Thyroid Nodules and Carcinoma

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Abbreviations

AD	Autosomal Dominant
AR	Autosomal Recessive
ATA	American Thyroid Association
ATC	Anaplastic/undifferentiated thyroid carcinoma
CEA	Carcinoembrionary Antigen
DTC	Differentiated Thyroid Carcinoma
FNAB	Fine-Needle Aspiration Biopsy
FTC	Follicular Thyroid Carcinoma
MEN	Multiple Endocrine Neoplasia
MTC	Medullary Thyroid Carcinoma
PTC	Papillary Thyroid Carcinoma
RAI	Radioactive Iodine
rhTSH	Recombinant Human TSH
THW	Thyroid Hormone Withdrawal

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15.1 Epidemiology and Classification

Thyroid nodules in children are rare [1]: studies estimated a 1.8 % prevalence in children by palpation [2, 3] and 0.2–5 % by ultrasound [4–6]. With respect to adults, infantile thyroid nodules are much less frequent, but conversely, nodule malignancy rate is estimated to be much higher [7]: up to 25 % of pediatric thyroid nodules are reported as malignant [4, 8] *vs* 5–15 % of adult ones [9]. A recent work on nodules ≥1 cm in the two populations statistically confirmed this data reporting a 22 % cancer prevalence in children and 14 % in adults [10]. Thyroid carcinoma is the commonest endocrine tumor in children [11]: in the U.S.A., the incidence across 1975–2006 was of 1 per million for 5–9-year-old children, 5 per million in 10–14-year-olds, and 18 per million in 15–19-year-olds [1, 11].

Most nodules are non-neoplastic and arise as a result of glandular hyperplasia with or without a cystic component, possibly in the context of goiter. Benign tumors account for approximately 10 % of all nodules [3] and are primarily represented by toxic follicular adenomas. Thyroid carcinomas are classified according to the cell of origin: those arising from follicular epithelium and those arising from parafollicular calcitonin-producing C cells. Other less common types of thyroid tumors may occur, either of thyroid or extrathyroid origin [12, 13]. Thyroid follicle-derived tumors, namely, well-differentiated thyroid carcinoma (DTC), are largely prevalent in childhood (90–95 % of cases), including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC and FTC are further subdivided into several histological variants: follicular, tall cell, diffuse sclerosing, and columnar variants for PTC; Hürthle cell, clear cell, and insular variants for FTC [11]. Calcitonin-producing cell-derived tumors and medullary thyroid carcinomas (MTC) are much rarer (5–10 % of thyroid carcinomas). Anaplastic/undifferentiated carcinomas (ATC) are exceptional in childhood and arise from the follicular cells of the thyroid gland but do not retain the biological features of the original cells.

PTC is often multicentric (about 40 % of childhood cases), whereas FTC is mostly sporadic and encapsulated. PTC disseminates primarily through the lymphatic system to pretracheal lymph nodes, but distant metastases, most commonly to lungs, are detected in about 20–30 % children *vs*. 2 % adults [14], while FTC metastasizes through the bloodstream to the lungs and liver and MTC to cervical lymph nodes. Both DTCs have usually a good prognosis with a survival rate of >95 % [15]. The behavior of MTC is usually more aggressive than that of DTC. ATC is considered one of the most aggressive cancers in humans with an overall survival <6 months since diagnosis. Of note, it may arise de novo or from a new mutation (usually in p53) in a preexisting DTC.

Although differentiated thyroid cancer is usually slowly growing, a prompt diagnosis and accurate multistep workup are recommended in children, because greater tumor size, distant spread, and greater atypia are factors associated with a worse prognosis and increased mortality [4]. Of note, because of their rarity, almost all the reports on thyroid nodules and cancer in pediatrics are retrospective, therefore data and guidelines should be interpreted critically and cautiously.

15.2 Causes, Predisposing Factors, and Associated Diseases

Thyroid nodular disease refers to a heterogeneous group of clinical entities encompassing isolated thyroid nodules, syndromic diseases with thyroidal involvement, multinodular goiters, nodules in the context of autoimmune thyroid disease, and thyroid incidentalomas discovered following thyroid or neck ultrasound for familiarity or other conditions [4].

Infrequently, cases of malignant thyroid nodules are found in patients with congenital hypothyroidism due to both dyshormonogenesis or dysgenesis and thyroglossal duct cysts [4]. Recent evidence suggests that genes encoding proteins involved in thyroid hormone synthesis mutated in congenital hypothyroidism may be convincing candidates for contributing to inheritable forms of goiter and be involved in nodule development [16]. Interestingly, the prevalence of thyroid nodules in infants with congenital hypothyroidism has been recently estimated at 4.2 %, with none malignant [17].

As concerns the relationship between thyroid autoimmunity and cancer, which is a matter of some controversy [18–20], few studies evaluated the topic in the pediatric context. In a recent series of children with autoimmune thyroiditis, 9.6 % had nodules ≥1 cm, and thyroid cancer was diagnosed in one out of three of such cases [21]. This estimate, closely paralleling that of patients without thyroiditis, questions whether autoimmunity itself represents a risk factor for cancer. Moreover, this observation implies that nodules ≥1 cm should be investigated notwithstanding an underlying thyroid benign disease.

