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SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules

SFE-AFCE-SFMN 2022 Consensus on the management of thyroid nodules : Thyroid nodules in children

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ABSTRACT

The SFE-AFCE-SFMN 2022 consensus deals with the management of thyroid nodules, a condition that is a frequent reason for consultation in endocrinology. In more than 90% of cases, patients are euthyroid, with benign non-progressive nodules that do not warrant specific treatment. The clinician's objective is to detect malignant thyroid nodules at risk of recurrence and death, toxic nodules responsible for hyperthyroidism or compressive nodules warranting treatment. The diagnosis and treatment of thyroid nodules requires close collaboration between endocrinologists, nuclear medicine physicians and surgeons, but also involves other specialists. Therefore, this consensus statement was established jointly by 3 societies: the French Society of Endocrinology (SFE), French Association of Endocrine Surgery (AFCE) and French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). The present section deals with the specific aspects of the management of euthyroid nodules in patients under 18 years of age.

This section will focus on the specific aspects of managing euthyroid nodules in patients under 18 years of age.

1. Epidemiology

Thyroid nodules are rarer in children than in adults; prevalence is difficult to estimate, but is probably between 0.2% and 5%. Revelation is mainly clinical, by cervical palpation by the doctor or the family (80%), and then ultrasound as part of specific surveillance [1]. Prevalence increases with age, particularly after puberty, and several risk factors have been identified: iodine deficiency, previous thyroid disease, accidental or therapeutic exposure to ionizing radiation, and certain genetic predisposition syndromes.

The risk of cancer in case of nodules is clearly higher in children than adults, at 20%, compared to 5%. The majority of cases are papillary thyroid carcinomas [2]. Children are generally diagnosed with more advanced disease than adults, and the risk of metastasis is 25% [3]. Nevertheless, prognosis in children is excellent [4].

The incidence of thyroid cancer in France has been relatively stable since 1990 [5].

Recommendation 9.1. Given the rarity of this clinical situation, we recommend that children with one or more thyroid nodules be referred to a physician experienced in childhood thyroid pathology. Level of evidence ++ Grade A.

2. Genetic predisposition syndromes

The discovery of a thyroid nodule on clinical examination in children may be the gateway to diagnosing a genetic disease, whether syndromic or not. Interview and physical examination should therefore look for associated signs that may point to a tumor predisposition syndrome such as NEM2, DICER1 syndrome,

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Table 1
Risk of thyroid cancer according to TI-RADS score [16–21].

	TI-RADS 2	TI-RADS 3	TI-RADS 4	TI-RADS 5
	0–14%	0–27%	8–21%	38–100%
Ahmad [17]	0/44	4/51	6/35	3/8
Shapira [18]	5/97	4/40	24/113	19/50
Lim-Dunham [19]	1/7	0/6	2/24	17/36
Scappaticcio [20]	1/9	3/10	2/16	6/6
Richmann [21]	6/117	7/109	18/116	46/62
Kim [16] (meta-analysis)	6%	11%	21%	59%

Cowden syndrome (macrocephaly, developmental delay) [6,7] with a pathogenic variant of PTEN or, more rarely, Carney's complex, APC gene abnormalities, tuberous sclerosis or xeroderma pigmentosum (skin signs) [8,9].

DICER1 syndrome (OMIM#601200), linked to the presence of a pathogenic germline variant of DICER1, is a syndrome predisposing to benign or malignant tumor with predominantly pediatric onset (lung, kidney, ovary, thyroid, etc.), but which may be expressed phenotypically only by thyroid signs (nodule, multinodular goiter and differentiated cancer). It is recommended that the gene be studied, if possible in conjunction with a panel of predisposition genes, when there is:

- a multinodular goiter or differentiated cancer in a child;
- several cases in the same family;
- or the association of a multinodular goiter with other tumors on the spectrum [10,11].

The value of systematically measuring calcitonin in case of thyroid nodule in children, outside the known familial context of NME2, has not been proven, but should be carried out as part of the preoperative assessment, as in adults.

Early diagnosis of these genetic diseases allows personalized management of thyroid nodules, screening for associated pathologies, and appropriate genetic counseling of the patient and family.

Recommendation 9.2.

The discovery of a thyroid nodule in a child should lead to screening for personal and familial clinical history, which may point to a tumor predisposition syndrome, particularly in case of multinodular thyroid (DICER1 and PTEN). Level of evidence: ++ Grade A.

3. Diagnostic specificities of thyroid nodules in children

The specific ATA recommendations for the management of thyroid nodules in children <18 years, made in 2015, have been reinforced by subsequent studies and a recent meta-analysis [12–14].

As thyroid nodules in children generally have a clinical expression that leads to diagnosis, sensitivity/specificity analyses of thyroid ultrasound and fine-needle biopsy are mainly based on the analysis of macronodule series. For this reason, there are no studies of active surveillance of suspect small nodules.

In case of unrestrained TSH, the attitude will be guided by cervical ultrasound.

A systematic review and meta-analysis showed that several ultrasound criteria were more often associated with malignancy (relative risk of cancer diagnosis > 1) [15]:

- suspicious lymphadenopathy (OR 12);
- microcalcifications (OR 9);
- solid nodule (OR 7), or nodule longer than wide (OR 5);
- irregular margins (OR 4);
- increased intranodular vascularity (OR 3);
- hypoechoic nodule (OR 2).

