Hormone Research in Paediatrics

Research Article

Horm Res Paediatr
DOI: 10.1159/000541134

Received: May 31, 2024
Accepted: August 19, 2024
Published online: August 26, 2024

Two Decades of Thyroid Nodule Cytology in Children: Malignancy Risk Assessment at a Tertiary Care Center

Consuelo Pino[a] José Miguel Dominguez[b] Antonieta Solar[c] Pablo Zoroquiain[c] Francisco Cruz[d] Cristian García[d] Florencia De Barbieri[d] Lorena Mosso[b] Nicole Lustig[b] Hernán Gonzalez[e] Augusto León[e] Ignacio Goñi[e] Andy Contreras[a] Francisca Grob[a]

[a]Division of Pediatrics, School of Medicine, Pontificia Universidad Católica, Santiago, Chile; [b]Department of Endocrinology, School of Medicine, Pontificia Universidad Católica, Santiago, Chile; [c]Department of Pathology, School of Medicine, Pontificia Universidad Católica, Santiago, Chile; [d]Department of Radiology, School of Medicine, Pontificia Universidad Católica, Santiago, Chile; [e]Department of Oncological Surgery, School of Medicine, Pontificia Universidad Católica, Santiago, Chile

Keywords
Thyroid nodule · Pediatric thyroid cancer · Fine-needle aspiration · Risk assessment · Epidemiological monitoring

Abstract

Introduction: Pediatric thyroid nodules exhibit higher malignancy rates compared to adults and are associated with increased incidences of metastases and recurrences. The American Thyroid Association recommends surgery for indeterminate thyroid biopsies in children based on these higher malignancy risks, though this approach may lead to overtreatment. However, there remains a lack of comprehensive pediatric data to inform clinical decisions. This study examines the risk of malignancy (ROM) in pediatric thyroid nodules using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) and assesses the diagnostic accuracy of fine-needle aspiration (FNA) biopsy compared to histological outcomes. ***Methods:*** A retrospective cross-sectional analysis was performed on patients under 19 years with thyroid nodules who underwent FNA and thyroidectomy at a tertiary care center. The sensitivity, specificity, positive predictive value, negative predictive value, and ROM of cytological biopsies were evaluated using TBSRTC criteria, with histology serving as the gold standard. Two analyses were conducted to assess diagnostic accuracy: (a) TBSRTC II as negative and TBSRTC VI as positive and (b) TBSRTC II as negative with TBSRTC V and VI as positive. For neoplasia detection, TBSRTC II was deemed negative, while TBSRTC IV, V, and VI were considered positive. TBSRTC categories III and I were excluded from the performance analysis and evaluated separately. Follicular neoplasm or lesions suspicious for follicular neoplasm (FN/SFN) were treated as positive outcomes, correlated with the presence of adenoma or carcinoma in the surgical specimen. ***Results:*** Of 75 nodules from 73 patients, 28 (37.3%) were benign and 47 (62.6%) malignant. No significant differences in gender or age were noted between groups. The ROM in each TBSRTC was Bethesda I 0/2, 0%; II 0/13, 0%; III 2/7, 29%: IV 6/14, 43%; V 10/10, 100%, and VI 29/29, 100%. A sensitivity of 78.38%

karger@karger.com
www.karger.com/hrp

Correspondence to:
Francisca Grob, francisca.grob@uc.cl

and specificity of 100% for FNA in detecting malignancy was found, with an even higher sensitivity (100%) for detecting neoplasia in TBSRTC IV. ***Conclusions:*** This study reveals that indeterminate thyroid nodules in pediatric patients exhibit a higher rate of malignancy compared to adults, yet align with rates previously reported in the pediatric population. These findings highlight the critical need for guidelines tailored specifically to the management of thyroid nodules and thyroid cancer in children.