TSH signaling *via* TSH-cAMP intrathyroidal pathway has a well-known growth-promoting effect on follicular cells and may hypothetically lead to cancer growth; however, direct evidence linking its elevation with thyroid follicular cells' malignant transformation is lacking as yet. On the other hand, since Boelaert et al. [22] found that mild serum TSH elevations can be employed as a predictor of PTC, many studies in adults [23] replicated their results. Also, recent studies in children [24, 25] confirmed this relationship, which appears to be even stronger than that found in adults: most cases with PTC have serum TSH in the upper normal range (i.e., >2.6 mU/l) or mildly elevated (4.4–10 mU/l). Therefore, serum TSH in children with thyroid nodules demonstrated very high sensitivity in detecting PTC. In spite of these observations, to date evidence supporting the utility of TSH measurement in cancer prediction in clinical practice is limited, also taking into account observations on the natural course of idiopathic subclinical hypothyroidism in childhood [26].

Ionizing radiations are a well-known risk factor for thyroid cancer, and children are much more sensitive to the their carcinogenic action than adults. Thyroid cancer risk increases parallel to radiation dosages of up to 20, is steady up to 29 Gy, and then decreases for doses >30 Gy, probably because of cell killing and gland fibrosis [27]. A great deal of our knowledge in this field has been achieved from observations on the high incidence of thyroid cancers following the widespread employment of radiotherapy for benign pathologies of the head, neck, and chest in the 50s and 60s [28] and the exposure to radioactive isotopes in the fallout from Chernobyl [29, 30]: almost exclusively, PTC developed in such cases [31]. Currently, radiation is mostly employed

in the treatment of childhood malignancies: in the last decade, several observations evidenced that patients who underwent such treatments in childhood are prone to develop both cancerous and noncancerous thyroid diseases subsequently [32]: the radiation-induced risk for thyroid cancer persisted elevated for decades after the primary cancer [33–35]. Some authors advise an ultrasound selective screening of such cases aiming at an early diagnosis: contrarily, other authors do not recommend screening procedures as they may lead to unnecessary and invasive treatment and have not been shown to reduce morbidity or mortality in this population [14]. Recently, data supporting a carcinogenetic role for radiations employed in the diagnostic phase of childhood cancer is accumulating [32]. It has been observed that the increasing incidence of PTC observed in the last decades is paralleled by an increasing exposure to medical radiation; however, at present it is not clear both whether PTC incidence is really increasing (or rather reflects improved detection of sublinical cases) and which portion of PTC cases can be consequent to medical radiation exposure [32].

15.3 Genetics and Inheritance of Thyroid Neoplasms

15.3.1 Medullary Thyroid Cancer Syndromes

Inheritance of thyroid neoplasms of medullary origin is well documented and studied. It accounts for 5 % of all thyroid tumors [36] with the familial form representing 20–25 % of cases. The latter belongs either to pure familial MTC syndrome or to multiple endocrine neoplasia (MEN) type 2 syndromes, when associated with the development of pheochromocytoma. In MEN type 2A, hyperparathyroidism and parathyroid gland tumors are additional features. In MEN type 2B, the association includes mucosal neuromas, intestinal ganglioneuromatosis, and marfanoid habitus [37]. Both MEN syndromes are autosomal dominant and caused by specific gain-of-function mutations in the RET (REarranged during Transfection) proto-oncogene (95 % of cases). Familial MTC is commonly associated with mutations at codons 618 and 620 and with noncysteine mutations at codons 768 and 804 [38, 39]. MEN 2A is caused by germline RET mutations in exons 10 and 11 [39]. On the contrary, in MEN 2B, most mutations occur *de novo*. RET activating mutations lead to constitutive intracellular C-cell signaling, hesitating in hyperplasia, calcitonin hypersecretion, and malignant transformation. Aiming at detecting such cases, serum calcitonin dosage is employed as a screening in thyroid nodules and as a disease marker in patients thyroidectomized for MTC.

15.3.2 Genetics of Pediatric Differentiated Thyroid Cancer of Follicular Origin

Molecular investigations are still limited to the research setting but in the near future will likely contribute to refine the predictability of malignancy on cytology specimens. The mitogen-activated protein kinase (MAPK) signaling pathway is

commonly overactivated in PTC: rearrangements in genes implicated in this pathway have a pivotal role in pediatric cases while adult ones predominately harbor point mutations. Pediatric PTC exhibits an increased rate of various RET/PTC (40–70 %, even more in cases following radiation exposure) or AKAP9–BRAF (11 %) rearrangements leading to the creation of fusion genes with increased signaling activity. Mutations in genes involved in the same PTC pathway may occur in the two oncogenes BRAF and RAS. FTC mostly shows PAX8/PPRAR-γ (peroxisome proliferator-activated receptor-gamma) rearrangements or RAS mutations, while alterations in the PI3K/AKT pathway or CTNNB1 and TP53 mutations have been implicated in the development of poorly differentiated thyroid cancers [40, 41]. Recently, mutations in genes of the thyroid morphogenesis pathway (involved in thyroid gland formation, differentiation, function, and hormone synthesis) have been hypothesized as players in modulating thyroid cancer risk [42].

