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;167:886-92)*.

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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. Institutional IRB approval is warranted for retrospective studies consisting in review of cases. 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), free T4, 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, free T4, 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), and 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 data normality. 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 differences in 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