Not Immediately Submitted to Surgery

Table II reports the follow-up of the patients with nodules not immediately submitted to surgery. Overall, 146 cases had follow-up data available on a 6- to 12-month basis with clinical, laboratory, and US evaluation. Of these, 68 were treated with LT4, because of goiter with a TSH in the upper one-half of the reference range (n = 20), hypothyroidism with autoimmune thyroiditis (n = 32), or to induce nodule shrinkage (n = 16). Overall, LT4 was administered for 3.7 ± 3.4 years. During the follow-up, all cases with malignant nodules had an increase in nodule size, independently of LT4 administration, significantly higher than in the group of patients with benign nodules.

Individuation of the Predictors of Malignancy and Their Diagnostic Accuracy

Two binary linear regression models were designed to analyze those factors disclosing significant difference between benign and malignant nodules. The first model included all the 176 patients (group A vs group C), whereas the second model included only the 121 cases with available cytology (group A vs group C1). Both models provided consistent results detecting as independent predictors of malignancy the presence of microcalcifications, hypoechoic US pattern, increased intranodular vascular flow, and US lymph node alterations, with a significant association with TSH concentration at nodule diagnosis. The ORs of malignancy of each of the predictors are given in Table III. Table IV (available at www.jpeds.com) shows the sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the features found in benign vs malignant nodules in the whole cohort (group A vs group C).

Discussion

In order to assess their ability to predict thyroid nodule malignancy in childhood, we compared the panel of clinical, laboratory, and US features of pediatric nonhyperfunctioning thyroid nodules and their respective outcomes.

Among the predictors studied, we identified several differences in nodule characteristics at presentation. The

Table II. Nodule changes during follow-up and under LT4: nodules were classified as malignant (group A) and goitrous (C) based on cytology (C1) or follow-up only (C2)

	Malignant nodule		Goitrous nodules (group C)			
			Based on cytology		Based on follow-up	
	Group A		Group C1		Group C2	
	n	%	n	%	n	%
Patients	29	-	92	-	55	-
Surgery at nodule diagnosis	20	-	1	-	0	-
Lost at follow-up	0	-	9	-	0	-
Followed up	9	36.0%^{C}	82	89.1%^{A,C2}	55	100%^{A,C1}
Patients with no LT4 treatment	5	55.6%	48	58.5%	25	45.5%
Nodule largest diameter variation						
Increased	5	100.0%^{C}	10	20.8%^{A}	4	16.0%^{A}
Unmodified	0	0.0%^{C}	27	56.3%^{A,C2}	7	28.0%^{A,C1}
Decreased	0	0.0%^{C}	11	22.9%^{A}	7	28.0%^{A}
Disappeared (less than 5 mm)	0	0.0%	0	0.0%	7	28.0%^{C1}
Patients under LT4 treatment	4	44.4%^{C}	34	37.0%^{A,C2}	30	54.5%^{A,C1}
Nodule largest diameter variation						
Increased	4	100.0%^{C}	8	23.5%^{A,C2}	1	3.3%^{A,C1}
Unmodified	0	0.0%	11	32.4%	10	33.3%
Decreased	0	0.0%	13	38.2%	6	20.0%
Disappeared (less than 5 mm)	0	0.0%	2	5.9%^{C2}	13	43.3%^{C1}

Significant differences between groups have been marked in superscript.

Table III. Independent predictors of malignancy at binary logistic regression analysis

	All patients included, N = 176		Only cases with FNAB, N = 121	
	OR (95% CI)	P	OR (95% CI)	P
Microcalcifications	9.7 (1.2-79.6)	.034	8.9 (1.1-75.1)	.045
Hypoechoic pattern	7.3 (1.5-36.8)	.016	6.4 (1.2-33.8)	.029
Increased intranodular vascular flow	18.8 (4.5-79.5)	<.001	20.8 (4.4-97.7)	<.001
Lymph node alterations at US	6.9 (1.2-41.7)	.32	11.2 (1.3-65.9)	.028
TSH at nodule diagnosis	1.6 (1.1-2.5)	.49	1.8 (1.1-3.1)	.019