Interestingly, a certain degree of familial aggregation is observed in histotypes of follicular origin [11, 43], although the genetic background of these conditions is still far from being unraveled. Familiar nonmedullary thyroid cancer represents 3–6 % of all thyroid cancer cases and has an autosomal dominant pattern of inheritance with high penetrance. Its susceptibility genes have not been identified so far, therefore an early genetic screening as for MEN2 syndromes is not feasible; interestingly, no difference between sporadic and familial varieties of nonmedullary cancer is detectable in the type or number of mutations [43]. Besides isolated familial nonmedullary thyroid cancer, two syndromic variants exist: one associated with renal cell carcinoma and one with multinodular goiter.

15.3.3 Syndromic Disorders with Thyroid Nodules and Cancer

In the pediatric context, the variety of inherited syndromic disorders of genetic origin associated with thyroid nodules, goiter and cancer, mostly represented by overgrowth, hamartomatous, or cancer predisposition conditions (Table 15.1). The awareness and attentive scrutiny of such conditions is of crucial importance to detect inheritable disorders, perform appropriate genetic studies and family counseling, and early diagnose various kinds of tumors by appropriate cancer screening strategies.

15.4 Diagnostic Workup

Once a nodule is evidenced, either clinically or echographically, the usual diagnostic includes the collection of patient's history, clinical examination, laboratory tests, thyroid ultrasound, and fine-needle aspiration biopsy (FNAB) [58]. Although it has been pointed out that the diagnostic process employed in children should be the same as that in adults, the peculiarities of the pediatric age should prompt in the clinician a higher degree of suspicion; as Niedziela does [7], we think that the simple application of adult guidelines [9] to the pediatric population should be cautious.

Table 15.1 Syndromes and inheritable conditions with thyroid nodules and cancer

Condition	Additional phenotype	Thyroid involvement	Genetics
Cowden OMIM #158350 [44]	(PTEN – hamartoma tumor syndrome spectrum), benign and malignant tumors of uterus, breast, bowel	Thyroid nodules of follicular type within hyperplastic multinodular goiter (50–67 %); thyroid carcinomas in 5–10 % of cases	Germline inactivating mutations of the PTEN tumor suppressor gene
Bannayan-Riley-Ruvalcaba OMIM #153480 [45, 46]	(PTEN – hamartoma tumor syndrome spectrum), macrocrania, lipomatosis, retarder neuropsychomotor development, scoliosis, seizures, myopathy, joint laxity, hyperpigmented spots of the glades	Thyroid adenomas usually are of follicular type ± autoimmune thyroiditis, multinodular goiter and thyroid carcinomas are encountered in >50 % and 5–10 % of cases	Germline inactivating mutations of the PTEN tumor suppressor gene
Carney complex OMIM #160980 [47, 48]	Skin, breast, and cardiac myxomas, lentiginosis and endocrine glands neoplasias	Goitrous multinodular disease, usually of follicular origin and benign nature; malignant evolution in 10–15 % of cases	AD, gain of function mutations of PKA subunits (PRKACB, PRKAR1A)
Familial adenomatous polyposis OMIM #175100 [47]	Multiple intestinal polyps, initially benign but prone to malignant transformation ± mandibular osteomas, fibromas, and sebaceous cysts in Gardner syndrome	Increased risk of thyroid cancer, especially follicular histotype	AD, APC gene mutations
Peutz-Jeghers syndrome OMIM #175200 [49, 50]	Multiple gastrointestinal hamartomatous polyps, melanocytic macules of the lips and oral mucosa, increased cancer risk	Increased risk of thyroid cancer, especially follicular histotype	AD, STK11 and LKB1 gene mutation
MEN IIA OMIM #171400 [51]	Medullary thyroid cancer, pheochromocytoma, and parathyroid tumors	C-cell hyperplasia and medullary thyroid cancer	Proto-oncogene RET mutations
MEN IIB OMIM #162300 [51]	Medullary thyroid cancer, pheochromocytoma, mucosal neuromas, marfanoid habitus	C-cell hyperplasia and medullary thyroid cancer	Proto-oncogene RET mutations
DICER1 OMIM #138800 [52]	Cancer predisposition (pleuropulmonary blastoma, cystic nephroma, cervix embryonal rhabdomyosarcoma, primitive neuroectodermal tumor, ovarian Sertoli-Leydig cell tumors, and Wilms tumor)	Familial multinodular goiter	AD, DICER1 haploinsufficiency

(continued)

Table 15.1 (continued)

