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The international approach of pediatric thyroid nodules and thyroid differentiated carcinoma. The starting point for the Romanian pediatric guideline

Andreea-Ioana Stefan[1], Cristina Blag[2], Gheorghe Popa[3], Monica Dragomir[4,5], Rodica Cosnarovici[6], Doina Piciu[1,7]

[1] Doctoral School, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2] Department of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3] "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[4] "Prof. Dr. Al. Trestioreanu" Institute of Oncology, Bucharest, Romania
[5] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[6] Department of Pediatric Oncology, "Prof. Dr. Ion Chiricuta" Institute of Oncology, Cluj-Napoca, Romania
[7] Department of Endocrine Tumors and Nuclear Medicine, "Prof. Dr. Ion Chiricuta" Institute of Oncology, Cluj-Napoca, Romania

ABSTRACT

Background. The incidence of pediatric differentiated thyroid carcinoma (DTC) is increasing even though that this is a rare disease. It is known that there are important differences between adults and children especially in clinical presentation and genetic alterations. The only guideline for the diagnostic and therapeutical approach for the children with thyroid nodules and differentiated thyroid carcinoma is the American Thyroid Association (ATA) guideline published in 2015, but there could be improvements that we need to highlight in order to reduce the apparition of comorbidities and to improve the quality of life. There is also no national guideline in Romania for the treatment of this pathology in children.
Materials and methods. This study is a review of the literature published in the last 5 years concerning the diagnostic and treatment of the pediatric thyroid cancer.
Results. The management of the children with the suspicion of thyroid nodule should be done in specialized centers in a specialized, multidisciplinary team, with high volume surgeons. The diagnostic approach should include genetic testing. The surgical management could be less radical in certain cases. The presurgical evaluation and intraoperative laryngeal nerve monitoring should reduce the apparition of comorbidities.
Conclusion. A European and also a national guideline for the management of pediatric thyroid nodules and thyroid carcinoma is mandatory to reduce the apparition of comorbidities and to improve the quality of life of the patients.

Keywords: pediatric differentiated thyroid carcinoma, pediatric thyroid nodules, diagnostic and treatment guideline

INTRODUCTION

Pediatric differentiated carcinoma (DTC) in Romania has a growing incidence, as we can see from our previous studies (1-3), but the incidence is worldwide rising despite the fact that the DTC is a rare disease. There are important differences between adult and pediatric DTC which is why a separate Pediatric Recommendation is necessary. The risk factors, the clinical aspects and the genetic alterations are different in children compared with adults. As we know, pediatric DTC often presents with more advanced disease but, despite the more aggressive presentation, the DTC has an excellent prognosis.

Corresponding author:
Andreea-Ioana Stefan
E-mail: andreea.stefan24@gmail.com

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The most common genetic alterations in DTC are RET-PTC and NTRK fusion while mutation in BRAF, and RAS point mutations are less frequent (4). The inclusion of genetic testing of the thyroid cytology is an important aspect which could make a difference in the treatment protocol, and the result may be different from that in adults. The consequences of possible adverse effects of DTC treatment may be different for children because of their longer life span.

There is no European recommendation for treatment of pediatric nodules and pediatric DTC, nor Romanian national recommendation. In 2015, American Thyroid Association (ATA) published the pediatric guideline (5) but there could be improvements that we need to highlight. We also need specific, European recommendations (6,7).

In Romania, the management of the pediatric DTC it is made based on the local protocols but there is no national consensus in this way.

The purpose of this study is to collect all the relevant data from the literature as a starting point of the Romanian national guideline for the pediatric thyroid nodules and DTC. The main goal is to improve the quality of life of the patients by reducing the treatment comorbidity rate.

MATERIALS AND METHODS

We performed an electronic search on the PubMed database using the following terms: ”thyroid carcinoma children”, ”treatment” / ”guideline” / ”recommendation”, ”hypocalcemia”, ”treatment outcome”, ”thyroid surgery”. After applying the filters – publication date – of the last 5 years, we had a selection of 950 articles of that 228 published in the last year, we eliminated the double entries and we choose only the relevant papers for our study so, in the end, we had a selection of 20 articles (Fig. 1).

We will use the 2015 ATA published guideline and we will analyze the most important aspects of it with new and concise recommendations from the international literature. The most relevant papers used for this study are the ”New national recommendations for the treatment of pediatric differentiated thyroid carcinoma in the Netherlands” (7) and the ”Consensus statement by the American Association of Clinical Endocrinology (AACE) and the American Head and Neck Society Endocrine Surgery Section (AHNS-ES) on Pediatric Benign and Malignant Thyroid Surgery”, published in 2021.

