

**Review****Management of thyroid nodules in children and adolescents**

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Thyroid nodules in childhood and adolescence are less prevalent but more often malignant than in adulthood. Malignant nodules are predominantly papillary cancers; benign nodules are mostly solid colloid nodules/adenomas, but can be cystic or due lymphocytic thyroiditis. Previous neck irradiation (nowadays mostly encountered in childhood cancer survivors) is a clear risk factor for developing nodules. Neck irradiation for childhood Hodgkin's disease has a relative risk of 27 for the development of thyroid nodules. Female sex, a thyroid radiation dose  $\geq 2500$  cGy, and time since irradiation of  $\geq 10$  yr are independent risk factors. This subset of patients deserves long-term follow-up. The diagnostic steps for thyroid nodules in children and adolescents are not different from those in adults. First, history and physical examination should identify risk factors for malignancy of the nodule. Second, thyroid function should be assessed by serum TSH, followed by a thyroid scan in the case of a suppressed TSH. Serum calcitonin might be measured if there is suspicion of medullary thyroid carcinoma (e.g. a family history of MEN). Thyroid ultrasound is useful, especially in guidance of FNAC for optimal results, but presently should not be used for final decisions on the benign or malignant nature of the nodule. FNAC has the highest diagnostic accuracy in recognizing malignant nodules and should be applied in all nodules  $\geq 1$  cm and in nodules  $< 1$  cm only if there is suspicion for cancer (e.g. by ultrasound characteristics). Surgery is the most cost-effective treatment option for thyroid nodules, solving the problem fast. Levothyroxine treatment has a low efficacy. Experience with other treatment options like ethanol injection or laser therapy is still limited.

**Key words:** Adolescence thyroid nodules, Childhood thyroid modules, Neck irradiation

**INTRODUCTION**

Thyroid nodules are less common in children and adolescents than in adults, the prevalence of palpa-

ble thyroid nodules in childhood being about 1.5%, whereas in adulthood it is 4-7%.<sup>1,2</sup> In contrast, thyroid nodules are more often malignant in childhood than in adulthood: in children, 26% of thyroid nodules are malignant, while in adults the corresponding figure is 5-10%.<sup>2,3</sup> Risk factors for developing thyroid nodules in children are female sex, post-pubertal age, previous or co-existing thyroid disease, previous irradiation of the neck, and a family history of thyroid disease.

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## CLASSIFICATION

Many thyroid diseases present clinically as thyroid nodules. Table 1 lists the relative frequency of the various etiologies among children and adolescents with solitary thyroid nodules. The data from two large studies (collecting cases of pediatric thyroid nodules over several decades) are combined in the Table.<sup>4,5</sup> The sex distribution of the 128 children was 104 (81%) girls and 24 (19%) boys and the mean age was 13 years (range 1-18 yr). The vast majority of patients were euthyroid; only one subject was thyrotoxic, and some with lymphocytic thyroiditis were hypothyroid. Most cases of benign nodules represented colloid/hyperplastic nodules or follicular adenomas. The histology of some benign nodules showed chronic lymphocytic thyroiditis. Nodular thyroid disease can thus be one phenotypic expression of Hashimoto's thyroiditis. Other studies mention Pendred syndrome or teratoma as the underlying thyroid disease presenting as nodules.<sup>6,7</sup>

Thyroid nodules can be solid, cystic or of mixed nature. One specific study on cystic thyroid nodules in 24 children (19 girls, 5 boys, mean age 13 yr with range 6-18 yr) disclosed pure cysts in 5 and mixed cystic/solid lesions in 19 patients.<sup>8</sup> Only one of the patients had suppressed TSH, and two had detectable microsomal antibodies. Positive family history of thyroid disease was found in 30% of the cases. On thyroid scintiscan, 6 lesions were hot (increased uptake), 13 were cold (decreased uptake), 2 were mixed, and 3 showed normal uptake. The final diagnosis was follicular adenoma in 9, cystic degeneration in 6, multinodular goiter in 4, thyroid carcinoma in

2, bronchial cleft cyst in 1, and indeterminate in 2. Intrathyroidal thyroglossal duct cysts have also been detected.<sup>9</sup>

Thyroid nodules can be solitary, or multiple giving rise to a multinodular thyroid gland (MNTG). In one study on MNTG in 16 children (9 girls, 7 boys, mean age 13 yr with range 7-19 yr), two or more nodules on ultrasound were detected in all subjects (distributed over both thyroid lobes in all except one), whereas 12 patients had 2 or more palpable nodules but 4 patients had only one palpable nodule.<sup>10</sup> These findings point to the fact that ultrasonography is more sensitive than palpation in detecting thyroid nodules. Many patients with a single palpable thyroid nodule may harbour more than one nodule. The etiology of these 16 childhood cases of multinodular thyroid glands is listed in Table 2.