Condition	Additional phenotype	Thyroid involvement	Genetics
McCune-Albright OMIM #174800 [53–55]	Polyostotic fibrous dysplasia, cafe-au-lait skin spots, peripheral precocious puberty, hyperfunction of the thyroid, pituitary or adrenal glands	Multinodular/cystic toxic goiter	Mosaic (somatic) GNAS1 gain-of-function mutations
Birt–Hogg–Dubè OMIM #135150 [56]	Genodermatosis with fibrofolliculomas and increased risk of pulmonary air cysts, spontaneous pneumothorax and renal tumours	Euthyroid usually multiple and benign thyroid nodules in 65 % of cases	AD, FLCN tumour-suppressor gene mutations
Werner [57] OMIM #277700	"Adult progeria" more common in Japan, elderly appearance with thin skin, wrinkles, alopecia, and muscle atrophy, osteoporosis, cataracts, diabetes, peripheral vascular disease, melanoma, soft-tissue sarcoma, osteosarcomas	Increased risk for follicular and anaplastic thyroid carcinoma which is the most common among the malignancies (16 % of cases)	AR, WRN gene mutations (DNA repair gene)

Abbreviations: *AD* autosomal dominant, *AR* autosomal recessive

15.4.1 Family and Patient's History

Attention should be focused on family history of thyroid cancer, especially MTC, and on history of exposure to radiation for previous oncohematological diseases. Medical history should be evaluated with peculiar attention to traits and diseases evocative of familial/syndromic forms of thyroid nodules and cancer. Reports suggest that male sex is associated with a higher malignancy likelihood of thyroid nodules.

15.4.2 Clinical Evaluation

The objective examination aims at detecting (a) associated lymph node enlargement, (b) signs and dysmorphic features in syndromic patients, (c) signs or symptoms of local compression (dysphagia, dysphonia, discomfort, or shortness of breath), or (d) signs or symptoms of hyperthyroidism.

Palpation of hard and firm nodules or lymph nodes and compression/invasion symptoms are considered indicative of malignancy. Lymph nodal enlargement is of the utmost importance in children as strikingly more common than in adult patients [8, 59] and presents in 80 % of cases [60, 61], although not implying a worse prognosis [62].

15.4.3 Laboratory Tests

Laboratory tests include the measurement of serum TSH, free T4 (fT4), calcitonin, and free T3 (fT3) in case of suspected hyperthyroidism. Most thyroid nodules occur without symptoms of thyroid hormone excess or defect: >90 % of cases are euthyroid, 5 % hypothyroid (mostly subclinically with normal fT4 and elevated TSH), and 1–5 % hyperthyroid. Calcitonin is usually employed as a screening marker for MTC [7]. If its dosage is mandatory in patients with suspect MTC, MEN2 syndromes, and cytology suggestive of medullary neoplasm, its systematical use in all cases of thyroid nodules is debated [63], mostly because of its cost-effectiveness. There is general agreement that calcitonin levels >100 pg/ml are almost certainly indicative of medullary thyroid cancer [64]. Difficulties arise in mild elevations (the 10–100 pg/ml "gray zone") as calcitonin serum concentration physiologically increases with age and weight, differs according to sex, and may be high also in other conditions (other neuroendocrine cancer, nephropathy, pancreatitis, hypergastrinemia, thyroid autoimmunity, sepsis). In these cases, in order to increase specificity, a confirmatory repeated dosage or a stimulation test (calcitonin dosage 2, 5, and 15 min after pentagastrin 0.5 μg/Kg i.v. bolus) has been suggested [64].

Some ancillary laboratory tests are performed in some specialized/research centers and mostly in adults, as the dosage of thyroglobulin/calcitonin in the washout fluid of neck lymph nodes: these two markers of follicular cancer and medullary cancer, respectively, are sensitive and specific for the early detection of cervical metastases. The test is mostly employed in cases with small thyroid nodules with enlarged lymph nodes [64–66].

15.4.4 Instrumental Evaluations

Thyroid ultrasound has a key role in the diagnostics of nodules, while I131/Tc99 scintiscan is less extensively employed nowadays with respect to some decades ago. On the other hand, novel techniques, like elastography, are progressively introduced in clinical practice. The employment of other imaging techniques like computer tomography and nuclear magnetic resonance is limited to exceptional cases and to define disease extension or characterize masses of unclear origin.

15.4.4.1 Thyroid Ultrasound

Given its advantages, thyroid ultrasound represents the cardinal imaging tool in the diagnostic workup and management of thyroid nodules. The disadvantage of this method is in its being operator dependent. Thyroid ultrasound is fundamental in assessing the number, size, and characteristics of the nodule; in guiding FNAB and in monitoring lymph nodes and remnant thyroid tissue of thyroidectomized patients. In the diagnostic workup, ultrasound allows a first-line screening for selecting nodules with suspicious characteristics and deserving further evaluations. Color Doppler sonography represents a strong asset in providing more detailed characteristics of the nodule and refining the diagnostic decision. Various features are

associated with malignancy: hypoechogenicity, undefined margins, microcalcifications, high intranodular vascular flow at color Doppler [4], and lymph nodal modifications (longitudinal-to-transversal axes ratio <1.5, rounded profile with absence of the ilium, thickened or eccentric cortical, nonhomogeneous pattern, and increased vascular flow [3, 4, 8, 9, 67]), and an increase in nodule size during the follow-up, especially if under levothyroxine therapy [21]. Conversely, cystic pattern, multinodular goiter, regular margins, and peripheral increased vascularization are considered suggestive of benignity.