RESULTS

The analyzed articles for this study are listed in table 1.

Medical history, clinical examination and identifying the possible risk factors for the apparition of the thyroid cancer are important steps in the therapeutical management.

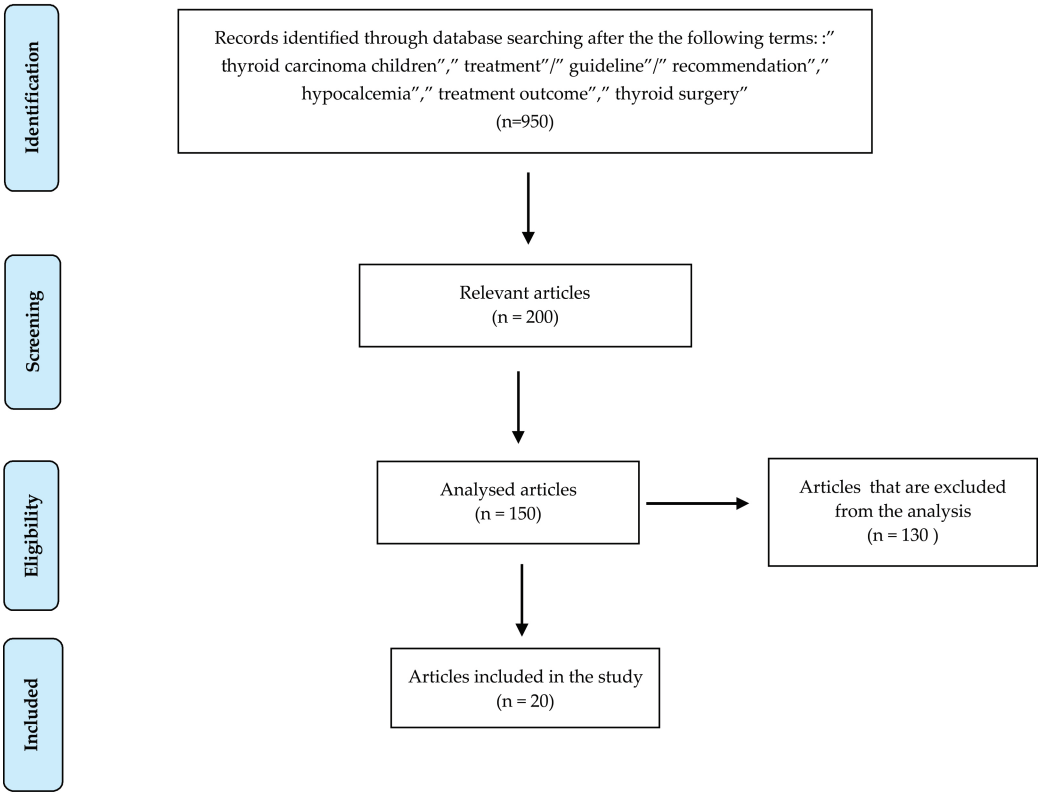

FIGURE 1. Prisma flow diagram

TABLE 1. The articles included in this review

No	First author	The year of publication	The tye of the study
1.	Haugen et al. (8)	2016	Guide
2.	Kluijfhout et al. (9)	2016	Retrospective
3.	Tuttle et al. (10)	2017	Guide
4.	Clement et al. (11)	2018	Guide
5.	Ogle et al. (12)	2018	Review
6.	Dekker et al. (6)	2018	Retrospective
7.	Efanov et al. (4)	2018	Retrospective
8.	Galuppini et al. (13)	2019	Retrospective
9.	Filetti et al. (14)	2019	Guide
10.	Paulson et al. (15)	2019	Review
11.	Lebbink et al. (7)	2020	Guide
12.	Hess et al. (16)	2020	Retrospective
13.	Radakrishnan et al. (17)	2020	Review
14.	Gonsalves et al. (18)	2020	Prospective
15.	Christison-Lagay et al. (19)	2020	Review
16.	Stack et al. (20)	2021	Guide
17.	Kao et al. (21)	2021	Review
18.	van Rooijen et al. (22)	2021	Retrospective
19.	Sharma et al. (23)	2021	Review
20.	Bebb et al. (24)	2021	Guide

The medical care should be performed in special pediatric centers with different pediatric specialist – pediatrician, pediatric endocrinologist, pediatric oncologist, pediatric radiologist, high volume surgeons, pediatric ENT specialist, nuclear medicine specialist, psychologist, to be able to reduce the apparition of comorbidities and to improve the quality of life.