All significantly different variables in Table I have been included in the regression model.

male-to-female ratio was 1:1 in patients with malignancies vs 1:4 among those with benign nodules. Malignant nodules were more commonly associated with microcalcifications and palpable lymph node enlargement, and more frequently had indistinct margins, hypoechoic US pattern, increased intranodular vascular flow, and pathologic alterations of satellite lymph nodes. Conversely, benign nodules more commonly showed regular margins, mixed echoic pattern, and peripheral-only blood flow pattern on US. TSH concentration was higher in patients with malignant nodules than in patients with benign ones, as previously observed.[27,28] Most of these differences have been already seen in studies on adults[18-21] and many were inconsistently observed in smaller pediatric cohorts.[12,14,15,18,29,30] To remove confounders and assess the relative weight of each predictor, we designed a regression model that confirmed that microcalcifications, hypoechoic pattern, increased intranodular vascular flow, lymph nodal sonographic alterations, and serum TSH concentration were independent predictors of malignancy. Increased intranodular vascular flow and microcalcifications were the strongest predictors of malignancy among factors studied.

The sensitivity and specificity of FNAB were in substantial agreement with that reported in literature,[11,31-34] with most false positive results falling within the category of "follicular lesion of indeterminate significance."[21] As no single characteristic has a diagnostic accuracy comparable with that of FNAB,[21] we calculated sensitivity, specificity, and predictive value of each one. Poor diagnostic accuracy and predictive value were encountered for sex, the presence of indistinct margins, mixed echoic pattern, and peripheral-only increased vascular flow. Palpable lymph nodes and TSH in the upper normal range had high sensitivity but poor specificity and predictive value, so are of modest usefulness in clinical practice. The hypoechoic US pattern and increased intranodular vascular flow had high negative predictive value and the highest sensitivity. Increased intranodular vascular flow also had high specificity. Microcalcifications and US lymph nodal alterations had the highest specificity and positive predictive value and, therefore, should be considered absolute indications to perform a FNAB.[18,30] Interestingly, the combination of color Doppler data to assess vascular flow and lymph node alterations offers a similar diagnostic accuracy to that of FNAB. Of note, sensitivity and specificity of color Doppler imaging in detecting increased intranodal vascular flow are consistent with those reported by Lyshchik et al.[35]

Responses to LT4 provided further prognostic ability; malignant nodules almost invariably grew during the observation period, even with LT4 therapy. On the other hand, benign nodules remained unmodified or decreased in size in more than 75% of cases. This has relevance in considering the role of TSH in promoting nodule growth and in the natural history and treatment of hyperthyrotropinemia in childhood thyroid cancer,[8,23,36-39] factors deserving further investigations. It should be emphasized that there are no current indications for medical therapy in thyroid nodule treatment, and our study is not designed to provide them. In fact, treatment was administered only to a small fraction of cases that had no indication of immediate FNAB or surgery. Specific studies on this matter are needed before we can draw any firm conclusions. Finally, TSH levels overlap in benign and malignant groups and nodule modifications under LT4 treatment, and although this reaches statistical significance, it may be of limited clinical relevance and insufficient to advise LT4 treatment.

Data concerning the coexistence of autoimmunity in nodular disease are relevant given its relationship with cancer, a matter of controversy in the literature.[40,41] In our cohort, we did not detect any role for positive thyroid antibodies; the proportion of differentiated thyroid cancer observed in the negative antibody group and in the autoimmune thyroiditis group overlapped (11% and 12%, respectively), consistent with previous reports on autoimmune thyroiditis in childhood.[14]

Although most of the literature reports a predominance of the female sex among cancer patients (1.5:1),[2] in our report, males represent approximately one-half of this group. This may be due to the inclusion of a consistent number of cases with thyroid nodules following radiotherapy. In fact, survivors of childhood cancer with thyroid nodules ~~– which are predominantly males~~[42] ~~– are~~ 27 in our cohort, ~~and, among them, the~~ 7 cancer cases were males.

