New insights into the management of differentiated thyroid carcinoma in children and adolescents (Review)

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Abstract. Differentiated thyroid carcinoma (DTC) is the most common malignant neoplasm of the endocrine system. In children and adolescents, DTC usually presents as a more aggressive disease than in the adult population, but patients often have a favourable prognosis, even in cases of advanced disease. Nevertheless, certain patients have persistent or recurrent disease leading to increased morbidity. A significant challenge in the management of DTC is identifying the subgroup of patients with a high risk of unfavourable outcomes. Prognostic factors related to the patient, tumour, and stratification systems (Tumor-Node-Metastasis/American Joint Committee on Cancer, American Thyroid Association risk classification and dynamic risk stratification) are used in an attempt to identify the individuals at increased risk. In the present review, the current risk classification systems applied for paediatric thyroid cancer are discussed, highlighting the major differences between paediatric and adult DTC in pathophysiology, clinical presentation and long-term outcomes. In recent years, genetic markers have also been proposed as prognostic factors for children and adolescents with DTC. Advances in the understanding of the molecular profile of paediatric DTC may aid individualized management, potentially improving diagnosis and treatment. This review article aims to critically review and update the current concepts on DTC management in children and adolescents, with an emphasis on clinical presentation, treatment, risk assessment, follow-up and future perspectives.

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1. Introduction

Thyroid cancer is rare in childhood, accounting for 1.5-3.0% of carcinomas in children and adolescents. Nevertheless, it is the most common malignant neoplasms of the endocrine system in this age group (1). Globally, the annual incidence of the disease in children varies between 0.5 and 10.0 cases per 100,000 (2,3). Notably, data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) and a North American population-based study show increases in the incidence in patients <20 years of age, at a 2.0% ratio per year (4,5).

The two most common histological types of thyroid cancer are papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), comprising differentiated thyroid cancers (DTCs). In children and adolescents, DTC is responsible for >95% of thyroid cancers, with PTC accounting for ~90% of cases (6,7). The contribution of other histological types, such as medullary, poorly differentiated or anaplastic thyroid cancer, is minor given their rarity in the paediatric population (8). Medullary carcinoma is most commonly diagnosed in the setting of prophylactic thyroidectomies for carriers of RET mutations in multiple endocrine neoplasia syndromes (9).

DTC is an indolent neoplasm with low morbidity and mortality rates. The prognosis in children and adolescents is excellent, even in cases of advanced disease (6,10,11). A North American population study conducted between 1992 and 2014 found 20-year survival rates of 99.7 and 96.3% for PTC and FTC, respectively, regardless of the disease stage (12). Notwithstanding, a subgroup of patients presents an aggressive clinical course, with increased morbidity and mortality (13-17). Currently, a significant challenge in the management of DTC is identifying patients at high risk of unfavourable outcomes.

In this context, the identification of prognostic factors to improve risk assessment is essential for proper management.

The present article aims to critically review and update the current concepts of DTC management in children and adolescents, with an emphasis on clinical presentation, treatment, risk assessment, follow-up and future perspectives.

2. Clinical presentation and treatment

The most common clinical presentation of DTC is a palpable nodule of the thyroid gland (13). It may also be diagnosed due to cervical adenopathy with or without a detectable thyroid nodule or as an incidental finding on non-thyroid imaging exams (18). Occasionally, however, the diagnosis follows the detection of distant metastases, most frequently in the lungs (19).

PTC usually presents with bilateral (30%) and multicentric (65%) tumours and cervical lymph node metastases (20-23). Haematogenous dissemination may occur in up to 25% of cases but is usually associated with significant metastases to the cervical region (18,20,24). The most common PTC variants are classical, solid, follicular and diffuse sclerosing (25). Conversely, FTC usually presents as a unique tumour and shows increased potential for haematogenous-related metastases to the lungs and bones in the initial presentation (21). In contrast to PTC, cervical lymph node metastases are rare in FTC (13).

DTC in children is a distinct disease from that observed in adults, with particularities in the pathophysiology, clinical presentation and long-term outcomes (10,13). Recently, the American Thyroid Association (ATA), accounting for these differences, published specific guidelines for thyroid nodule and DTC for children (13). DTC clinical presentation in children is usually more extensive than in adults (10,18). Tumour sizes tend to be larger, with earlier involvement of the thyroid capsule and adjacent tissues (26,27). Lymph node involvement is present in 40-90% of children, compared with 20-50% of adults, and the prevalence of distant metastases is 20-30% in children, compared with 2-5% in the adult population (18,28). The most prevalent sites of distant metastases in children are the lungs, bone and central nervous system (21). Notably, the same histological variants, such as the diffuse sclerosing and follicular variants of PTC, are more common in younger children (<10 years old) (29). Children are considerably less likely to die from DTC (≤2% long-term cause-specific mortality) than adults, which is partially explained by the differences in the molecular pathology of the tumour (18,20,21).