However, whether the nodule is single or multiple does not guide management; nor does association with autoimmune thyroiditis.

A meta-analysis of the diagnostic performance of the ATA and ACR TI-RADS scores in children, with nearly 900 assessments, showed 86% sensitivity (84% for ACR, 90% for ATA) and 58% specificity (64% for ACR, 50% for ATA) when the TI-RADS score was 4 or 5 [16]. The risk of thyroid cancer according to TI-RADS score is detailed in Table 1: ACR TI-RADS 1, 2 and 3 were associated with 5.5-11% cancer risk, and ATA TI-RADS 2 and 3 with 7.5-12%. On fine-needle biopsy of only TI-RADS 5 nodules, 22% of cancers would be missed.

As TI-RADS scores show only relative diagnostic performance in children, failing to diagnose malignancy in 15-22% of cases, and the frequency of cancer is high, use of ultrasound criteria to avoid or delay fine-needle biopsy is questionable in children and fine-needle biopsy should be easy to perform, especially for any clinically diagnosable nodule, and particularly for TI-RADS 3, 4 and 5 nodules larger than 1 cm [17]. In TI-RADS 2 nodules, the risk of malignancy is very low but not zero, and these patients should be monitored closely clinically and ultrasonographically every 6–12 months for 5 years, and fine-needle biopsy should be performed if there is any suspicion of progression.

Recommendation 9.3

We recommend fine-needle biopsy of any nodule > 1 cm because of the greater risk of malignancy than in adults for TI-RADS scores 3, 4 and 5. Level of evidence: ++ Grade A.

Recommendation 9.4.

Regular prolonged clinical and/or ultrasound monitoring of the thyroid every 3 to 5 years should be conducted in case of history of irradiation, especially if early, given the increased risk of thyroid cancer. Level of evidence: +++ Grade A.

Recommendation 9.5.

Fine-needle biopsy should always be ultrasound-guided, and if possible performed by a practitioner with expertise in thyroid fine-needle biopsy. Level of evidence, ++ Grade A.

Data on molecular biology study of fine-needle biopsy in children are as yet sparse: however, positive findings are very strongly associated with risk of cancer, and negative findings cannot be considered reassuring.

A combination of molecular markers could probably optimize the management of patients with nodules of undetermined cytology [18,19].

4. Particularities of surgery in children

Thyroid surgery in children is rare. No pediatric teams can match the experience of surgeons treating adults.

The morbidity of thyroid surgery is greater in children than adults, particularly in terms of the rate of permanent hypoparathyroidism, which a review of the literature found to be 10% [20]. Recurrent paralysis seems to be as frequent as in adults: 0 to 8.6% postoperatively and 0 to 2.5% permanently [21]. The risk factors for complications are accidental parathyroidectomy and lymph-node dissection [22,23]. The ATA considers surgical centers to be low volume for fewer than 3 thyroidectomies per year, medium volume for 4 to 30, and high volume beyond 30 [24].

If minimal specific pediatric experience is not available, an adult endocrine surgeon is to be preferred [25].

The retrospective study by Wesson et al. [25] reported the results of multidisciplinary management of thyroid disease in children [26]. A weekly meeting with surgeons, pediatric endocrinologists, pediatric oncologists, pediatric radiologists, nuclear medicine physicians and pathologists reduced the number of surgeons involved, increased their activity and reduced morbidity.

Recommendation 9.6.

We recommend that the surgical management of thyroid nodules in children be validated and carried out by a medical-surgical team trained in thyroid surgery and, as far as possible, that children be operated on in a pediatric setting. Level of evidence: ++ Grade A.

A retrospective cohort analysis for the period 2004–2009 reported results in 78 patients under 19 years of age with cytologically indeterminate nodules [27]. The frequency of malignancy was 41%, 75% and 79% for Bethesda III, IV and V nodules, respectively.

A multicenter study of 212 patients under 18 years of age, operated on for papillary cancer between 2010 and 2020 in 5 centers (3.8 per center per year) reported lymph node involvement in 73% of cases (bilateral in 27%) and multifocality in 46% (12% unilateral and 34% bilateral) [28]. Predictive factors for multifocality were age $\leq$ 10 years, stage T3 and bilateral stage N1b. However, as in adults, there are low-risk unifocal forms (tumor < 4 cm). A retrospective matched cohort study compared the results between total thyroidectomy and thyroid lobectomy in children <18 years with low-risk papillary cancer (T1b and T2) [29], and concluded that thyroid lobectomy was sufficient in such cases.

Recommendation 9.7

- Recommendation 9.7a - Given the significantly increased risk of cancer in Bethesda III, IV, V and VI cytology in children compared with adults, we recommend thyroid surgery, the modalities of which (lobectomy or total thyroidectomy) should be discussed in a specialized thyroid tumor board. Level of evidence: ++ Grade A.
- Recommendation 9.7b - If lobectomy is proposed, we recommend basing the discussion of the potential need for surgical totalization on the final histology findings. Level of evidence: ++ Grade B.

As in adults, radiofrequency treatment of benign thyroid nodules has shown good results [30] but there is currently insufficient experience to recommend this type of treatment in the pediatric population.

Recommendation 9.8.

We do not recommend radiofrequency treatment of thyroid nodules in children. Level of evidence: + Grade B.

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