Papillary Thyroid Carcinoma

Subjects: Oncology

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Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in both adult and pediatric populations, occurring more commonly in women at ages 50-59. PTC is characterized by the presence of cells arranged into papillae, presenting clear or ground-glass nuclei. It is further subdivided based on histological variants, such as the classic (CVPTC), follicular (FVPTC), solid (SVPTC), and diffuse sclerosing (DSVPTC) variants.

Keywords: papillary thyroid carcinoma ; thyroid carcinoma ; thyroid cancer ; thyroid ; carcinoma ; cancer

1. Introduction

Thyroid carcinoma is the most common malignancy of the endocrine system in adult and pediatric populations. In adults, this type of cancer is increasing dramatically in both men and women, with an average annual percentage change of 5.4% and 6.5%, respectively. It is projected to take the place of colon cancer and become the fourth leading cancer diagnosis in both sexes (second for women) by 2030 [1][2]. Thyroid cancer presents with relatively stable mortality, but it has been increasing globally since the 1970s [3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18]. It is estimated that by the end of the year 2020, thyroid cancer will claim the lives of 2180 of the 52,890 new projected cases, corresponding to 0.4% of all cancer related deaths and 2.9% of new cancers throughout the world, respectively [19].

In the pediatric population (≤18 y.o. at diagnosis), thyroid cancer corresponds to 6% of all pediatric cancers (2012–2016 data) [20][21]. Even though there is no indication of ethnic or race susceptibility in pediatric thyroid cancer, there has been a prevalence related to increasing age range, i.e., ages 5–9, 10–14, and 15–19 showing a prevalence of 10,000, 80,000, and 310,000, respectively [19]. Considering gender, the prevalence is observed above age 10, and females are the most affected (more precisely between ages 13 and 19) [22][23][24]. Overall, among adolescents (ages 15–19), thyroid carcinoma is the eighth most diagnosed cancer [25][26].

Differentiated thyroid carcinoma (DTC) originates in the follicular cells of the thyroid and is the most common type (80–90%) of thyroid malignancy [27]. DTC is classified into follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC). This classification relies on histological differences and the different metastatic dissemination routes between the two subtypes. FTC accounts for 10% of all DTC and is characterized by the presence of small follicles and the absence of ground-glass nuclei (characteristic of PTC). PTC encompasses the remaining 80–90% of all DTC and is characterized mainly by the presence of cells arranged into papillae, presenting clear or ground-glass nuclei. PTC is further subdivided based on histological variants, such as the classic (CVPTC), follicular (FVPTC), solid (SVPTC), and diffuse sclerosing (DSVPTC) variants. Among these variants, children under the age of 10 seem to be unaffected by the most common type, CVPTC, found in adults [26].

Oddly enough, regardless of studies suggesting that clinical presentation, pathophysiology, and long-term outcomes diverge between pediatric and adult populations, clinical assessment and treatment recommendations used in pediatric thyroid cancer are the same as those implemented for adults [21][28][29][30][31][32][33][34][35][36][37]. Looking closely, PTC differences in these populations could be explained by the distinct genetic alterations observed in the PTC of adults and children.

2. Epidemiology and Pathogenesis

According to the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of PTC in adults increased between 2000 and 2017, from 7.9 to 16.9 per 100,000, compared to 0.6 to 1.0 per 100,000 in the pediatric group (Figure 1, bottom lines) [19]. Remarkably, as represented in Figure 1, PTC in adults occurs more commonly in women at ages 50–59 (37.3 × 100,000) and to a lower rate (17.3 × 100,000) in men, for whom the peak of incidence occurs at ages 65–69.

Looking at the pediatric population, this difference in gender starts just above age 10, i.e., 0.3 per 100,000 for boys and 1.2 per 100,000 for girls (ages 10–14), with increasing distinction above age 15, where the incidence increases to 0.9 per 100,000 for boys vs. 5.3 per 100,000 for girls (ages 15–19) (Figure 1) [19].

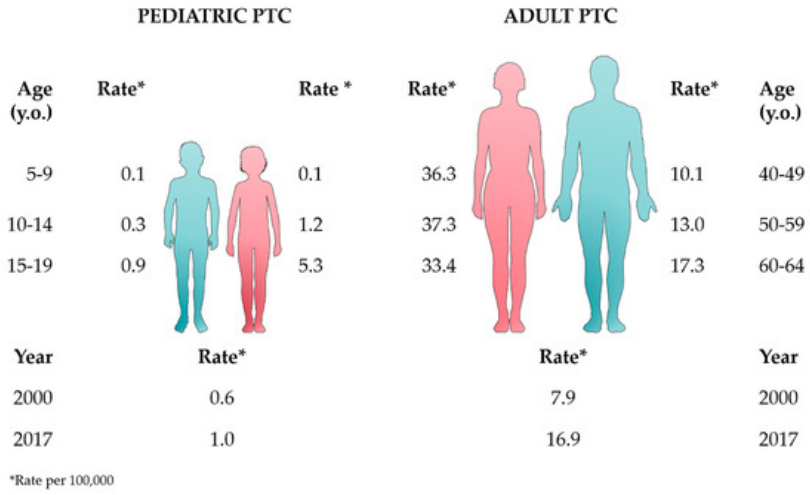

Figure 1. Epidemiologic data from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2017) [19] comparing the rates of pediatric and adult papillary thyroid carcinoma (PTC) according to age, gender, and year. This figure was created using images from Servier Medical Art (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