The ATA recommendation for initial treatment in paediatric DTC consists of total thyroidectomy, followed by radioactive iodine (RAI) and suppressive therapy with levothyroxine (13). The recommendation of total thyroidectomy is based on the high incidence of multifocal and bilateral disease, as well as an increased risk of recurrence in paediatric patients who undergo subtotal thyroidectomy or lobectomy (18,23). It should be emphasized that the two primary contemporary objectives of DTC management in the paediatric population are to maintain the low specific mortality of the disease and reduce the potential complications of treatment. A critical point in this process is an improved understanding of the clinical characteristics that predict response to these therapies and identify those who will benefit from more aggressive treatment.

Paediatric patients with advanced DTC disease also seem to present a better response to therapy. A systematic review that evaluated 112 paediatric patients with pulmonary metastasis observed a complete or partial response to RAI treatment in 47.3 and 38.3%, respectively (30), contrasting with 44% stable disease in the adult population (31).

The reported rate of disease-free survival at 10 years of follow-up varies in paediatric advanced DTC from 67-70% (21,32). Similar results were found in adults, as shown by two cohorts with 768 and 357 patients with DTC that demonstrated disease-free survival rates of 67.4 and 71.7%, respectively (33,34). However, paediatric patients with persistent disease usually present a more stable course, resulting in a more favourable progression-free survival (21,30).

3. Risk stratification

Due to the low mortality rates, one of the most critical steps in the evaluation of children and adolescents with DTC is risk stratification for persistent/recurrent disease (35). Several prognostic factors, such as age extremes, larger tumours, multicentricity, extrathyroidal extension, lymph node metastasis, vascular invasion and postoperative thyroglobulin (POTg) levels, are well established in the adult population (36). These factors are also used in young patients with DTC. Overall, these characteristics are split into patient (age and sex) and tumour-related factors (histological type, size, multifocality, disease extension, staging, lymph node and distant metastasis and completeness of initial surgery).

Role of individual prognostic factors. Several studies have evaluated the association of patient factors, such as sex and age, and disease outcomes with conflicting results (23,24,32,37-40). Certain studies found an association between younger age and the risk of persistent disease (23,38,40), whereas others have failed to find such an association (24,32,37,39). Males are more likely to have a poorer prognosis based on certain studies (24,39,40); however, other studies did not confirm these findings (23,32,37,38). The majority of studies showed no association between tumour size, histological type or extrathyroidal invasion, with a risk of persistent disease (23,24,37-40), but conflicting results have been reported on multifocality and tumour staging (24,32,37-40). Nevertheless, the majority of studies have shown an association between lymph node and distant metastasis with persistent disease (24,32,37,39). Of note, a study that evaluated prognostic factors in a population of 65 patients with DTC under the age of 20 years showed that lymph node and distant metastases were the only predictors for persistent disease (37). However, Mihailovic *et al* (38) observed different results in a population of 51 patients with DTC of the same age group. They found that diagnosis at a younger age, less radical primary surgery and tumour multifocality were also strong predictors for disease recurrence.

Different risk stratification systems combining several risk factors have been proposed to predict the outcome of patients with DTC. In general, these systems aim to estimate recurrence risk and mortality, guide follow-up and treatment, and ensure effective communication with patients and

Table I. Evaluation of the association between prognostic factors and persistent disease in children and adolescents with differentiated thyroid carcinoma.