Several limitations of this study should be discussed including sample size and the relatively small number of cancer cases studied. Although the sample size does not limit the statistical significance of our results, the wide CIs may hamper the clinical relevance of the findings. Second, most of the malignancies studied were classic papillary thyroid cancer; therefore, our results are mostly applicable to this group. Although the other rarer histologic variants did not show relevant differences, cases were too few to draw conclusions, and these variants may present with different clinical and US features. Third, this study was retrospective and not multicentric but represents the clinical experience of a single institution with uniform diagnostic behavior over many years. The historical nature of the cohort prevented us from providing data concerning the more recent classifications in thyroid cytology and US techniques

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(as elastography). The subclassification of indeterminate lesions into "follicular lesion of undetermined significance" and "follicular neoplasm"[26] was only recently embraced by the Royal College of Pathology, so the classification of follicular cytologic specimens has only been a standard at our institution since 2009. Elastography too has been employed in our center since 2009, but our data in the pediatric field are scanty to provide results. For the same reason, we could not provide pediatric data concerning the molecular/cytologic markers of malignancy,[43,44] that only recently become part of clinical practice. A further limitation is represented by the cases in which the nodule benignity was not confirmed histologically but based on follow-up. We expect that considering cases with reassuring features at subsequent clinical and US follow-up as benign is a reasonable approximation and will unlikely impact our conclusions. Furthermore, a selection bias is likely present in the definition of the 2 benign groups (ie, those submitted to FNAB and those followed-up only; the latter group has obviously smaller nodules, harboring a lower likelihood of malignancy). Nevertheless, a separate statistical analysis including only patients with available histology yielded consistent results. Actually, although routine FNAB is not recommended for subcentimetric nodules in adults,[11,21] we included them in our study to provide complete data on a consecutive cohort and because our study also took into consideration nodule modifications during the follow-up period. Indeed, the diagnostic approach in children with nodules between 5 mm and 1 cm is under debate.[8,11,21] Although the 1 cm cut-off is generally used to submit patients to FNAB in adults, size has never been a strict criteria for the evaluation of pediatric nodules as it should be related to the volume of the thyroid gland, which is obviously smaller in children. Finally, the results gathered by this cohort may be unpredictably influenced by factors affecting iodine sufficiency including area of origin and prophylaxis. It is well known that iodine deficiency may be responsible for an increased prevalence of thyroid nodules. Italy is a country with mild to moderate iodine deficiency,[45] with considerable differences among regions. In spite of a mild iodine deficiency in Piedmont[46] (the region where most of our patients live), goiter prevalence decrease has been recently reported (3.1% of children).[47] Moreover, goiter nodules in iodine-deficient areas are unusual among children and young adults (prevalence, 0.5%-2.1%).[3] Therefore, although an assessment of iodine status in our study group was not performed, we believe that iodine deficiency may have had only a marginal effect on our results.

In conclusion, the clinical, laboratory, and US features studied in this report can serve as predictors of malignancy in children. Although none of these predictors has diagnostic accuracy and predictive value as high as that of FNAB, data provided by color Doppler US almost reached its diagnostic accuracy. Several variables are consistently associated with thyroid cancer: male sex, lymph node enlargement, microcalcifications, indistinct margins, hypoechoic pattern, increased intranodular vascular flow and pathologic alterations of satellite lymph nodes, and serum TSH in the upper normal range. The combination of various data and nodule characteristics should be considered in order to address the diagnostic approach of children with thyroid nodules and to decide whether and when to submit them to FNAB. The latter should be performed immediately if microcalcifications, increased intranodular vascular flow, or sonographic lymph node alterations are present because these are features that are highly specific for malignancy. In the absence of these characteristics, nodules with a mixed/nonhypoechoic pattern, regular margins, serum TSH <1.6 mU/L, peripheral-only increased vascular flow, and absence of palpable lymph nodes should be considered for follow-up. During follow-up, nodule features should be reassessed at each visit, taking into account that nodule modifications, especially with LT4 treatment, are further predictive factors. If the diagnosis remains doubtful, FNAB has a high diagnostic accuracy. The implementation of recent cytologic classification and the latest molecular/cytologic markers of malignancy and elastography will likely result in further improvements in patient selection and treatment option. ■

