

Pediatric Versus Adult Papillary Thyroid Carcinoma: Different Diseases Requiring Different Surgical Approaches



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Abbreviations: PTC: Papillary Thyroid Cancer; RAI: Radioactive Iodine; LNM: Lymph Node Metastasis; TSH: Suppressive Hormone Therapy; ATA: American Thyroid Association; LND: Lymph Node Dissection; DM: Distant Metastases; NIS: Sodium-Iodide Transporter; TSH: Thyroid-Stimulating Hormone; LNM: Lymph Node Metastasis

Differentiated thyroid carcinoma is rare in young age and represents 0.5% to 3.0% of childhood carcinomas: the incidence increases with age, and peak incidence is observed between 15 and 19 years of age [1]. Even at large referral centers, only few pediatric thyroid cancers are treated every year; it may take ≥ 30 years for a major center to collect a series of 100 children and adolescents with thyroid cancer [2]. Papillary thyroid cancer (PTC), the most common type of differentiated thyroid cancer, spreads predominantly via the lymphatics to the local draining lymph nodes: cervical lymph node involvement in 60% to 80% of cases and lung metastases at diagnosis in 20% of cases [3]. Since pediatric thyroid cancer is such a rare disease, treatment recommendations have been based on expert opinion and retrospective data collected from different practices over decades [4-6]. Given the paucity of evidence-based pediatric data, guidelines for adult thyroid cancer occasionally have been generalized to children, treating them "just like little adults." Such extrapolations may not be warranted, in particular when it comes to postoperative morbidity after thyroidectomy [7].

Traditionally, in most institutions, the therapy for pediatric and adolescence PTC has been the same as for adults, aimed to the eradication of all clinical and subclinical neoplastic foci both at thyroid and lymph-node level. The reasons for such an approach were

- I. To have a better progression-free survival and overall survival,
- II. To detect subclinical metastases by radioactive iodine (RAI) scintigraphic scan and treat them by RAI ablation,
- III. To make the value of serum thyroglobulin level a very sensitive marker of post-treatment relapse, and
- IV. To avoid possible dedifferentiation of occult neoplastic microfoci over time [8]. PTC in children and adolescents is treated in similar fashion as that in adults, primarily because of rarity of disease in pediatric population and lack of availability of pediatric PTC treatment guidelines [9].

As well as in adults, the treatment of PTC is based on the combination of three therapeutic modalities: surgery, hormone replacement with levothyroxine, and radioiodine treatment. Surgery ranges from lobectomy to total thyroidectomy accompanied by different cervical lymphadenectomies. Latest guidelines recommend total thyroidectomy, mainly for tumors larger than 1 cm associated with cervical dissection of central or lateral compartment block if lymph node metastases are seen in preoperative imaging or during the surgery [10,11]. The main surgical complications include persist enthyppo parathyroidism and laryngeal nerve damage that may cause a wide spectrum of clinical consequences: from hoarseness to total vocal cord

paralysis, with need for definitive tracheotomy [12]. Thus, most societies recommend radioiodine ablation in the vast majority of patients under 45 years old but none of them make specific recommendations for children and adolescents [10,13].

In contrast to adults, pediatric PTC has some distinctive differences such as

- I. Larger primary tumor at the time of diagnosis,
- II. High prevalence of neck lymph nodes and distant metastases (DM) at the time of diagnosis,
- III. The high risk of recurrences [13], and
- IV. Multifocality [14,15]. Nevertheless, advanced pediatric cancers are more likely to respond to therapy and have a better prognosis compared to their adult counterparts [16].

The unusual association between the aggressive presentation of pediatric PTC and its favorable prognosis is behind the controversy regarding its most appropriate initial management, particularly when it comes to choose between total thyroidectomy and thyroid lobectomy. Despite its seemingly aggressive biologic behavior, pediatric PTC is considered a favorable prognosis cancer.