Factor	Jarzab *et al*, 2000	Wada *et al*, 2009	Vaisman *et al*, 2011	Mihailovic *et al*, 2014	Verburg *et al*, 2015	Pires *et al*, 2016	Zanella *et al*, 2018
Patient Factors							
Age	Y	N	N	Y	Y	N	N
Sex	N	Y	N	N	Y	Y	N
Tumor Factors							
Size	NE	N	N	N	NE	NE	Y
Multifocality	NE	Y	N	Y	NE	N	N
Histological type	N	N	NE	N	N	N	N
Extrathyroidal invasion	NE	N	NE	NE	NE	N	NE
Tumor staging	NE	Y	NE	N	N	NE	Y
Lymph node metastases	N	Y	Y	N	N	Y	Y
Distant metastases	NE	NE	Y	N	Y	Y	Y
Treatment factors							
Initial surgery	Y	NE	NE	Y	NE	NE	NE
Post-operative factors							
sPOTg	NE	NE	NE	NE	NE	NE	Y
ATA Risk	NE	NE	NE	NE	NE	NE	Y
DRS	NE	NE	NE	NE	NE	NE	Y

Y, yes; N, no; NE, not evaluated; sPOTg, stimulated post-operative thyroglobulin; ATA, American Thyroid Association; DRS, dynamic risk stratification.

diverse professionals while permitting benchmarking (36,41). However, the current systems have limitations, particularly for paediatric patients. Factors affecting disease recurrence/persistence and survival prediction are distinct. Additionally, these tools have poor performance in predicting outcomes for patients in the early stages of disease, considered low risk (primarily stages I and II), which comprise the majority of patients with DTC (26,42). Moreover, they employ only information regarding disease presentation, but do not incorporate response to treatment and have not been validated for several populations, including paediatric patients (41). As illustrated in Table I and discussed below, there is conflicting evidence on the performance of these prognostic factors in children and adolescents (23,24,32,37-40).

TNM/American Joint committee on cancer (TNM/AJCC). The TNM/AJCC staging system is the most commonly used staging system, and is recommended by the ATA DTC paediatric guidelines (13,36). This system is focused on predicting mortality. It includes as variables the age of the patient at diagnosis (stratified around 55 years), the size of the tumour, and the presence of lymph node and distant metastases. Adult patients are classified into four stages, with a progressive decline in survival for stages I, II, III and IV. Due to the age at which patients are stratified, children and adolescents are classified only in stages I and II (with or without distant metastases, respectively), limiting the discriminatory factor in determining the prognosis for this population. Patients classified as TNM/AJCC I have a survival rate close to 100% (43). The primary criticisms of this system are the lack of inclusion of variables known to influence the evolution and prognosis of patients such as, histological type/subtype and treatment-related data, and its inability to predict outcomes other than mortality (such as recurrences and persistent disease). The TNM/AJCC is updated periodically, and the 8th edition is the most recent version (Table II) (44).

ATA risk stratification in children and adolescents with DTC. Since DTC mortality rates in children and adolescents are very low, systems that capture the likelihood of relapse or persistent disease in the long-term follow-up are essential for defining the therapeutic strategies in this population. The ATA risk stratification incorporates a system that addresses the risk of persistent cervical disease and identifies which patients should undergo imaging to assess the presence of distant metastases (13). In this system, the patient is categorized into three levels of risk: Low, intermediate or high (Table III). However, its value is limited since it only considers histopathological data and does not consider the response to therapy.

Dynamic risk stratification (DRS), including the response to therapy in predicting disease outcome. The classification systems based on clinicopathological features use information from the patient's initial assessment for categorization of risk, without changes in this classification over time (13,44). The use of response to initial treatment has been advocated to estimate the risk of recurrence and death (45-50). This new modality risk stratification was termed DRS, based on

Table II[a]. TNM staging of DTC.

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤1 cm in greatest dimension limited to thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, limited to thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension, limited to thyroid
T3a	Tumor >4 cm limited to thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
Nx	Regional lymph nodes cannot be assessed
N0a	One or more cytological or histologically confirmed benign lymph node
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian or upper mediastinal) lymph nodes
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
M0	No distant metastasis
M1	Distant metastasis
Stage	Age <55 years
I	Any T, Any N, M0
II	Any T, Any N, M1

[a]Adapted from Tuttle *et al* (44). T, size; N, lymph node; M, metastasis; DTC, differentiated thyroid carcinoma.

Table III[a]. ATA risk classification in children and adolescents with DTC.

Risk	Definition
Low	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)
Intermediate	Extensive N1a or minimal N1b disease
High	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis

[a]Adapted from Francis *et al* (13). ATA, American Thyroid Association; DTC, differentiated thyroid carcinoma.

the observation that a patient's risk may change over time, according to new data gathered during follow-ups (45). In this system, patients are classified into four categories: Excellent, biochemical incomplete, structural incomplete and indeterminate response (Table IV) (46,47).