Plain Language Summary

Pediatric thyroid nodules are less common than those in adults, but they have a higher risk of being cancerous. This study reviews data from the past 20 years at a major healthcare center to understand how often these nodules are malignant in children and how accurate fine-needle aspiration (FNA) biopsies are in diagnosing them. The study analyzed 75 thyroid nodules from 73 children, finding that 62.6% of the nodules were malignant. The FNA biopsy, a key diagnostic tool, was shown to be very accurate, with a sensitivity of 78.38% and a perfect specificity of 100%. This means that FNA is highly reliable for identifying both cancerous and noncancerous nodules in children. One significant finding is that the risk of cancer in thyroid nodules categorized as indeterminate (uncertain) by the Bethesda System is much higher in children than in adults. This suggests that pediatric thyroid nodules behave more aggressively, underscoring the need for careful evaluation and tailored guidelines for children. These results are crucial for medical professionals as they highlight the importance of specialized approaches in managing thyroid nodules in children, ensuring accurate diagnosis and appropriate treatment to avoid overtreatment and unnecessary surgeries.

Introduction

Thyroid cancer, though relatively rare in pediatric populations, represents a significant clinical concern due to its unique biological behavior and long-term implications. Defined as a malignant growth originating from the thyroid gland's follicular or parafollicular cells, pediatric thyroid cancer differs notably from its adult counterpart in terms of aggressiveness, recurrence risk, and prognosis [1]. The incidence of thyroid cancer in children, although comprising a small percentage of pediatric cancers overall, has been observed to be rising at an annual increase of approximately 1.1%, globally [2, 3].

Differentiated thyroid cancer encompasses various histological subtypes, with papillary thyroid carcinoma being the most common, both in the pediatric and adult population. Other tumor subtypes like follicular thyroid cancer and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTPs) are rare in the pediatric population [4]. The relevance of thyroid cancer in pediatrics is underscored by its distinctive clinical progression. Children are more likely to present with advanced disease at diagnosis, including higher rates of regional and distant metastases compared to adults [5]; however, with a 10-year survival rate of over 98%, the prognosis is often very good [6].

Although thyroid nodules are less common in children than in adults, the likelihood of malignancy is higher, which has been estimated to be between 22% and 26% [7]. The evaluation of malignancy in the thyroid nodules can be performed with ultrasonography (US) which can identify features with higher risk of malignancy (ROM). Various US classifications have been developed in the adult population to establish the ROM, such as the ACR Thyroid Imaging Reporting and Data System (ACR TIRADS); however, it has not been extensively validated and accepted in children [8]. Fine-needle aspiration (FNA) biopsy, on the other hand, has emerged as a pivotal diagnostic tool in the management of thyroid nodules in the pediatric population, as it represents a moderately invasive and highly accurate method for the initial evaluation of thyroid nodules that allows the differentiation of benign from malignant lesions [9, 10]. While imaging techniques such as US provide valuable information about the nodule's characteristics, FNAB, typically performed under US guidance to enhance accuracy, offers definitive cytological evidence that can guide subsequent management decisions [1]. Thyroid nodule cytological results are categorized using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which provides a structured risk assessment of malignancy and guidance for subsequent clinical management [11]. The analysis of FNA with these criteria has demonstrated high sensitivity and specificity for the detection of thyroid cancer in children [12]. However, the assessment of the malignancy risk in FNA varies between centers due to multiple technical variables [13].

This study aimed to ascertain the ROM using TBSRTC criteria in FNA in a pediatric cohort at a tertiary care center. Furthermore, the diagnostic accuracy of FNA cytological analysis will be established by comparison to histological analysis as the gold standard.

Methods

We conducted a descriptive, observational, cross-sectional, and retrospective study. Patients under 19 years of age with thyroid nodules who underwent both FNA and thyroidectomy at the Hospital of the Pontificia Universidad Católica de Chile between 2006 and 2022 were included. We excluded individuals 19 years of age or older and those who had FNA and/or thyroidectomy performed at other institutions.