15.4.4.2 Elastography

Elastography is a novel technology for soft tissue elasticity mapping recently added in clinical practice for the noninvasive prediction of thyroid nodules' malignancy. The analysis of the speed of elastic waves passing through tissues estimates solid nodules' stiffness, which is increased in malignant nodules as they are firmer than the surrounding tissue [68]. In the last years, a number of studies have evaluated its use in this field with encouraging results [69]. It is a promising tool able to increase ultrasound performance in selecting nodules with higher malignancy likelihood and reducing unnecessary FNAB (of up to 60 %) [70–72]. The most relevant drawback of elastography is in its employment in cases with cystic or calcific nodules. Authors agree that further research is needed on its application in the differential diagnosis of indeterminate lesions and in other thyroidal diseases. Specific data on pediatric populations are not available as yet, although in our experience it appears reliable as in adulthood.

15.4.4.3 Scintigraphy

Scintiscan with Tc99 is much less used nowadays with respect to some decades ago. Current indications to perform a scintiscan include almost only benign tumors with overt/subclinical hyperthyroidism, namely, toxic adenoma. Scintiscan is used to confirm the diagnosis: in toxic adenoma, it usually displays a "hot" pattern with silencing of the remnant thyroid tissue. In these cases, FNAB typically does not offer much information [3, 8, 9] and is considered superfluous as surgery is needed in any case. At histological evaluation, PTC can been found in 1–5 % of these nodules [4].

15.4.4.4 Fine-Needle Aspiration Biopsy (FNAB)

FNAB is the most reliable test for nodule diagnosis and is recognized as the cornerstone and gold standard for the evaluation of solitary thyroid nodules. Data on pediatric cases [3, 21, 73, 74, 60, 75] are consistent with those on adults [76] and estimate its diagnostic accuracy as ranging from 75 to 95 %. As a consequence, in the last decades, FNAB has imposed as the gold standard also in pediatric thyroid nodules, demonstrating the highest sensitivity, specificity, and accuracy among other diagnostic investigations [60]. There is general agreement on performing FNAB in euthyroid and hypothyroid patients with palpable nodules and those with nodule diameters ≥1 cm and with sonographic features indicative of malignancy. However, the indications to perform FNAB in children are mostly inferred from adult

guidelines [9]; the increasing data on pediatric thyroid nodules suggest caution as in childhood clinical indications may be different and diagnostic threshold triggering further investigation lower. For nodules <1 cm, FNAB should be considered in selected cases with multiple clues pointing to a malignant lesion [8, 21, 77]: the diagnostic approach should be particularly aggressive in the presence of risk factors like radiation for malignancies of the head, neck, and thorax or family history of thyroid cancer. Besides nodule size, great importance for FNAB indications is represented by the variety of abovementioned anamnestic, clinical, laboratory, and echographic prognostic factors employed in clinical practice to assess malignancy likelihood. It is worth mentioning that multinodular thyroid diseases carry a malignancy risk comparable to that of solitary nodules [3, 63, 78]: clearly, in such cases, all suspect nodules should undergo FNAB.

In spite of high diagnostic accuracy, since a few years ago in up to 20 % of thyroid nodules, FNAB cannot provide diagnostic indications: the large part of results of uncertain interpretation were defined as "follicular lesion of undetermined significance" or commonly referred to as having an "indeterminate cytology" [79]. Major steps toward the standardization of the terminology employed and classification of cytology were reached in 2007 and 2008. In 2007, the British Thyroid Association and the Italian Society of Pathology and Cytology (SIAPEC-IAP) [80, 81] introduced a new classification. In 2008, the Bethesda system for reporting thyroid FNAB specimens [82] recommended that each report begin with one of six general diagnostic categories: I. Nondiagnostic or Unsatisfactory, II. Benign, III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance, IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm, specifying if Hürthle cell (oncocytic) type, V. Suspicious for Malignancy, VI. Malignant [80, 81]. The result of this novel classification system based on cytoarchitectural patterns was a reduction of superfluous and untimely thyroidectomies.

With the intent to better define malignancy risk of uncertain cytology, several molecular and histochemical markers on cytological smear have been studied in adults [83, 84]. Among them, telomerase [85], galectin-3 [86], CD44v6 [87], and HBME1 [88] alone or variously combined are considered to be more reliable in discriminating malignant cases. Obviously, calcitonin also is a reliable marker of medullary carcinoma. However, the main limitation of this approach is that none of these markers completely fulfill the diagnostic needs, but rather a complete panel of these markers should be employed in a reasoned diagnostic process.