The utility of DRS has been shown in several DTC cohorts (46-48). A study by Vaisman *et al* (48) showed that patients with an excellent response after the initial therapy had a risk of only 1.4% for persistent/recurrent disease (48). Conversely, amongst patients with persistent structural disease, only 9% were classified as excellent response, even after several additional therapies.

However, whilst DRS has been validated in the adult DTC population, the assessment of its role in children and adolescent management is still limited (49,50). Indeed, the current ATA guidelines for children with DTC do not suggest the use of DRS for children (13). Lazar *et al* (49) evaluated DRS in a cohort of 54 patients with a median age at diagnosis of 13.9 years and a median follow-up of 8.8 years. They found that patients classified as having an excellent response after the initial treatment presented a favourable prognosis: 82.9% of them remained classified as excellent at follow-up. Conversely, all patients with an incomplete response after the initial therapy remained with persistent disease. Sung *et al* (50) recruited a cohort of 77 paediatric patients with DTC and demonstrated that DRS was useful in predicting disease outcome at follow-up. When compared to the group with an excellent response, the risk of persistent/recurrent disease

Table IV[a]. Dynamic risk stratification.

Response	Definition
Excellent	Nonstimulated Tg level <0.2 ng/ml or stimulated Tg level <1 ng/ml and undetectable TgAc and negative imaging
Biochemical incomplete	Nonstimulated Tg level >1 ng/ml or stimulated Tg level >10 ng/ml or increasing TgAc levels and negative imaging
Structural incomplete	Structural or functional evidence of disease regardless of Tg or TgAc
Indeterminate	Nonspecific findings on imaging studies or faint uptake in thyroid bed on RAI scanning or nonstimulated Tg level 0.2-1 ng/ml or stimulated Tg level 1-10 ng/ml or TgAc levels stable or declining in the absence of structural or functional disease

[a]Adapted from Tuttle *et al* (46). Tg, thyroglobulin; TgAc, anti-thyroglobulin antibodies; RAI, radioactive iodine.

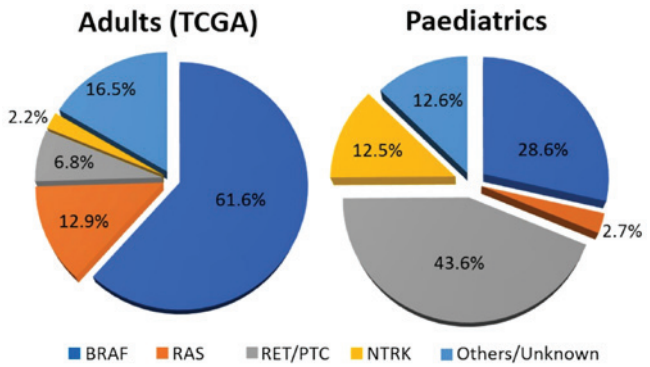

Figure 1. Prevalence of mutations in differentiated thyroid carcinoma in adult and paediatric populations, according to data from The Cancer Genome Atlas and paediatric cases. BRAF, serine/threonine-protein kinase B-Raf; RET/PTC, rearranged during transfection/papillary thyroid cancer; RAS, rat sarcoma viral oncogene homologue; NTRK, neurotrophic tyrosine kinase.

was significantly higher in patients with an indeterminate or incomplete structural response. Recently, our group conducted a multicentre study involving four institutions to evaluate DRS in children and adolescents (32). A total of 66 patients with a diagnosis of DTC before 18 years of age were included. In this study, a multivariate analysis including tumour size, lymph node and distant metastasis, ATA paediatric risk stratification and DRS was performed. The results showed that DRS was the only predictor of persistent/recurrent disease, with odds ratios (confidence intervals) of 35.2 (3.7-762.5), 54.9 (2.5-3,933.1) and 13.9 (1.1-313.7) for indeterminate, biochemically persistent and structurally persistent disease, respectively.

Postoperative staging. For the majority of patients, the initial postoperative evaluation is performed ~3 months after surgery (13). This assessment aims to evaluate persistent locoregional disease and identify patients who may benefit from RAI dosing, such as those with known or suspected distant metastases (13). Low-risk patients should undergo thyroglobulin (Tg) measurement using levothyroxine (Tg-T4) and cervical ultrasound. In turn, in patients at intermediate and high risk, the addition of stimulated Tg (sTg) for improved risk stratification and determination of the need for RAI treatment is useful. Thus, a more individualized and conservative approach to treatment and postoperative staging can reduce unnecessary exposure to RAI in children with no evidence of disease, in whom the risks of routine therapy with RAI probably outweigh the benefits. Additionally, certain patients will require additional imaging techniques, such as neck and chest computed tomography (CT), especially those with detectable Tg-T4. The value of PET/CT has been poorly studied in this population and is not routinely recommended for children (13).