The records of thyroid FNA obtained between 2006 and 2022 through FNA and histopathological findings from the Department of Pathology of the same institution were retrospectively analyzed. Electronic medical records were reviewed to collect variables including date of birth, sex, reason for consultation, date of FNA and thyroidectomy, TSH levels at the time of FNA, US description of the suspicious nodule, cytological diagnosis according to TBSRTC, and histological diagnosis. Histopathological findings from surgical specimens were categorized as "benign" or "malignant," where benign conditions included follicular adenoma, colloid follicular hyperplasia and NIFTP, and malignant conditions comprised papillary carcinoma, medullary carcinoma, and follicular carcinoma. The TNM Classification of Malignant Tumors was applied to determine the extent of the disease.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FNA were assessed using two distinct strategies for the detection of malignancy and neoplasia, with histological diagnosis serving as the gold standard. To evaluate the diagnostic accuracy of FNA in identifying malignancy, two separate analyses were performed: (a) one considering TBSRTC II as negative and TBSRTC VI as positive and (b) another considering TBSRTC II as negative and TBSRTC categories V and VI as positive. For the detection of neoplasia, nodules classified as TBSRTC II were deemed negative, whereas those classified as TBSRTC IV, V, and VI were considered positive, following previously described criteria [14]. TBSRTC categories III and I were omitted from the performance analysis since they could not unequivocally be categorized as positive or negative tests; they were instead separately evaluated. Follicular neoplasm or lesions suspicious for follicular neoplasm (FN/SFN) were treated as positive outcomes and were correlated with the presence of adenoma or any carcinoma found in the surgical specimen. Consequently, a true positive in this context implies the identification of a neoplastic process within the surgical specimen.

Statistical Analysis

Categorical variables are expressed as numbers and frequencies; continuous variables are presented either as mean and standard deviation or median with range as appropriate. Categorical comparisons were performed with Fisher's exact test, and continuous variables were compared using Student's t test parametric or non-parametric tests, as appropriate. A p value of <0.05 was considered significant. Statistical analysis was performed using SPSS (v.25: SPSS, Inc., Chicago, IL).

Results

A total of 300 FNA and 170 thyroidectomies were performed in children and adolescents during the studied period at our institution. The cytopathology results of 75 thyroid nodules corresponding to 73 patients obtained through FNA and the corresponding surgical histopathology findings providing a definitive diagnosis were included in this study. Among these, 28 (37.3%) were benign and 47 (62.6%) malignant. No significant difference in gender or age was observed between both groups (Table 1). Notably, the malignant group had a lower height standard deviation score (SDS) at diagnosis ($p = 0.000$) and higher TSH levels ($p = 0.009$). A greater proportion of the malignant group had US imaging ($p = 0.046$) and findings were classified as ACR-TIRADS 4 or 5. Most patients underwent total thyroidectomy, with a higher percentage in the malignant group (Table 1). Thyroiditis was more prevalent in malignant cases. Papillary carcinoma was the dominant cancer type, with lymph node involvement in half of the malignant cases and pulmonary metastases in 2 (4.3%) (Table 1).

The FNA and histological findings are summarized in Table 2, with the observed ROM, compared to the risks reported in both adult and pediatric populations. The following cytological findings in the FNA samples and respective ROM were as follows: two nondiagnostic or unsatisfactory (0%), 13 benign (0%), 7 with atypia of undetermined significance (29%), 14 suspicious for follicular neoplasm (43%), 10 suggestive of carcinoma (100%), and 29 malignant (100%). Histopathology revealed 28 benign lesions (19 follicular hyperplasia, 7 follicular adenomas, and 2 NIFTPs) and 47 malignant lesions (45 papillary carcinomas, 1 poorly differentiated, and 1 medullary).

The diagnostic accuracy of FNA for malignancy was evaluated through two analytical approaches using TBSRTC. For the initial analysis, we classified TBSRTC II as negative and category VI as positive, yielding a

Table 1. Demographic characteristics of patients who underwent FNA and surgery for thyroid nodule(s)

	Benign *N* = 28 (37.3%)	Malignant *N* = 47 (62.6%)	*p* value
Male	14	4	0.279
Age (mean±SD), years	15±2.66	15±2.07	NS
Height SDS at diagnosis (mean±SD)	0.89±1.02	−0.14±1.29	0.000
TSH at FNAB (mean±SD)	2±0.99	3±1.82	0.009
With US data, *n* (%)	16 (61.5)	40 (85.1)	0.046
ACR-TIRADS			
3	6	1	0.001
4	6	6	0.007
5	0	29	0.0001
Surgery, *n* (%)			
Thyroidectomy	21 (76.9)	42 (89.3)	
Lobectomy	7 (23)	5 (10.6)	
Histopathology, *n* (%)			
Thyroiditis	12 (46.2)	33 (70.2)	0.076
Multifocal	0	22 (46.8)	
Types of thyroid Cancer, *n* (%)			
Papillary	0	44 (93.6)	
Follicular	0	0	
PDTC	0	2 (4.3)	
Anaplastic	0	0	
Medullary	0	1 (2.1)	
Lymph node compromise, *n* (%)	0	24 (51)	
Distant Metastases, *n* (%)	0	2 (4.3)	

SDS, standard deviation score; US, ultrasound; ACR-TIRADS, ACR Thyroid Imaging Reporting and Data System; PDTC, poorly differentiated thyroid cancer.