One last critical aspect is in which cases FNAB should be repeated: this aspect should take into consideration that PTC is commonly slow growing with an indolent course even after local and pulmonary metastatization. Studies report that PTC occurs in 1.3 % of patients with a previous benign FNAB repeated yearly [89]. We suggest to monitor clinically and echographically nodules on a 6–12 months basis (based on the initial malignancy likelihood assessment) and repeat FNAB according to change in the clinical and imaging picture. Obviously, in case of multinodular goiter, all suspect nodules should undergo FNAB evaluation.

15.5 Management and Treatment of Benign Thyroid Nodules

Management and treatment guidelines in children with benign nodules are scanty. Surgical intervention, usually hemithyroidectomy, is required to resolve the hyperthyroid state of toxic adenoma [3, 28]. Several options are available in other cytologically benign nodules: in asymptomatic cases, a conservative approach is largely employed, consisting in observation with yearly recheck with or without (sub)suppressive medical treatment with levothyroxine [90, 91] aiming at reducing TSH and inducing nodule shrinkage. When nodules are growing or responsible for symptoms of local compression, (hemi)thyroidectomy and radioiodine thyroid ablation remain the current standard. Recently, several minimally invasive techniques have been introduced to avoid the so far employed surgical/radiotherapy approach: percutaneous ethanol injection therapy is mostly employed in the treatment of prevalently cystic nodules; percutaneous thermal ablation by radiofrequency or laser or microwaves or high-intensity focused ultrasound is employed in highly specialized centers [92, 93]. Further data are needed to assess indications, limitations, and safety of these procedures compared to the standard ones in both adults and children.

15.6 Treatment of Thyroid Carcinoma

15.6.1 Surgery of DTC

Guidelines and randomized trials specific for children have not been designed because of the uncommon occurrence of this disease. Although surgery is the primary therapy for pediatric patients with DTC, there is continuing controversy regarding the optimal surgical option (total thyroidectomy, near-total thyroidectomy, subtotal thyroidectomy, or lobectomy) as well as the role of prophylactic central neck dissection. Currently, total or near-total thyroidectomy in pediatric patients with DTC is considered the best approach by most surgeons and according to the American Thyroid Association (ATA) guidelines [9, 16]. Lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal PTC. The facilitation of radioiodine treatment and imaging and the use of serum thyroglobulin as a tumor marker for recurrent/residual disease [94] are considered other practical advantages of extensive surgery. A primary procedure with less than total thyroidectomy has been demonstrated to significantly increase the need for repeating surgery [95]. Moreover, tumor size should not be considered as a determinant for the type of surgery in children [14]. Although TNM scoring system for differentiated thyroid cancer includes age because of its strong prognostic, it is commonly considered to be imperfect in childhood when the risk of recurrence is high [96].

Since lymph node involvement at the diagnosis is common [8, 59], central neck dissection has been recommended, and modified neck dissection should be performed for clinically apparent and biopsy-proven lateral neck disease. Prophylactic lateral neck dissections are not recommended [94]. On the other hand, complications

of total thyroidectomy and potential harms of the central compartment dissection such as hypoparathyroidism and injury to the recurrent laryngeal nerve should also be considered. Although these risks are minimized when surgery is performed by an experienced endocrine or pediatric surgeon, a high prevalence of hypoparathyroidism and both temporary and permanent recurrent laryngeal nerve palsy has to be taken into account. Recently, age (<16 years), familial history of thyroid cancer, preoperative gross neck lymph node diffusion, tumor diameter, and extrathyroidal invasion were identified as risk factors for disease-free survival in children with PTC. Preoperative gross lymph node metastasis and distant metastasis at diagnosis were identified as relevant factors for cause-specific survival, suggesting that total thyroidectomy alone could not be considered sufficient in all childhood patients [97].

15.6.2 Surgery of MTC

In general, treatment of MTC consists in total thyroidectomy for both sporadic and hereditary forms associated with prophylactic central lymph node dissection, whereas lateral neck dissection is needed for patients with positive preoperative imaging. When distant metastatic disease is detected at diagnosis, less aggressive surgery might be appropriate in order to preserve speech and prevent morbidity. The improved understanding of molecular basis of MEN2 syndromes and isolated MTC allows to define risk groups for cancer development and recommended timing schedule for prophylactic treatment. The latter is the standard of care in pediatrics, since patients with hereditary forms of MTC can develop metastases before the age of 5 [38, 97–99]. Prophylactic thyroidectomy in MEN is recommended within 1 year of age for patients with 883, 918 RET codon mutations, before 5 years for cases with mutations in codons 611, 618, 620, 634, and before 10 years for those with mutations in codons 609, 630, 768, 790, 791, 804, 891.