Role of stimulated (s)POTg. Serum Tg levels serve as a marker of recurrent disease, and ultrasensitive serum Tg assays are considered the most sensitive method for the detection of residual thyroid cancer (13,51). Measurement of serum Tg levels is critical for the management of paediatric patients with DTC, both at the initial postoperative staging and during long-term follow-up (13). Therefore, monitoring Tg under levothyroxine therapy (Tg-T4) is the ideal approach to evaluate disease recurrence or progression (13). Interestingly, the Tg levels may be higher in children than in adults with a similar extent of disease (52).

The role of sPOTg as a prognostic factor for DTC in the paediatric population has been recently addressed by several studies. The first study included 32 children and adolescents diagnosed with DTC <18 years old and found that the ideal cut-off value for the prediction of excellent response was 31.5 ng/ml, with a sensitivity and specificity of 100% (53). Similar results were observed in a larger sample of 66 young patients: A cut-off of 37.8 ng/ml showed 81% sensitivity and 100% specificity (32). More recently, a Chinese study with 118 paediatric patients (<20 years old) evaluated the prognostic factor of pre-ablation sPOTg and found that the ideal cut-off to predict disease-free status was 17.8 ng/ml, with a negative predictive value of 96.8% (54).

Anti-thyroglobulin antibodies (TgAc). TgAc are present in ~25% of patients with DTC, and their positivity may determine laboratory interference with Tg measurement (55). As the concentrations of TgAc respond to changes in circulating Tg antigen levels and thus indirectly represent changes in thyroid tissue mass, TgAc levels may serve as a surrogate tumour marker for DTC (13,55). As a result, it is recommended to evaluate TgAc levels in all patients with DTC during their follow-up (56).

Table V. Studies evaluating DTC pediatric mutations, prevalence and outcomes.

Author, year	Country	N	Mutation, %				Outcome
			RAS	RET/PTC	BRAF	NTRK	
Nikiforov *et al*, 1997	USA	38[a]/23	-	77[a]/65	-	-	NE
Fenton *et al*, 1999	USA	31	6.5	-	-	-	NA
Fenton *et al*, 2000	USA	33	-	45	-	-	NA
Kumagai *et al*, 2004	Japan	15[a]/31	0[a]/0	15[a]/31	0[a]/3.2	-	NA
Penko *et al*, 2005	USA	14	0	58	0	-	NE
Nikiforova *et al*, 2005	Ukraine	34	-	71[a]	0[a]	-	NE
Rosenbaum *et al*, 2005	USA	20	-	-	20	-	NA
Sassolas *et al*, 2012	France	27	3.7	29.6	7.4	-	NA
Ricarte-Filho *et al*, 2013	Sweden	26[a]/27	0[a]/7.4	57.6[a]/25.9	0[a]/25.9	11.5[a]/7,4	NE
Henke *et al*, 2014	USA	27	-	-	63	-	NA
Givens *et al*, 2014	USA	19	-	-	36.8	-	NA
Prasad *et al*, 2016	USA	27	0	22	48	26	NTRK-disease extension; aggressive histology
Alzahrani *et al*, 2016	Saudi Arabia	53	-	-	22.6	-	Persistent/recurrent disease
Nikita *et al*, 2016	USA	28	3.6	21.4	32.1	-	BRAF-young patients
Onder *et al*, 2016	Turkey	50	-	-	30	-	Local Recurrence/DFS
Gertz *et al*, 2016	USA	13	0	15	31	-	NA
Ballester *et al*, 2016	USA	25	0	24	40	3.7	NE
Picarsic *et al*, 2016	USA	18	16.5	16.6	16.6	22.6	NTRK-aggressive histology
Cordioli *et al*, 2017	Brazil	35	0	37	9	9	RET-size; multifocality BRAF-size
Geng *et al*, 2017	China	48	-	-	35.4	-	Age <10 years; multifocality; disease extension
Poyrazoglu *et al*, 2017	Turkey	56	-	-	25	-	NA
Hardee *et al*, 2017	USA	50	-	-	48	-	NA
Alzahrani *et al*, 2017	Saudi Arabia	79	2.5	-	26.4	-	NA
Wasserman *et al*, 2018	Canada	30	-	23	16	-	NE

[a]Radiation exposure patients. DTC, differentiated thyroid carcinoma; N, number; USA, United States of America; NE, not evaluated; NA, not associated; DFS, disease free survival.