Table 2. Comparative analysis of cytological findings and malignancy risk in pediatric versus adult thyroid nodules [15]

Bethesda Cytology	Pathology		ROM, %	Reported risk in adults, %	Reported risk in children, %
	benign	malignant			
I	2	0	0	12	14
II	13	0	0	4	6
III	5	2	29	22	28
IV	8	6	43	30	50
V	0	10	100	74	81
VI	0	29	100	97	98

ROM, risk of malignancy.

sensitivity of 78.38%, a specificity and PPV of 100%, and an NPV of 77.78%. These figures indicate that FNA was highly effective in correctly identifying both malignant and benign nodules. When the criteria were broadened in the subsequent analysis to include TBSRTC V and VI as positive, the sensitivity improved to 82.98%, with the

Table 3. TNM classification of thyroid cancer in pediatric patients (N = 45)

TNM	*n* (%)
T	
1a	20 (42.5)
1b	15 (31.9)
2	6 (12.8)
3	4 (8.5)
N	
0	19 (40.4)
1a	11 (23.4)
1b	13 (27.7)
M	
M0	43 (95.7)
M1	2 (4.2)

One patient did not have information about lymph node compromise in the clinical records review.

specificity and PPV remaining at 100%, and the NPV consistent at 77.78%, underscoring the enhanced ability of FNA to accurately detect malignancy without compromising precision. A distinct evaluation considered follicular adenomas within TBSRTC IV as positive, which led to a sensitivity of 100%, signifying the identification of all neoplastic cases. However, specificity decreased to 65%, while the PPV remained notably high at 86.79%. These statistics demonstrate the efficacy of FNA in discerning neoplastic tissue within the examined categories. Overall, the diagnostic accuracies were computed as 85.07% for the initial analysis, 88.33% for the subsequent analysis, and 77.25% for the separate neoplastic assessment.

As outlined in Table 3, according to the TNM classification, 42.5% of nodules were classified as T1a (<1 cm) and 31.9% were T1b (>1 cm and ≤2 cm). The presence of regional lymph node metastases (N1b) was observed in 51.1% of cases, with 27.7% having clinically apparent nodal metastases. Distant metastases were rare and were pulmonary in only 2 (4.2%) patients (M1). These data highlight the predominance of early-stage disease in our cohort, although with a notable proportion of regional lymph node involvement.

Discussion

These findings reveal that the malignancy rates in the indeterminate TBSRTC categories are significantly higher in this pediatric population compared to adults. This different behavior highlights the aggressive nature of pediatric thyroid nodules and the necessity of cautious interpretation of cytological findings in this group of patients.

The high incidence of papillary carcinoma in this study (94%), which is the predominant form of thyroid malignancies in pediatric cases, along with the rare occurrence of NIFTP, is consistent with published data [16, 17]. Approximately 47% of the papillary carcinoma cases exhibited multifocality, echoing findings of widespread disease in previous research, which bears significant influence on the decision-making process regarding surgical intervention – namely, the choice between total thyroidectomy and lobectomy. Predominantly, cases were adolescent females, with only one prepubertal patient, mirroring the higher incidence of thyroid cancer in females and adolescents within the pediatric population [18].

In our study, we calculated the ROM based only on lesions that underwent surgical resection as the gold standard (cytohistologic correlation), potentially overestimating the ROM due to selection bias [19]. To mitigate this, we additionally assessed the ROM and risk of neoplasia, which allows for a more comprehensive evaluation of FNA. The concordance of FNA with histological results in patients with Bethesda I, II, V, and VI, yielding a 77.25% diagnostic accuracy in our study, is comparable to other studies. The accuracy rate of FNA has been reported between 77.2% and 98.6%, with a sensitivity range of 63–100% and a specificity range of 63–100% among different studies [20, 21]. The high diagnostic accuracy of cytological analysis in this study is probably indicative of the cytopathologists' expertise at a tertiary care center, and possibly influenced by other factors such as aspiration techniques, quality of samples, and equipment. Therefore, the transferability of these results may not be generalizable to all medical settings. These results have implications for surgical decision-making, as the accurate preoperative identification of malignancy could spare pediatric patients from unnecessary surgeries and their associated risks.