The serological tests should include the calcium – phosphorus metabolism, the level of vitamin D, thyroid function (TSH, FT3, FT4, ATPO).

The neck and thyroid ultrasound is the clinical extension of physical examination. All the children with suspicion of thyroid nodules should have neck and thyroid US performed by an experienced doctor in order to identify suspicious elements for malignancy.

FNA should be done by experienced doctors and the cytologic material should be completed with genetic tests.

In the case of cytologic result of Bethesda 5 and genic mutation positive in the BRAF gene, total thyroidectomy is advised.

Preoperative management must include vitamin D and calcium prophylaxis, the completion of presurgical imaging by CT or MRI if it is necessary, an ENT evaluation with flexible fiberoptic laryngoscopy by an experienced pediatric otorhinolaryngologist. A vocal cord palsy suggests a more advanced stage so a more aggressive surgical management should pe considered.

Total thyroidectomy is the surgical treatment of choice for all the cases of pediatric thyroid carcinoma. Some studies suggest a less aggressive approach for selected cases discussed in medical committees. Also for nonaggressive microcarcinoma lobectomy could be considered.

The intraoperative laryngeal nerve monitoring is recommended in order to reduce the risk of recurrent laryngeal nerve injury.

The I-131 activity is not well established. Further studies are needed in order to determine the appropriate value. The value of 100 MBq/kg of I-131 for treatment of known metastasis is advised.

The postsurgical ENT evaluation is essential to determine any degree of vocal cord impairment which is important for the safety of deglutition.

The follow-up of the patients will be made according to the ATA guideline for a long period of time, with a careful transition to the adult medical services.

A psychological guidance is recommended for all the patients and their parents

DISCUSSIONS

The current therapeutical approach of the children with thyroid nodules and DTC in Romania

There is no national guideline for the management of the children with thyroid nodules or DTC. They are treated after the local, hospital protocols and the therapeutical approach may be different from the international recommendations, as we can see from our previous studies (1,3). In many cases, the child is addressed to the pediatric oncologist after several month from the beginning of the symptoms, the diagnostic approach is different in many hospitals, fine needle aspiration is rarely made in children, the surgical interventions are performed by different surgeons so the rate of the apparition of the complications after the surgery is high and there are unsteady management of the pre- ant postsurgical evaluation. In this way, the quality of life of these children is influenced.

Diagnostic suspicion

The first steps in the management of a child with the suspicion of thyroid nodules are the medical history and the careful physical examination. The practitioner should identify the risk factors of the apparition of the thyroid cancer: medical syndromes associates with thyroid cancer (multiple colon polyps, colon cancer, autoimmune thyroiditis, thyroid nodules, familial adenomatous polyposis, PTEN hamartoma tumor syndrome, Carney complex, MEN-1, MEN-2A, MEN-2B, McCune-Albright syndrome, Peutz-Jeghers syndrome, DICER1 syn-

drome, Sipple syndrome, familial papillary thyroid carcinoma/papillary renal neoplasia, familial nonmedullary thyroid carcinoma with oxyphilia, familial nonmedullary thyroid carcinoma, familial multinodular goiter (5,15,20), exposure factors such as medical radiation (computer tomography, radiotherapy – head and neck irradiation, bone marrow transplantation) will be sought (20).

The clinical examination will be focused on difficulty in swallowing and/or breathing, hoarseness, pain at the site of the nodule but a careful full medical examination will be made.

Diagnostic confirmation

Biological testing

The primary biological determinations should include the thyroid stimulating hormone (TSH), free thyroxine, thyroid autoantibodies (ATPO) (5,20). In the recent literature a panel which includes calcium, albumin, phosphorus, magnesium, 25-OH vitamin D and the level for parathyroid hormone is also indicated (20). It is not advise to determine the level of thyroglobulin and antithyroglobulin in the presurgical phase because those are not useful in the differential diagnosis of nodular goiter vs thyroid carcinoma (8). If the clinical suspicion is highly positive for medullary thyroid carcinoma, the level of basal calcitonin can be determined (8).

Ultrasound

The cervical and thyroid ultrasound (US) is the next step, this is considered to be an extension of the physical examination, it can characterize the extent of thyroid pathology and regional adenopathy (12,20). This should be done by experienced practitioners.