## THE ROLE OF PREVIOUS NECK IRRADIATION

Previous neck irradiation is a risk factor for developing thyroid nodules which may turn into malignant ones. Whereas between 1940 and 1960 neck irradiation was mostly applied for radiotherapy of benign conditions like tinea capitis, scrofula, and an enlarged thymus, nowadays a history of previous neck irradiation is obtained mostly in childhood cancer survivors.

Two follow-up studies reporting on the incidence of thyroid nodules after neck irradiation for childhood Hodgkin's disease showed the following: in 93 children irradiated at a mean age of 12 yr, thyroid ultrasonography ten years later revealed abnormalities in all, including focal lesions in 37% and thyroid

**Table 1.** Classification of solitary thyroid nodules detected in 128 children and adolescents.<sup>4,5</sup>

<b>MALIGNANT NODULES (19%)</b>		
• papillary carcinoma	17	(13%)
• follicular carcinoma	4	(3.6%)
• anaplastic carcinoma	2	(1.6%)
• medullary carcinoma	1	(0.8%)
<b>BENIGN NODULES (81%)</b>		
• colloid nodule/adenoma	67	(52%)
• cyst	19	(15%)
• lymphocytic thyroiditis	18	(14%)

**Table 2.** Characteristics of multinodular thyroid glands (MNTG) in 16 children and adolescents.<sup>10</sup>

<b>MALIGNANT MNTG (25%)</b>	
• thyroid carcinoma	4
<b>BENIGN MNTG (75%)</b>	
• benign isolated MTNG	3
• benign MTNG with cystic renal disease and polydactyly	3
• benign MTNG with McCune-Albright syndrome	2
• benign MTNG after previous neck-irradiation	1
• Hashimoto's thyroiditis	3

cancer in 5.4%.<sup>11,12</sup> Focal lesions were associated with younger age of irradiation, longer follow-up, and longer duration of an elevated TSH. Similar data were observed in the very large Childhood Cancer Survivor Study: the risk of thyroid nodules was 27 times, of hypothyroidism 17 times, and of hyperthyroidism 8 times higher than that in sibling controls.<sup>13</sup> The actuarial risk of a female survivor of Hodgkin's disease developing a thyroid nodule is 20% at 20 yr from diagnosis. Female sex, a radiation dose to the thyroid of 2500 cGy or more, and time from radiation of  $\geq 10$  yr were independent risk factors for thyroid nodules (Table 3).

Thyroid nodules continue to occur even decades after neck irradiation. From a cohort of individuals irradiated for benign conditions in the head and neck area between 1939 and 1962, 54 subjects were selected who in 1974-1976 had a normal thyroid by palpation and by scan and were restudied twenty years later.<sup>14</sup> One or more discrete ultrasound-detected nodules were present in 47 of the 54 (87%) subjects. There was a total of 157 nodules, 40 of which were  $\geq 1.0$  cm. These 40 nodules occurred in 28 (52%) subjects; 10 of the 40 nodules were not recognised on the scan. Of these nodules, only 5 were palpable. None of the 5 fine needle aspirations were suggestive of malignancy. However, in one of these patients, who died of unrelated causes, the large nodule (diameter 16 mm on ultrasound) was a papillary cancer. The authors express concern that the high sensitivity of ultrasonography may give rise to unneeded additional tests and surgery.

Ultrasound screening of the thyroid gland has been performed in 3,051 Belarus children 4-14 years of age who had been exposed to radioactive fallout due to the Chernobyl accident in 1986.<sup>15</sup> Screening done in

1990, 1993, and 1998 demonstrated that with time the prevalence of thyroid nodules increased from 1.2% to 3.5%, but the prevalence of thyroid carcinoma decreased from 0.6% in 1990 to 0.3% in 1993 and 0% in 1998. Systematic ultrasound screening is thus useful for the early detection of thyroid carcinoma in children exposed to radioactive fallout.