15.6.3 Radioiodine Therapy

Radioactive iodine (RAI or radioiodine 131I) therapy is a mainstay of postsurgical treatment in DTC. 131I has been demonstrated to destroy thyroid tumor cells several decades ago [100]; moreover, a postsurgery 131I uptake by residual thyroid tissue is usually demonstrated. The frequent multifocal disease extension, nodal involvement, and distant metastases in pediatric patients with DTC together with a sodium iodine symporter expression greater than in adult forms, possibly accounting for a more successful treatment [101], are generally considered as factors making RAI a therapeutic challenge. To date, it is generally suggested that most children should be treated with 131I in order to ablate residual disease, reduce the risk of disease recurrence, and positively affect progression-free survival rate, as recently reviewed [14, 94, 95, 101, 102].

In order to obtain 131I uptake by remnant and residual tissue, TSH elevation greater than 30 mU/l is needed. Levothyroxine administration should be discontinued 2–3 weeks in children and 4 weeks in adults before radioiodine

administration ("thyroid hormone withdrawal," THW); alternatively, patients can be treated with 0.7 mcg/kg triiodothyronine for at least 1 month to be discontinued 2 weeks before 131I administration. TSH rise can also be achieved with recombinant human TSH (rhTSH) to be administered on 2 consecutive days. The use of rhTSH is approved in adults; however, it has to be emphasized that, at present, rhTSH use is not approved for children by drug-regulatory agencies in U.S.A. or E.U. Although it has the potential to reduce whole-body radiation exposure associated with 131I therapy and its clinical use has been reported in children with DTC, data showing comparable efficacy to THW are lacking in pediatrics [9, 14, 94, 103].

Main purposes of the use of RAI treatment include therapy of residual microscopic disease, metastatic or unresectable lesions, together with an accurate patient staging by means of 131I whole-body scanning, usually performed within 4–7 days of RAI therapy, for the detection of distant metastases. In addition, the postsurgery ablation of remaining thyroid tissue in the neck ("thyroid remnant ablation") allows the use of thyroglobulin as a tumor marker during the follow-up. There is no specific recommendation for the timing of 131I after total thyroidectomy; however, it is generally done within 3–6 weeks till 3 months after surgery. 131I administration dosage strategies can be summarized in administering fixed activities (eventually based on the patient's weight); dosing based on the administered activity that is as high as safely administrable, recently defined as the lowest safe limit administered activities up to 5 mCi/kg (185 MBq/kg) for treatment of distant metastases and DTC recurrence in children; and applying specific activities for tumor ablation, dosimetry, which is suggested to be mainly considered for individuals with lung metastases [14, 104]. The use of pretherapy scans is limited because of its low impact on the decision to ablate and because of 131I-induced stunning phenomenon, defined as a reduction in uptake of the RAI therapy dose induced by a pretreatment diagnostic activity. On the other hand, since it can be difficult to distinguish residual disease from thyroid remnant at post-therapy whole-body scan and when the extent of the thyroid remnant cannot be accurately ascertained from the surgical report or neck ultrasonography, 123I (1.5–3 mCi) or low-activity 131I (1–3 mCi) pretherapy scans may provide additional information [9, 14] in order to distinguish residual disease from thyroid remnant and then to plan more adequate therapeutic strategies.

Risks associated with RAI treatment include second primary malignancies, reproductive risks, pulmonary fibrosis, gastritis, and sialoadenitis. Evidence suggests that RAI does not increase the risk of second neoplasms in children nor long-term effect on female fertility. Given the possibility of cumulative gonadal damage in males, sperm banking should be considered before therapy [14].

15.6.4 Levothyroxine Therapy

Levothyroxine therapy is a fundamental part of the treatment of thyroid carcinoma; it is well recognized that TSH suppression can reduce rates of recurrence for DTC, whereas there is no role for it in MTC. The ATA task force recommends in low-risk

adult DTC patients a plasmatic TSH target of 0.1–0.5 mU/l and a more aggressive suppression for high- and intermediate-risk patients, with TSH <0.1 mU/l. Benefits from TSH suppression have been widely reported in adults in terms of decreased progression and recurrence rates and cancer-related mortality. For adults, recommendations state that suppression should be maintained for 5–10 years [9]. On the other hand, specific evidence of benefits from TSH suppression in pediatrics is lacking to date. Moreover, compared with adults, TSH suppression presents peculiar difficulties: actually, in children higher doses of levothyroxine per kg are needed to achieve a complete suppression, and a condition of subclinical iatrogenic hyperthyroidism may impact growth, behavior, and learning ability. Recently, a proposed scheme for children is to initially suppress TSH levels <0.1 mU/l and then allow a TSH rise to 0.5 mU/l once remission is obtained [14, 94].

15.6.5 Other Therapies

External beam radiation does not have a clear role in the treatment of DTC, its use being beneficial as a palliative measure in advanced disease stages. Chemotherapy is not considered in the initial therapy of DTC; newer agents are being evaluated for patients with metastatic or recurrent disease. Treatment of anaplastic thyroid cancer, the most aggressive histotype and one of the most aggressive cancers in humans, has not been standardized as yet and appears largely inefficient; surgery, chemotherapy, radiotherapy alone or in combination are used with almost no impact on survival rate. Most used cytotoxic agents include doxorubicin, cisplatin, and bleomycin.