The reasons associated with this progressive trend are controversial. Several authors propose that the increase in cases is due to better diagnosis, since this tendency coincides with the increased use of high resolution imaging techniques [3][8][38][39][40]. Others suggest that the reason is multifactorial and is related to environmental and lifestyle factors. Diet, obesity, smoking, drinking, sex hormones, iodine deficiency, and a history of benign nodules in the family may contribute to the increased PTC incidence [41][42][43][44].

In the pediatric population, the only consolidated risk factor is the exposure to radiation in childhood, either environmental or as part of radiotherapy for a prior malignancy or treatment for another benign condition [45][46]. In fact, several studies have demonstrated a much greater sensitivity to radiation in children compared with adults. In the past 60 years, the incidence of pediatric cases peaked twice. The first peak occurred in the 1950s, due to the use of external irradiation of the head and neck to treat children with various benign non-thyroid disorders such as the enlargement of the thymus, tinea capitis, adenoids or neck lymph nodes, acne, eczema, otitis, and others [45][46][47]. The use of external radiation therapy on the neck essentially ended in the early 1960s, when a cause–effect relationship between radiation exposure and PTC was established [45][46][47]. However, radiation is still used in clinical practice to treat different types of cancers. Radiation-induced malignancies, such as thyroid cancer, are late complications of radiotherapy treatment, with increased frequency among survivors of both pediatric and adult cancers [48].

Although there was a sharp increase in the incidence of childhood thyroid cancer in the Minsk and Kiev centers 4–5 years after the explosion of the Chernobyl Nuclear Power Plant reactors in 1986, the second peak of incidence occurred just 10 years after the accident in some Eastern European countries. The high-risk group comprised children under the age of four at the time of exposure. Consequently, in this second peak, the majority of clinically evident tumors were present in children ~10–14 years old [22][24][26]. Regarding the Fukushima Daiichi nuclear disaster (March 2011), it is still unclear whether the radiation released after the nuclear accident could be considered the cause of a “third peak” of thyroid cancer incidence in the pediatric group, or if a potential peak is just an artefactual result of the intense screening of this population. The adverse effects of the Fukushima accident might have been partially mitigated by the measures taken, i.e., evacuation from most of the contaminated areas and the recommendation of a low iodine alimentary intake and food restrictions, which could have reduced the uptake of iodine-131. With an average radiation dose of < 1 mSv for the majority of Fukushima residents and a maximum of 30 mSv in few cases from evacuated sites near to the Fukushima Nuclear Power Plant, the first round of thyroid ultrasound screening, performed in all affected children under age 18, showed no clear evidence of a thyroid cancer increase due to radiation exposure [49]. Other studies have found a significant dose–response relationship between the rate of thyroid cancer detection and the external effective dose-rate in both the first and second rounds of the thyroid ultrasound screening [50][51]. The third and the fourth rounds of examinations are still in progress and further data may bring more light into this issue. Interestingly, as discussed in the next section, the pathological findings observed in the Fukushima PTC cases are similar to the pediatric cases found in non-exposed areas and to the mutational profile reported in adult PTC [52][53].

3. Clinical Features, Prognosis, and Treatment

The differences in clinical presentation and outcomes between pediatric and adult PTC are significant [54][55][56]. Compared to those of adults, pediatric thyroid cancers usually present with more advanced disease. Though the recurrence rates are higher than in adults, pediatric PTC has a better long-term outcome, with minimal or no mortality in most cases [54][57][58]. Pediatric PTC typically manifests as a palpable thyroid nodule/tumor, with or without cervical lymphadenopathy [59]. Although rare in children and adolescents, the presence of nodules in pediatric patients is clinically important. Thyroid nodules are associated with increased malignancy compared to adults (26% vs. 5%) [60][61]. Additionally, the mean tumor size is typically larger in pediatric patients. Hay et al. (2018) studied 190 children and 4242 adults consecutively treated during 1936–2015. They described a mean tumor size of 2.56 cm (median = 2.15 cm) in children vs. 1.94 cm (median = 1.5 cm) in adult patients [56]. Papillary thyroid microcarcinoma (≤1 cm) accounts for ~40% of tumors in adults [62] and represents < 10% of pediatric PTC [63]. This difference is probably due to the common practice of thyroid cancer screening in adults and the early detection of smaller tumors [64].