Most studies in adult populations have reported that recurrence, persistence, or a rising trend in postoperative TgAc concentrations are significant risk factors for persistent or recurrent disease (57). However, it is not known whether a positive TgAc value correlates with disease extension/invasiveness or prognosis (58). A decline in TgAc levels suggests a decreasing disease burden, considering an average of 3 years to eliminate TgAc after cure of DTC (59). A significant increase in TgAc may indicate disease progression, and this should be assessed in more detail. Similar to Tg measurements, the trend in TgAc concentrations is more relevant for disease detection than a single determination (58).

4. Perspectives: Precision medicine

Several genetic markers have been proposed as prognostic factors for children and adolescents with PTC (60,61). These advances in the molecular profile of paediatric DTC may help with individualized management, potentially improving diagnosis and treatment (62,63).

Genetic alterations in effectors of the mitogen-activated protein kinase signalling pathway (MAPK) are the most well associated with the development and aggressiveness of DTC (63). The intracellular MAPK signalling pathway serves a central role in cell growth, division, proliferation, differentiation and apoptosis. Data from The Cancer Genome Atlas Research showed that the most frequent genes involved in DTC pathogenesis were, in descending order, BRAF, RAS, RET/PTC and neurotrophic tyrosine kinase type (NTRK) (Fig. 1) (64). Nevertheless, it should be noted that the study included nearly 500 patients with DTC, but only nine were under the age of 20 at diagnosis. The results from small cohorts of children and adolescents show that the prevalence