An important difference between thyroid carcinoma in pediatric and adult age is related to the high prevalence of expression of sodium-iodide transporter (NIS) in metastatic focus found in children [17]. In the absence of stimulation of thyroid-stimulating hormone (TSH), the expression of NIS is undetectable in 65% of papillary tumors in patients under 20 years of age [18]. In contrast, the expression of NIS is absent or negligible in 90% of differentiated carcinomas in adults [19]. The greater expression of NIS in the pediatric population results in greater responsiveness to radioiodine treatment and better prognosis. In young patients, the recurrence risk increases in patients that do not express the protein NIS when compared to those that express it. Thus, the degree of NIS expression correlates with radioiodine avidity by metastases and lower clinical recurrence rates [20]. The management of patients with PTC consisted basically of primary surgery followed by evaluation for RAI treatment. Criteria for RAI ablation in patients with PTC was tumor size >1cm, lymph node metastasis (LNM), presence of extra thyroid extension, macroscopic postoperative residual disease in the neck, and/or DM [21,22].

Another important difference between PTC in pediatric and adult age was represented by a very high sensitivity shown by pediatric PTC to hormonal manipulation consisting of L-thyroxine administration at TSH-suppressive doses that can inhibit normal and neoplastic proliferation, thus preventing cancer progression and relapse. These findings, together with the significant morbidity of radical surgery and RAI therapy, led to the proposal by several groups for a conservative approach for pediatric PTC, not aimed at the eradication of all clinical and

subclinical neoplastic foci by surgery plus RAI therapy, but rather the removal of only the grossly detectable disease, followed by TSH-suppressive hormone therapy to control subclinical disease, and reserving more aggressive approaches to selected cases. All these results highlight the extremely high sensitivity to hormonal manipulation that can control subclinical disease and prevent the occurrence of clinical relapse. This sensitivity to hormonal manipulation seems to represent an important biological difference with respect to adult PTC.

All these observations are in keeping with the proposal made by Cady et al. [23] on clinical grounds and supported by genetic findings that thyroid carcinomas in children and adults are different diseases and not merely different stages in a single disease, with specific prognosis and therapy needs [23,24]. Thus, the category of microcarcinoma (including tumors with less than 1cm), commonly used in adults, should be avoided in children, since a 1cm tumor constitutes a very important finding in this age group. Regarding the molecular biology of these tumors, apparently RET-PTC rearrangements occur in childhood more frequently than in adults, especially in the radiation-related tumors [25].

The prognosis remains excellent with a low rate of mortality even in advanced stages [26], but local recurrence is more frequent than in adults, leading to reoperation [27]. Predictive factors of recurrence remain incompletely known, although some factors have been suggested from retrospective studies [15,28,29]. They include young age (<16 years), lymph node involvement or DM at diagnosis, and histopathologic characteristics (mainly the diffuse sclerosing papillary variant, which is frequent in children) [30]. Among them, nodal status is considered one of the most statistically significant predictors for an adverse prognosis in young patients [31-33].

The American Thyroid Association (ATA) guidelines for pediatric PTC doesn't recommend prophylactic lymph node dissection (LND) in children clinically negative for LNM due to the higher rates of complications as recurrent laryngeal nerve injury and hypocalcemia, which ranges from 1-4% even in experienced hands [34-38]. Moreover for ATA, in patients with pre-operative evidence of central and/or lateral neck metastasis, a therapeutic LND should be performed. For this kind of patients, LND is associated with a decreased risk of persistent/recurrent locoregional disease as well as the potential to increase the efficacy of RAI ablation for distant metastases [39,40]. According with ATA, Borson-Chazot et al. [41] suggest a lymph node dissection with the addition of RAI ablation, in presence of palpable cervical lymph nodes at diagnosis because it is associated with more invasive forms of malignancy and is a predictive factor of recurrence.

Tumors with diffuse sclerosing variant are more common in younger patients between 15 and 30 years of age according to Koo et al. [30]. In their study pediatric patients with diffuse

sclerosing variant had a higher incidence of bilateral thyroid involvement, extrathyroidal extension, lymph node involvement and recurrence. Also for Lloyd et al. [42], the diffuse sclerosing variant tumors are characterized by diffuse involvement of the thyroid (both lobes are typically involved), lymph node and lung metastasis, but the tumors do not usually lead to the demise of the patient.

Recently, indications for an optimal surgical management have been proposed [15,43]: patients with tumor smaller than 2cm, limited to one lobe, no lymph node involvement and absence of distant metastasis can be treated with conservative surgery. In absence of these parameters, radical surgery should be performed.

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