The US characteristics of thyroid nodules highly suggestive of malignancy are hypoechogenicity, invasive or irregular margins, microcalcifications, increased intranodular blood flow, nodules with taller-than-wide morphology, abnormal cervical lymph nodes (5,8,11,25). A special attention should be made for the diffuse sclerosing variant PTC (DSVPTC) which is characterized by diffuse thyroidal enlargement with hypervascularization and abundant microcalcifications which can give the ”snowstorm” sonographic aspect (5,19,20). The dimension of the thyroid nodule is not a criteria for malignancy as it is in adults (5).

Fine needle aspiration and genic studies

The recent studies recommend the introduction of the genetic analysis of the FNA cytology. According to those findings, the therapeutical approach could be changed. Lebbink et al (7) recommends total thyroidectomy in the case of cytologic result of Bethesda 5 and genic mutation positive in the BRAF gene. BRAF mutation corelates strongly with PTC and with more aggressive tumors (13). Other genic alterations should be noted as well, like RET/PTC or NTRK fusion.

Genic and molecular test made on the Bethesda 3 and 4 cytology will also help to determine the malignancy criteria of the nodule without repeating the FNA, which is an invasive procedure (20). The absence of BRAF mutation doesn't exclude the presence of PTC so, if the FNA result is highly suggestive for malignancy, diagnostic hemithyroidectomy must be performed (5,7).

Preoperative management

The careful US evaluation of the entirely cervical region is highly important in order to evaluate the nodular extension of the TC. If it is necessary, computer tomography (CT) without iodine contrast and also the cervical and thoracic magnetic resonance imaging (MRI) can be made if there are signs of important local invasion (vocal cord paralysis, large mobile of fixed thyroid masses, large metastatic adenopathy, local invasion of the esophagus or of the trachea) (5,7).

For the prevention of hypocalcemia after total thyroidectomy, there is no international consensus of the administration of the calcium and vitamin D prophylaxis (17) but there are studies which recommends the beginning of prophylaxis (7,18). In the 2021 American consensus it is mention that three days prior surgery, should be administered 0.5 μg calcitriol twice a day with or without calcium supplements (20).

Further studies are needed in order to decide the specific protocol especially that total thyroidectomy is an important risk factor in the apparition of severe hypocalcemia (21). We should take into consideration that an important number of adolescents in Romania are with low vitamin D level (26).

Preoperative laryngeal assessment is important, a disfunction of vocal cords could be a sign of local invasion, so the surgical management will be more aggressive (20). This evaluation should be done with flexible fiberoptic laryngoscopy by an experienced pediatric otorhinolaryngologist (20).

The treatment of DTC

The surgical treatment

Total thyroidectomy (TT) is the treatment of choice in pediatric DTC based on ATA guideline published in 2015 (5). A small thyroid fragment (1-2% of the thyroid gland) could be kept in place in order to reduce the comorbidities - hypoparathyroidism or recurrent laryngeal nerve injury (5).

Concerning the fact that TT is invalidating, the child being forced to take thyroid hormone substitution for life, the medical communities are trying to adjust this recommendation in the benefit of the patient.

A study published in 2016 (9) propose thyroid lobectomy or subtotal thyroidectomy for the pa-

tients from the ATA low risk groups (the absence of extrathyroidal extension, N0/Nx or microscopic N1a, the absence of distant metastases) and very low risk group as Toronto classification (without marginal invasion, the absence of ipsilateral multifocality, no nodal invasion, no risk factors, N0/Nx).

Lebbink et al. (7) propose the discussion of selected cases (tumoral foci < 1 cm, limited to the thyroid gland, no nodal invasion) in medical committees in order to decide if a lobectomy or a hemithyroidectomy is a better surgical option.

This is an important step in the management of pediatric thyroid microcarcinoma which could be treated less aggressive.

The recent American guideline recommend intraoperative laryngeal nerve monitoring in order to reduce the risk of recurrent laryngeal nerve injury (20).

Compartmental neck dissection is required only for biopsy-proven malignant nodal diseases (N1a or N1b), elective neck dissection isn't recommended (20).

Central neck dissection will be made only in selected cases: gross extrathyroidal extension or malignant cytology after FNA of a central adenopathy. For the rest of the cases, the dissection of the central compartment will be made only after a careful selection cases, based on the surgeon experience (5,7,20).