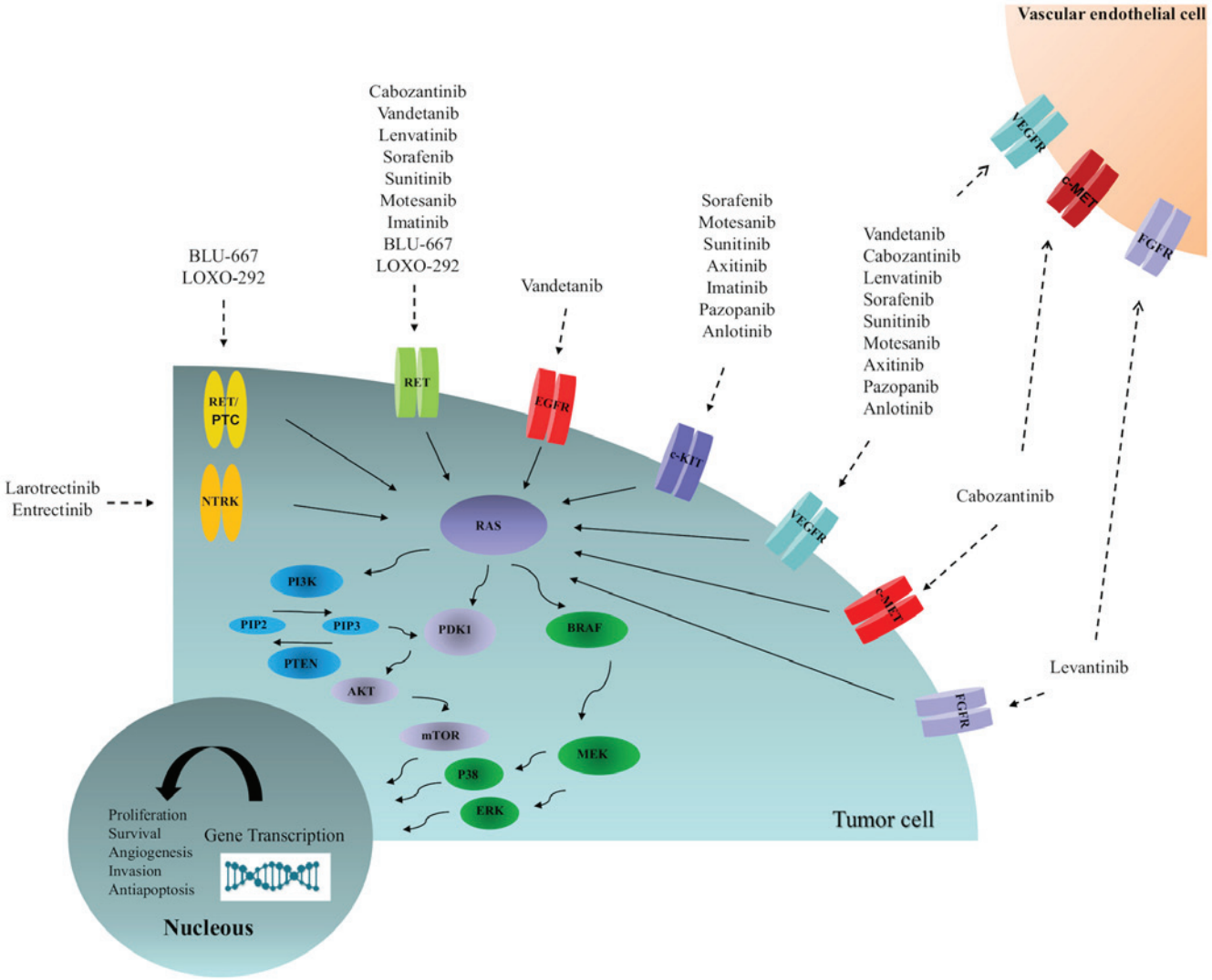

Figure 2. Schematic of the activated pathways responsible for the proliferation and progression of thyroid cancer, as well as molecular targeted-related compounds. AKT, v-akt murine thymoma viral oncogene homologue; BRAF, serine/threonine-protein kinase B-Raf; c-KIT, tyrosine-protein kinase Kit; c-MET, hepatocyte growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; p38, mitogen-activated protein kinase; PDK1, pyruvate dehydrogenase kinase isozyme 1; PI3K, phosphatidylinositol-3 kinase; PIP2, phosphatidylinositol (4,5) biphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homologue; NTRK, neurotrophic tyrosine kinase; RAS, rat sarcoma viral oncogene homologue; RET, rearranged during transfection; RET/PTC, rearranged during transfection/papillary thyroid cancer; VEGFR, vascular endothelial growth factor receptor.

of mutations in this population differs from that observed in adults (Fig. 1) (65-88). Differences in the molecular tumour profile may be one of the reasons for an improved response to RAI in children with PTC. This may also partially explain their low mortality rates and rare progression to undifferentiated tumours. However, studies on this matter have shown conflicting results regarding the prevalence of genetic mutations, and their role as prognostic factors for paediatric DTC remains uncertain (Table V) (65-88).

RET PTC. The proto-oncogene RET, located on chromosome 10q11.2, encodes a tyrosine kinase receptor (89,90). At least 12 types of RET/PTC rearrangements have been described, with types 1 and 3 being the most common (89,90). In the paediatric population, RET/PTC mutations are the most common type of mutations, ranging from 15-77% based on different studies (65, 67-70,72,73,76,78,80-83,88).

Several studies have examined the role of RET/PTC as a prognostic factor in paediatric DTC patients. Whilst the majority of studies have failed to demonstrate an association (67,68,72,76,78,80,82), a recent Brazilian study reported an association between RET/PTC3, larger tumour size and multifocality (83).

BRAF. BRAF kinase, whose encoding gene is located on chromosome 7, is the most potent activator of the MAPK pathway (89,90). Over 40 mutations of the BRAF gene have been identified, with the T1799A mutation being the most common (89,90). This missense mutation, due to a somatic transversion of thymine to adenine at position 1,799 in exon 15, results in the substitution of a valine amino acid for glutamic acid at position 600 (BRAFV600E). In children and adolescents, this is the second most prevalent mutation, found in ~28% of cases, with prevalence ranging from 0-68% (68-88).

The association of the BRAFV600E mutation with disease outcome in paediatric patients is still controversial. Alzahrani *et al* (77) evaluated 55 children and adolescents with DTC and found that persistent/recurrent thyroid cancer was more prevalent in patients with the BRAFV600E mutation (66.7 vs. 34.1%) and more pronounced in patients with classic PTC (77.8% vs. 33.3%). Onder *et al* (79) observed that the classic architecture with multicentricity and local recurrence was correlated with BRAFV600E mutation (79). In contrast, several studies found no association between BRAFV600E mutation and disease prognosis (68,71,72,74-76,80,82,85-87).