The ROM associated with TBSRTC categories III and IV observed in our research was higher relative to that reported in adult populations, yet it was on par or even below the rates documented in pediatric studies [22]. Notably, in our cohort that included children diagnosed with NIFTP, the incidence of malignancy for TBSRTC categories III and IV was found to be 29% and 43%, respectively. Other study comparing pediatric and adult population [13] has reported higher malignancy rates, of 44 and 71% in categories III and IV, respectively. Initial

research suggested heightened malignancy risks in pediatric thyroid nodules [22], leading the American Thyroid Association (ATA) to advise surgical intervention for TBSRTC III categories in young patients [1]. However, emerging evidence indicates that the ROM for children and adolescents may align more closely with that observed in adults [15, 19]. In the TBSRTC categories with the highest risk of cancer (Bethesda V and VI), there were no discordances between FNA and histology, which resulted in a diagnostic accuracy of 100%. Furthermore, the favorable histological outcomes in TBSRTC categories I and II are also reassuring, as there were no cases of malignancy, contrasting with reports from other pediatric cohorts where a malignancy rate of 14 to 6% has been reported [11]. Factors that may explain this finding include that surgery was primarily based on nodule size, which is not a strong sonographic predictor of malignancy compared to other factors such as echogenicity, borders, and calcifications, given that in this low-risk group, the mean size was 24 ± 8.7 mm. Other factors that may have prompted surgery rely on personal variables, such as patient preference or risk factors.

The assessment of malignancy risk in pediatric thyroid nodules, particularly within indeterminate TBSRTC, demonstrates considerable variability among different study results, which can primarily be attributed to the modest number of pediatric cases incorporated into cytopathological investigations. Furthermore, this variability is compounded by factors such as the heterogeneity in cytopathologists' interpretations of TBSRTC, divergences in FNA methodologies, discrepancies in specimen processing techniques, and the diversity in study methodologies and patient follow-up protocols [19]. Additionally, the results' interpretation is constrained by differences in data collection and calculation of ROM across different studies. Higher ROM may be related to different factors, such as the inherent biological differences in thyroid tumors between children and adults, with a higher propensity for aggressive characteristics in the former.

One of the limitations of this study is that our tertiary center often deals with complex referred cases which could lead to a higher malignancy rate, which might not reflect the broader pediatric population. The retrospective design of the study might be also a limitation. Moreover, the relatively small number of samples in TBSRTC categories III and IV may not be sufficient to determine accurately malignancy rates for these categories with certainty. Additionally, preoperative genetic testing was not undertaken, which may have resulted in a higher rate of surgery in the indeterminate categories compared with the adult population, where this diagnostic tool is available and can inform therapeutic decisions [15]. The utility of genetic testing in thyroid nodules with indeterminate cytology lies in its ability to enhance diagnostic accuracy and risk stratification. Genetic markers and molecular tests can help differentiate between benign and malignant lesions in adult patients, thereby reducing the number of unnecessary surgeries and facilitating more informed and precise clinical decision-making [23]. However, gene expression classifier tools have not yet been widely tested or validated in pediatric populations. To date, only next-generation sequencing (NGS) tests have undergone validation in children, although large-scale comprehensive studies are still needed [24].

Future studies with multicenter designs, larger sample sizes, and prospective methodologies are needed to validate and expand upon our findings. The study possesses significant strengths, including the systematic application of TBSRTC, which standardizes malignancy risk assessment across all samples. Historical data have been meticulously reclassified to align with the current Bethesda criteria, ensuring uniformity in the evaluation of samples collected before 2010. The use of a single, experienced cytopathology group for all FNA interpretations minimizes interobserver variability, enhancing the reliability of cytological assessments. The longitudinal nature of this study, spanning 20 years and concentrating on pediatric patients, addresses a vital gap in literature predominantly centered on adults.