The value of regular ultrasound screening in survivors of childhood Hodgkin's disease who received neck irradiation is debated. Some argue against ultrasound screening because the majority of thyroid nodules have an indolent clinical course and do not undergo malignant transformation.<sup>16</sup> They favour further investigation only in the case of a palpable nodule. Others favour regular ultrasound screening.<sup>11,12</sup>

Children and adolescents are much more sensitive to the effects of ionizing irradiation than adults, as became again all too evident in the aftermath of the Chernobyl accident. One explanation of this interesting biologic phenomenon is that thyrocytes have a very low division rate at adult age compared to younger age groups. Radiation-induced mutations are thus less likely to be transmitted to later generations of cells in higher age groups in view of the early expiration of the potency of thyrocytes to divide.<sup>17</sup>

## DIAGNOSIS

The diagnostic steps for thyroid nodules in children and adolescents are not different from those in adults. The first step is the clinical examination of the patient, which specifically serves the purpose of assessing the pretest likelihood of malignancy. Risk factors for malignancy of thyroid nodules are a fast growing nodule, a family history of (medullary) carcinoma, previous neck irradiation, hoarseness, a very firm nodule, fixation of the nodule to adjacent structures, and cervical lymphadenopathy. Further work-up consists of:

1. blood tests: TSH (and calcitonin if medullary carcinoma is suspected);
2. thyroid scan: in cases of a suppressed TSH;
3. thyroid ultrasound: very useful, also for guidance to perform FNAC (fine-needle aspiration cytology);

**Table 3.** Relative risks of thyroid nodules after neck irradiation for childhood Hodgkin's disease.<sup>13</sup>

	Relative Risk	95% CI
• Risk of thyroid nodules compared to siblings as controls	27.0	13.6-63.9
• Independent risk factors		
- time since diagnosis $\geq 10$ yr	4.8	3.0-7.8
- female sex	4.0	2.5-6.7
- thyroid radiation dose $\geq 2500$ cGy	2.9	1.4-6.9

4. FNAC: in suspicious nodules, and in nodules  $\geq 1$  cm.

Whereas serum TSH should be assayed in every patient with a thyroid nodule, opinions differ as to whether or not serum calcitonin should also always be measured. In terms of cost-effectiveness, it is apparently preferable to order a calcitonin assay only if medullary carcinoma is suspected, e.g. in patients with a family history of MEN. One should be aware, however, that the reference range of serum calcitonin is wider in children than in adults.<sup>18</sup>

The diagnostic accuracy in recognizing malignant nodules is highest for FNAC. The performance of thyroid scan in this respect is poor, and that of ultrasound intermediate. Table 4 lists comparative figures obtained in 46 children.<sup>19</sup> Similar results are reported from Italy: the accuracy of diagnosing malignancy in thyroid nodules of 42 children was 53% for thyroid scans (cold nodule), 67% for thyroid ultrasound (hypoecho-genecity), and 90% for FNAC.<sup>20</sup> Test characteristics of FNAC in childhood nodules as reported in the literature are given in Table 5.

FNAC is thus currently the best method – short of surgery with histologic examination – for assessing the benign or malignant nature of the nodule. Nonetheless, there remain difficulties in distinguishing thyroid carcinoma from benign lesions, particularly in the case of follicular thyroid carcinoma versus follicular adenoma or the follicular variant of papillary thyroid carcinoma. The employment of immunocytochemical and molecular studies in fine-needle aspirates from nodules may offer greater precision in this respect. So far it has not been proven that evaluation of galectin-3 in the aspirate as a marker of malignancy improves the diagnostic accuracy of FNAC,<sup>21</sup> and

the same holds true for other proposed markers.<sup>22</sup> Nevertheless, new data arising from cDNA arrays identifying novel markers of malignancy make this a growing area of interest.<sup>23</sup>

Several ultrasound characteristics have been studied as potential predictors of thyroid malignancy. These characteristics are solid lesions, hypoecho-genecity, microcalcifications, irregular margins, no halo, intranodular vascularity, and lesions more tall than wide.<sup>29-31</sup> Although there are certain trends in the ultrasound distinction between benign and malignant thyroid nodules, there is also overlap in their appearances. A consensus conference statement recommended US-guided FNAC of solitary nodules in the event of: a) microcalcifications and diameter  $\geq 1$ cm, b) solid nature or coarse calcifications and diameter  $\geq 1.5$  cm, c) mixed solid and cystic nature or almost entirely cystic with solid mural component and diameter  $\geq 2$  cm, d) substantial growth since prior ultrasound examination.<sup>29</sup> It remains to be seen how valid these recommendations are for childhood thyroid nodules. In a study of 103 pediatric patients with solid thyroid nodules living in Belarus, the most reliable diagnostic criteria for malignancy in nodules with a diameter  $\leq 1.5$  cm were irregular margin, subcapsular location, and increased intranodular vascularization.<sup>32</sup> However, for thyroid nodules  $> 1.5$  cm the accuracy of ultrasound diagnosis was much lower; the only reliable criterion for cancer in this group was hypoecho-genecity with a sensitivity of 60% and a specificity of 84%.