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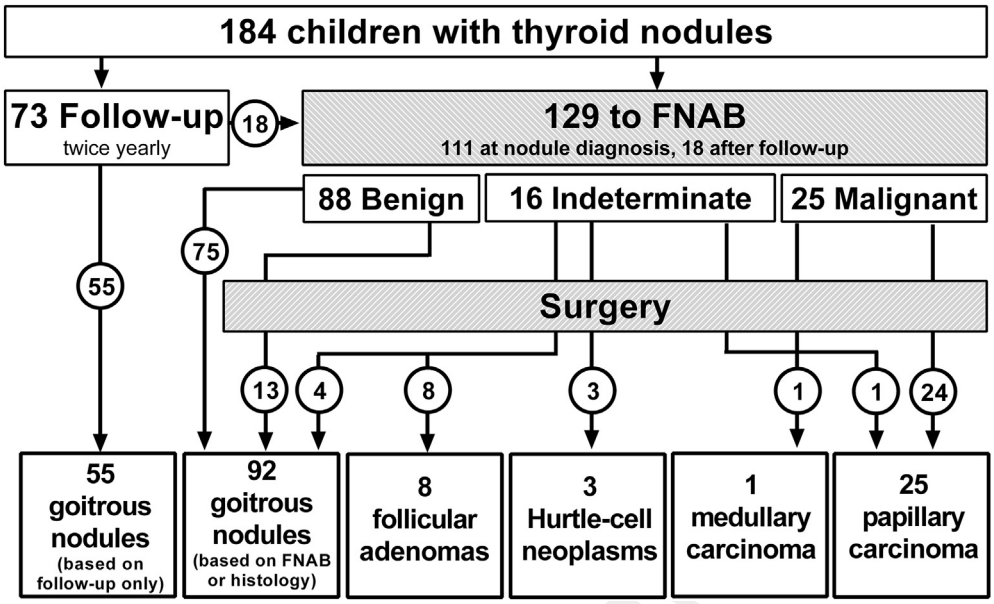

Figure. Diagnostic pathway of the 184 patients included in the study with respective outcomes.

Table IV. Sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the various predictors of malignancy and benignity

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Malignancy predictors					
Male sex	51.7%	77.6%	31.3%	89.1%	73.3%
Palpable lymph nodes	69.0%	70.7%	31.7%	**92.0%**	70.5%
Microcalcifications	44.8%	**97.3%**	**76.5%**	89.9%	**88.6%**
Indistinct margins	48.3%	76.2%	28.6%	88.2%	71.6%
Hypoechoic	**75.9%**	55.8%	25.3%	**92.1%**	59.1%
Central ± peripheral pattern	**80.0%**	**86.4%**	62.5%	**93.8%**	**85.0%**
Lymph node alterations at US	48.3%	**95.9%**	**70.0%**	**90.4%**	**88.1%**
TSH at nodule diagnosis >1.6 mU/L*	**87.0%**	50.5	28.2%	**94.5%**	57.1%
Benignity predictors					
Mixed	17.2%	63.0%	8.5%	79.3%	55.4%
Peripheral pattern only	12.0%	44.3%	5.8%	63.9%	37.2%
Regular margins	13.8%	65.3%	7.3%	79.3%	56.8%

*1.6 mU/L was chosen based on: (1) the median of serum TSH concentration of the benign nodule population; and (2) previous reports.[28]

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