In summary, the data presented in this study indicate that FNA, coupled with expert cytopathological analysis, is a robust tool for the assessment of thyroid nodules in children. The higher malignancy risk in pediatric nodules highlights the need for a vigilant approach to nodule evaluation, with an emphasis on specialized pediatric protocols to manage these patients. Future research should aim to replicate these findings in a multicenter setting to validate the applicability of these results more broadly.

Acknowledgment

The authors thank Mrs. Helena Poggi for critical review of the manuscript.

Statement of Ethics

This study protocol was reviewed and approved by the Scientific Ethics Committee of the Pontifical Catholic University of Chile, Approval No. ID230707002. The need for written and informed consent was waived by the same committee as per their decision dated March 9, 2023.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Francisca Grob conceived and designed the study. Consuelo Pino and Francisca Grob drafted the initial manuscript and reviewed and revised the manuscript. Consuelo Pino coordinated data collection, managed the database, and performed the statistical analysis. Antonieta Solar and Pablo Zoroquiain were responsible for the analysis and interpretation of pathological data and contributed to the writing of the pathology sections of the manuscript. Francisco Cruz, Cristian García, and Florencia De Barbieri conducted the imaging studies, analyzed the radiological data, and contributed to the drafting and critical revision of the relevant sections. Francisco Cruz, Lorena Mosso, and Nicole Lustig performed the FNA. Hernán Gonzalez, Augusto León, and Ignacio Goñi conducted the oncological surgeries, contributed to the design of the surgical methodology, and critically reviewed the surgical content of the manuscript. José Miguel Dominguez ensured the integrity of the work and assisted in the final drafting of the manuscript. Andy Contreras contributed to the data collection and database management.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015;25(7):716–59. https://doi.org/10.1089/thy.2014.0460

2 Bernier M-O, Withrow DR, Berrington de Gonzalez A, Lam CJK, Linet MS, Kitahara CM, et al. Trends in pediatric thyroid cancer incidence in the United States, 1998-2013. Cancer. 2019;125(14):2497–505. https://doi.org/10.1002/cncr.32125

3 Vaccarella S, Lortet-Tieulent J, Colombet M, Davies L, Stiller CA, Schüz J, et al. Global patterns and trends in incidence and mortality of thyroid cancer in children and adolescents: a population-based study. Lancet Diabetes Endocrinol. 2021;9(3):144–52. https://doi.org/10.1016/S2213-8587(20)30401-0

4 Bauer AJ. Thyroid nodules in children and adolescents. Curr Opin Endocrinol Diabetes Obes. 2019;26(5):266–74. https://doi.org/10.1097/MED.0000000000000495

5 Sapuppo G, Hartl D, Fresneau B, Hadoux J, Breuskin I, Baudin E, et al. Differentiated thyroid cancer in children and adolescents: long term outcome and risk factors for persistent disease. Cancers. 2021;13(15):3732. https://doi.org/10.3390/cancers13153732

6 van de Berg DJ, Kuijpers AMJ, Engelsman AF, Drukker CA, van Santen HM, Terwisscha van Scheltinga SCEJ, et al. Long-term oncological outcomes of papillary thyroid cancer and follicular thyroid cancer in children: a nationwide population-based study. Front Endocrinol. 2022;13:899506. https://doi.org/10.3389/fendo.2022.899506

7 Heider A, Arnold S, Jing X. Bethesda System for reporting thyroid cytopathology in pediatric thyroid nodules: experience of a tertiary care referral center. Arch Pathol Lab Med. 2020;144(4):473–7. https://doi.org/10.5858/arpa.2018-0596-OA

8 Tuli G, Munarin J, Scollo M, Quaglino F, De Sanctis L. Evaluation of the efficacy of EU-TIRADS and ACR-TIRADS in risk stratification of pediatric patients with thyroid nodules. Front Endocrinol. 2022;13:1041464. https://doi.org/10.3389/fendo.2022.1041464

9 Rana C, Nigam N, Agarwal S, Mishra P, Singh A, Bychkov A. Cytological evaluation of thyroid nodules in children and young adults: a multi-institutional experience. Endocrine. 2023;80(3):580–8. https://doi.org/10.1007/s12020-022-03297-0