**Table 4.** Diagnostic steps for the discrimination between malignant and benign thyroid nodules in 46 children.<sup>19</sup>

	Sensitivity %	Specificity %	Pos. PV %	Neg. PV %	Accuracy %
Thyroid scan	30	42	12	68	39
Thyroid ultrasound	60	59	15	92	59
FNAC	100	95	67	100	95

PV = predictive value

**Table 5.** Test characteristics of fine-needle aspiration cytology for the discrimination between malignant and benign thyroid nodules in childhood.<sup>20</sup>

Year (ref.)	N	Malignancy %	Sensitivity %	Specificity %	Accuracy %
1996 (5)	57	18	80	86	85
1996 (24)	18	33	73	80	75
1998 (25)	24	21	60	90	80
1998 (26)	57	25	93	81	84
2001 (27)	41	5	87	100	87
2001 (19)	46	7	100	95	95
2001 (20)	42	48	95	86	90
2005 (28)	32	44	100	65	81
total	317	23	60-100	65-100	75-95

## THERAPEUTIC APPROACH

Treatment options for solitary benign thyroid nodules are listed in Table 6.<sup>2</sup> A few papers mention the outcome of treatment. In a series of 46 children with thyroid nodules, six (13%) were sent immediately to surgery because of malignant or suspicious FNAC, 15 (33%) had a satisfactory response to thyroxine treatment for 6 months (i.e. nodules either disappeared or decreased in number and/or size), and 25 (54%) were sent to surgery later because nodule size did not change or increased despite thyroxine treatment.<sup>19</sup> In pediatric Hodgkin lymphoma survivors, 10 of 67 patients (15%) with thyroid nodules had lesions that disappeared on follow-up 24 months later (some of them were receiving thyroid hormone therapy at the time the nodules were diagnosed by ultrasonography).<sup>16</sup>

Thyroxine treatment thus has some benefit, but its efficacy remains low. Recent guidelines address thyroxine therapy for FNAC-benign thyroid nodules:<sup>32</sup>

1. T<sub>4</sub> treatment may be considered: in iodine-deficient areas, in young patients with small nodules;
2. T<sub>4</sub> treatment should be avoided: in large nodules, in cases of inadequate or suspicious FNAC;
3. T<sub>4</sub> treatment results: reduction of nodule volume only in a minority; full TSH suppression (<0.1 mU/L) should be avoided; nodule regrowth usually occurs after discontinuation of T<sub>4</sub>; growth of the nodule during T<sub>4</sub>, consider FNAC and surgery.

Thyroidectomy (usually restricted to lobectomy) thus remains the most effective treatment modality. This is also true for cystic thyroid nodules in childhood.

**Table 6.** Treatment options for solitary benign thyroid nodules in childhood.

1. Surgery	- definite histologic diagnosis - nodule ablation
2. Levothyroxine	- may slow growth of (new) nodules - low efficacy
3. Observation	- psychological burden and cost of long-term follow-up
4. Ethanol injection	- limited experience - side effects
5. Laser therapy	- still experimental

In a series of 24 children with cystic lesions, one child (4.1%) did not receive any treatment.<sup>8</sup> The remaining 23 children received T<sub>4</sub> suppression therapy, but only two (8.3%) responded. Cyst aspiration was attempted in six children, but was successful in only four (16.6%), requiring repeat aspirations in three of them; two were sent to surgery subsequently. Thyroidectomy was done in 17 of the 24 children (71%).

Recommendations for follow-up of survivors of childhood Hodgkin's disease are:<sup>12</sup>

1. Careful palpation of the thyroid gland;
2. TSH and FT<sub>4</sub> assay every 6 months for 5 yr, thereafter annually;
3. If TSH is elevated, thyroxine treatment aiming at TSH <1.0 mU/l;
4. First ultrasound 3 yr after radiotherapy, and yearly thereafter;
5. FNAC for thyroid lesions ≥1 cm.

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