In advanced MTC, chemotherapy has not shown significant clinical benefit. Radiation may be used in the presence of local invasion or in the setting of bone (together with bisphosphonates to control symptoms) or central nervous system metastasis although there are no clear data indicating an effect on long-term survival. Novel drugs of the family of RET kinase inhibitors may have a relevant clinical impact in the near future: among these compounds, the Food and Drug Administration recently approved vandetanib, which has been shown to lengthen progression-free survival. Prognosis of MTC, however, has been most closely related to the stage of disease at presentation and to the extent of surgery [94, 105].

15.7 Follow-up Recommendations

ATA management guidelines for DTC are considered appropriate to children. Notable exceptions have been considered with regard to timing of repeated ultrasound evaluation in indeterminate FNAB cytology, tumor size as a determinant for the type of surgery, central compartment neck dissection for some lesions, need for RAI administration, TSH suppression, and thyroglobulin measurements as primary tool for assessing treatment effectiveness or recurrence.

15.7.1 Differentiated Thyroid Cancer

Lifelong follow-up of DTC patients is extremely important as tumor recurrences have been demonstrated to occur decades later [14, 94, 101, 102]. Regular assessment of circulating thyroid hormone levels, ultrasonography of the neck, measurement of thyroglobulin, and whole-body 131I scans are employed in the follow-up care. TSH, fT4, and fT3 levels' assessment is indicated every 6 months and 1–2 months after every levothyroxine dosage changes. Thyroglobulin measurement is the mainstay of DTC follow-up in the absence of antithyroglobulin antibodies, which is a confounding factor in its measurement. The disease-free state has been reached when thyroglobulin levels after rhTSH challenge or thyroid hormone withdrawal are undetectable. Levels in the 0.1–10 mcg/l range may indicate residual disease, addressing to perform follow-up neck ultrasonography. In case of thyroglobulin levels >10 mcg/l, neck imaging is indicated: if gross cervical disease is detected, reoperation is needed, whereas 131I treatment with 100–150 mCi (3.7–5.5 GBq) is sufficient. A regular 6 months interval basal thyroglobulin measurement by second-generation assays has been recently shown to correlate with stimulated thyroglobulin levels. On levothyroxine treatment, thyroglobulin values <0.1 mcg/l correlate with a stimulated level <2.0 mcg/l; in case of basal thyroglobulin rise, disease relapse needs to be considered [14, 15, 94, 101–103, 105, 106].

Neck ultrasonography should be performed every 6 months in order to detect residual thyroid tissue and lymph nodes. Attention is needed in order to assess whether lymph nodes represent potential metastatic foci. FNAB of lymph nodes may be indicated for persistent or enlarging lymph nodes, together with thyroglobulin measurement in lymph node aspirates.

Diagnostic whole-body scintigraphy is performed using 123I or 131I 2–5 mCi (0.074–0.185 GBq) generally at 6–12 months after diagnosis. In patients with detectable antithyroglobulin antibodies, scintigraphy is useful in identifying potential residual disease. On the contrary, its employment in patients with no metastases is debated: recent data show that three consecutive negative post-treatment scintiscans are strongly predictive for a low risk of recurrence, while other data suggest that it adds only a modest information to the combination of thyroglobulin assessment and ultrasonography [14, 102, 107, 108].

15.7.2 Medullary Thyroid Cancer

Post surgery, monitoring of calcitonin levels is the backbone of MTC follow-up. After surgery, serum calcitonin levels normalize (undetectable) in 60–90 % of cases in patients with no lymph node involvement but in only 20 % of those with lymph node diffusion. Carcinoembrionary antigen (CEA) levels also have a predictive role after surgery. Calcitonin and CEA doubling times should be used to predict outcome and to help plan long-term follow-up of patients with MTC. The first level should be obtained 6 weeks to 4 months after surgery; persistent marker elevation indicates residual disease. There is no agreement on the imaging techniques to be

employed in the follow-up of MTC, and the choice should be driven by disease location. Distant metastases predominantly occur in patients with a large-sized tumor, extrathyroidal growth, and lymph node involvement [94, 99, 105].

15.8 Prognosis

Usually, even in the presence of metastatic disease, the prognosis of pediatric thyroid cancer is reported to be good: in spite of being usually more aggressive at the time of initial evaluation than adult ones, reports show that pediatric form is ultimately less lethal [109]. In the review by Reiners et al. [110], mortality is reported to be usually low, in the range of 1–2 %, and recurrence rates approximate 30 % (7–58 %). Long-term follow-up data show 30-year survival rates for children of 90–99 % [14, 109–111]: this likely reflects that most pediatric patients have well-differentiated tumor histotypes which mostly respond well to therapy. Data concerning prognosis are still scanty, and collaborative studies are needed to provide more accurate figures.

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