10 Canberk S, Barroca H, Girão I, Aydın O, Uguz A, Erdogan K, et al. Performance of the Bethesda System for reporting thyroid cytology in multi-institutional large cohort of pediatric thyroid nodules: a detailed analysis. Diagnostics. 2022;12(1):179. https://doi.org/10.3390/diagnostics12010179

11 Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for reporting thyroid cytopathology. Thyroid. 2023;33(9):1039–44. https://doi.org/10.1089/thy.2023.0141

12 Seminati D, Ceola S, Pincelli AI, Leni D, Gatti A, Garancini M, et al. The complex cytomolecular landscape of thyroid nodules in pediatrics. Cancers. 2023;15(7):2039. https://doi.org/10.3390/cancers15072039

13 Cherella CE, Angell TE, Richman DM, Frates MC, Benson CB, Moore FD, et al. Differences in thyroid nodule cytology and malignancy risk between children and adults. Thyroid. 2019;29(8):1097–104. https://doi.org/10.1089/thy.2018.0728

14 Ghaznavi SA, Clayton H, Eszlinger M, Khalil M, Symonds CJ, Paschke R. Accuracy of thyroid fine-needle aspiration cytology: a cytohistologic correlation study in an integrated Canadian health care region with centralized pathology service. Acta Cytol. 2022;66(3):171–8. https://doi.org/10.1159/000521562

15 Grob F, Carrillo D, Martínez-Aguayo A, Zoroquain P, Solar A, Nicolaides I, et al. Diagnostic yield of fine-needle aspiration cytology for the detection of thyroid cancer in pediatric patients | Concordancia de la citología por punción con aguja fina para la detección de cáncer de tiroides en pediatríaConcordancia de la citología por punción con aguja fina para la detección de cáncer de tiroides en pediatría. Rev Med Chil. 2014;142(3):330–5. https://doi.org/10.4067/S0034-98872014000300007

16 Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res. 2009;156(1):167–72. https://doi.org/10.1016/j.jss.2009.03.098

17 Wang H, Correa H, Sanders M, Neblett WW, Liang J. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in children: an institutional experience and literature review. Pediatr Dev Pathol. 2020;23(2):121–6. https://doi.org/10.1177/1093526619866584

18 Martucci C, Crocoli A, De Pasquale MD, Spinelli C, Strambi S, Brazzarola P, et al. Thyroid cancer in children: a multicenter international study highlighting clinical features and surgical outcomes of primary and secondary tumors. Front Pediatr. 2022;10:914942. https://doi.org/10.3389/fped.2022.914942

19 Loberg MA, Tigue ML, Gallant JN, Wang H, Canberk S, Weiss VL. Evolving approaches in paediatric thyroid cytopathology: a review. Cytopathology. 2024;35(1):60–9. https://doi.org/10.1111/cyt.13311
20 Rossi ED, Mehrotra S, Kilic AI, Toslak IE, Lim-Dunham J, Martini M, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in the pediatric age group. Cancer Cytopathol. 2018;126(1):27–35. https://doi.org/10.1002/cncy.21933
21 Amirazodi E, Propst EJ, Chung CT, Parra DA, Wasserman JD. Pediatric thyroid FNA biopsy: outcomes and impact on management over 24 years at a tertiary care center. Cancer Cytopathol. 2016;124(11):801–10. https://doi.org/10.1002/cncy.21750
22 Smith M, Pantanowitz L, Khalbuss WE, Benkovich VA, Monaco SE. Indeterminate pediatric thyroid fine needle aspirations: a study of 68 cases. Acta Cytol. 2013;57(4):341–8. https://doi.org/10.1159/000351029
23 Zafereo M, McIver B, Vargas-Salas S, Domínguez JM, Steward DL, Holsinger FC, et al. A thyroid genetic classifier correctly predicts benign nodules with indeterminate cytology: two independent, multicenter, prospective validation trials. Thyroid. 2020;30(5):704–12. https://doi.org/10.1089/thy.2019.0490
24 Gallant J-N, Chen S-C, Ortega CA, Rohde SL, Belcher RH, Netterville JL, et al. Evaluation of the molecular landscape of pediatric thyroid nodules and use of a multigene genomic classifier in children. JAMA Oncol. 2022;8(9):1323–7. https://doi.org/10.1001/jamaoncol.2022.1655