Postsurgical evaluation

The TSH suppression therapy has the double role of hormonal substitution but also of the inhibition of tumoral growth cells. Levothyroxine is the treatment of choice, it will be started 24 h after the surgical intervention at 1.5-2 μg/kg/day (20). The thyroid hormonal level will be checked after 4-6 weeks or after every dose adjustment. At 6 weeks after surgery the thyroglobulin and antithyroglobulin level will be measured (20).

The postsurgical ENT evaluation is essential to determine any degree of vocal cord impairment which is important for the safety of deglutition (20).

All cases will be classified in risk groups (low, intermediate or high) in accordance with ATA recommendation (5).

Radioactive iodine (RAI) therapy

RAI is important to reduce the disease recurrence risk, to eliminate the thyroid residual tissue for a better follow up of the patients based on the thyroglobulin level. Due to increased long-term complications of RAI (pulmonary fibrosis, transient effects on fertility, risk of salivary malignancy), there is an effort of medical community to find the best indication for RAI with minimal I-131 activities.

ATA guideline recommend RAI administration only for the treatment of iodine sensitive nodules who cannot be surgically removed or iodine sensitive distant metastasis (5) but Lebbink et al propose RAI to all surgically treated patients (7). The American guideline (20) recommend a more careful approach, so RAI therapy will be administered in the case of aggressive histology with/without > 5 nodal metastasis. In this case TT will be completed with compartmental neck dissection. All intermediate and high ATA risk group patients will follow RAI because of the high recurrence risk; RAI will be administered to all cases with pulmonary metastasis (20).

The I-131 activity isn't well established, ATA mention a bodyweight approach (1-1.5 mCi/kg; 37-56 MBq/kg) (5) but, in general, the I-131 activity is empirical and in accordance with nuclear medicine service experience with higher activities for the patients with pulmonary or bone metastasis (5,6).

Lebbink et al. (7) recommends a total I-131 activity of 1100 MBq for total resections, T1-T3a tumors, without nodal invasion of distance metastasis.

For distant metastasis, the I-131 activity will be measured according to the bodyweight 100 MBq/kg with maximal activity of 5550 MBq for less radical surgeries (macroscopically tumor in the resection margin on pathology evaluation), with T3b, N1 tumors, or maximal activity of 7400 MBq for T4/M1 tumor. Higher I-131 activities will be discussed in medical committees.

The follow-up of pediatric DTC

Regularly check-ups will be made, with focus on clinical aspects, thyroglobulin evolution and US aspect of cervical aria and with completion of whole-body scan (WBS) aspects for selected cases, according to ATA guideline (5).

A special attention should be made for the children with persistent high Tg level despite negative WBS – TENIS syndrome. In this case PET/CT F18-FDG could help localize the metastatic lesion but there are a few studies in children (5).

According to ESMO guideline (14), complete remission is defined as the absence of clinical, scintigraphy or radiological signs of the disease in association with an undetectable serum Tg after six months from the last administration on 131-I, under TSH stimulation. Incomplete remission (biochemical persistence) is defined as the absence of the radiological or scintigraphy signs of the disease in the presence of positive tumoral markers (Tg, anti-Tg), and the persistent disease as the absence of remission. Recurrent disease is defined as the presence of thyroid cancer (radiological, scintigraphy, or serological) after remission.

Concerning the fact that the diagnosis and the treatment of the pediatric patient with thyroid cancer has a great impact on psychological state of the

children and also of his family, we propose that all the patients should receive phycological counseling.

The follow-up should be done for a very long period, at 10 years evaluation the majority of patients are in complete remission but there are reported cases of the apparition of clinical recurrence after 40 years of a free interval of disease (5,14). For this reason, the adult transition for the follow-up should be carefully done.

All the patients with thyroid cancer should be included in national registries to be able to evaluate the clinical evolution of the cases and to rapidly adapt the diagnostic and therapeutical approach in the benefit of the patient.

CONCLUSIONS

The therapeutical approach of a pediatric patient with thyroid nodules respective differentiated thyroid carcinoma should be done in a multidisciplinary service with special trained doctors in this pediatric pathology. The regional excellence centers with high volume surgeons are needed. The genetic testing of the cytologic result could change the therapeutical approach. A careful pre- and postsurgical evaluation and the prevention therapy will decrease the apparition of comorbidities. The surgical treatment can be less aggressive in selected cases.

Following a special pediatric diagnostic and therapeutic protocol we can decrease the apparition rate of comorbidities and, in this way, the hospitalization time will be lower. Also, the quality of life of these patients will improve.

We need an European guideline for the management of the pediatric thyroid nodules and differentiated thyroid carcinoma.

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