NTRK. The NTRK1 receptor gene, located on chromosome 1, encodes the high-affinity nerve growth factor receptor and is activated via the MAPK pathway (73). ETV6-NTRK3 is the result of an interchromosomal translocation (12; 15) (p13; q25) that juxtaposes exons 1-4 of ETV6 to exons 12-18 of NTRK3 (73). This gene has recently been studied and is gaining importance due to its high prevalence (~12%, ranging from 7-26%) being the third most common in the paediatric population. Moreover, studies have shown an association between NTRK fusions and worse clinical outcomes (73,76,81-83). Compared with BRAF mutations, the presence of fusion genes has been associated with larger tumours (2.2 vs. 1.5 cm), aggressive histology (84% vs. 0%), and lymph vascular invasion (92.3% vs. 46.1%) (76).

RAS. RAS genes encode highly related G proteins, which serve a central role in intracellular signal transduction by activating the MAPK and other signalling pathways, such as PI3K/AKT (89,90). Amino acid modifying mutations of RAS generally occur at codons 12, 13 or 61 of H-RAS, K-RAS or N-RAS proteins (89,90).

Mutations in the RAS gene were the first studied in the DTC paediatric population. RAS mutations are much less prevalent in paediatric patients than in the adult population, with an estimated rate of 2.7% (prevalence range, 0-16%) (66,68,69,72,73,76,78,80-83,87). No associations have been reported between RAS mutations and disease presentation in paediatric DTC (66,72,78,82,87).

Targeted therapy. Despite the excellent prognosis of DTC in paediatric patients, a small subset of this population may show progressive and RAI refractory disease (13-17). In such a case, systemic therapy should be considered (13). Identifying tumour molecular profiles may be critical in selecting the most appropriate therapy (Fig. 2) (91). Of note, the majority of the current knowledge of targeted kinase inhibitors in this population is based on case reports and anecdotal clinical experience (8,13). In addition, long-term side effects in the paediatric age group are unknown (91). Two drugs have been approved by the Food and Drug Administration (FDA) for DCT refractory disease, namely, sorafenib and levantinib, although several other drugs are in clinical trials (8,92,93). Anti-neoplastic therapy in children should be performed in centres experienced with the use of these therapeutic agents in paediatric patients (13).

Sorafenib therapy has been reported in three patients with lung metastatic and progressive disease (14-16). The first case was a 14-year-old girl who experienced a significant reduction in lung metastasis after 2 months of sorafenib therapy, although with side effects, such as cutaneous toxicity and neutropenia (14). The second patient was an 8-year-old boy with hypoxaemia and a need for mechanical ventilation (15). The patient was weaned off mechanical ventilation, and CT showed regression of the pulmonary metastasis after 2 months of therapy. The third case was an 11-year-old boy who showed stable disease after 24 months of sorafenib use (16).

Treatment with levantinib has been used in a small series of paediatric patients with extensive bilateral metastatic pulmonary disease, including one patient who previously used sorafenib (17). All three patients had respiratory distress requiring oxygen therapy. After a few weeks of treatment with levantinib, all patients were successfully weaned off oxygen. The drug was well tolerated, and proteinuria was the only major adverse effect. Two patients had stable disease at 11 and 23 months after the initiation of levantinib. The third patient switched treatment to a tumour-specific target.

More recently, larotrectinib, a highly selective inhibitor of tropomyosin receptor kinase, was approved by the FDA for patients with solid tumours harbouring NTRK fusions in adult and paediatric populations (94). The drug was tested in a phase I/II clinical trial, which included 24 children with solid tumours and two with PTC. These two patients showed stable disease for >7 months of follow-up (94,95). In another phase II study, 55 adolescent and adult patients were included, with five diagnosed with thyroid cancer. Of these, four patients presented with a partial response, and one showed complete response (94).

5. Conclusions

In conclusion, the incidence of DTC has been increasing in recent years. The disease has an excellent prognosis in the paediatric population, despite a more aggressive clinical presentation than in adults. Nevertheless, a few patients will present progressive disease and require closer attention and additional therapy. Early identification of patients at high risk is a fundamental step in the therapeutic strategy. The risk stratification systems TNM, ATA and DRS are particularly useful in this regard. The advent of molecular markers may offer additional help in individualizing management. Preliminary reports of targeted therapy in paediatric patients with DTC with progressive disease have shown encouraging results, but appropriate clinical trials are still necessary.

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Author's contributions

ABZ, RSS, LW, JMD, and ALM contributed to the conception of the subject of the review and writing the manuscript. ABZ was responsible for the literature review. All authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

Competition interests

The authors declare that they have no competing interests.

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