Furthermore, when compared to adults, childhood thyroid carcinomas are more frequently locally invasive. The metastatic involvement of regional lymph nodes at diagnosis was reported in ~50–75% of pediatric cases (Table 1) [55][56][65][66], compared to ~20–40% in adult PTC [56][66]. With respect to distant metastasis, data available from the literature also demonstrate a high frequency in pediatric vs. adult PTC patients [56]. The lungs are the most common site of distant metastases in all age groups, occurring in ~5–16% of pediatric PTC (Table 1) and in 2–4% of adults [54][55][56]. Liu et al. (2019) investigated the occurrence of factors influencing distant metastasis in pediatric thyroid cancer and identified the age at diagnosis as an important factor, with distant metastasis occurring in 1.73% of patients aged 15 and above, and in 6.73% of patients under the age of 15 [67].

Table 1. Clinical pathological features of pediatric PTC.

Reference	*n*	Distant Met. (%)	LN Met. (%)	Mean Age (y.o.)	Gender F:M	Mean size (cm)	Mean Follow-up (years)	% NED	Mortality
Zimmerman et al. [29]	58	6.9	89.7	< 17	2.2: 1	3.1	26.7	52	14%*
Dottorini et al. [68]	85	18.8	60	14.7	2.86: 1	X	9.25	63.5	0
Kuo et al. [69]	77	18	6.4	12.9	3.3: 1	6.93	8.2	89.6	0
Vaisman et al. [70]	65	29.2	61.5	14	3: 1	2.99	12.6	50.8	0
Fridman et al. [71]	94	20	66	15.1	3: 1	1.2	4.2	97	0
Pires et al. [72]	118	26.9	67.3	13.3	2.6: 1	2.5	8	63.5	0
Cordioli et al. [73]	38	26.3	73.7	11.8	3.2: 1	2.6	7.8	54.1	0
Poyrazoğlu et al. [74]	75	13.3	45.3	12.4	2.1: 1	2.2	4.3	65.3	1 patient
Hampson et al. [75]	62	19.3	46.7	13.8	2.5: 1	2.3	3.6	59.6	Not reported
Galuppini et al. [76]	59	20.8	51	14.4	2.7: 1	2.0	5.9	66.7	Not reported

Despite the higher rate of disease recurrence when compared to adults, overall survival is higher in pediatric PTC [29][77]. Mazzaferri et al. (2001) [78], in a series of 16.6 years' follow-up, found a disease recurrence rate of ~40% in patients under the age of 20 and ~20% in patients above the age of 20. Additionally, Demidchik et al. (2006) [79], with a cohort of 741 patients, found a survival rate of 99.3% at age 5 and 98.5% at age 10. Lazar et al. (2009) [80] demonstrated that patients under the age of 10, mainly pre-pubertal patients, presented a worse prognosis than older ones or those in more advanced puberty stages. It seems that large tumors (>2 cm), extra-thyroidal extension, and younger age are factors associated with worse prognosis. However, the ideal cut-off for age and pubertal status awaits future investigation. The same is true for gender, which two studies showed to be an important prognostic factor [70][72], whereas another study showed no significance [67].

PTC treatment is based on the combination of three therapeutic modalities: surgery, radioiodine therapy, and hormone replacement with levothyroxine. Surgery can range from lobectomy to total thyroidectomy, accompanied by cervical lymphadenectomy. The extent of thyroid surgery for adult PTC patients has shifted in a more conservative direction in most recent guidelines [30]. Since then, lobectomy has been an acceptable surgical treatment for low-risk tumors without extrathyroidal extension or clinical lymph node metastases. However, the American Thyroid Association (ATA) management guidelines for children with PTC recommend total thyroidectomy for the majority of children [21][30]. The rationale for this approach is based on an increased incidence of bilateral and multi-focal disease in pediatric patients. It consists of the dissection of the central cervical compartment, with the removal of lymph nodes and adjacent tissues suspected to present metastasis. Modified lateral cervical dissection is indicated in cases of metastasis to lateral lymph nodes. The main surgical complications include persistent hypoparathyroidism and injury to the recurrent laryngeal nerve, which can cause hoarseness to complete closure of the vocal cords, requiring a definitive tracheostomy [81][82]. Fridman et al. (2019) [83] have reported a number of complications of thyroid surgery in childhood PTC. However, they concluded that prophylactic neck dissections should be recommended in children and adolescents due to the high rates of node metastases. On the other hand, to avoid surgical morbidity, Francis et al. (2015) [21] proposed that surgery for pediatric patients should take into account the risk stratification variables, in which patients are divided into a low, intermediate, and high risk of recurrence.

After total or almost total thyroidectomy, the volume of the remaining gland must be <2 mL at cervical ultrasound, performed up to 1 month after surgery [77][84]. Interestingly, even after total thyroid removal, with no thyroid detected by ultrasound, radioiodine (RAI) uptake in the thyroid bed occurs [85]. This phenomenon is usually attributed to remaining thyroid cells. However, since multifocality and metastasis are more common in the pediatric age group, the possibility that such foci still have malignant cells cannot be ruled out. Despite this, most societies recommend the ablation of reminiscent tissue in the majority of pediatric patients [21]. The pediatric recommendations regarding indications for RAI are still controversial. The National Comprehensive Cancer Network for adults suggests clinical features including tumor size >2–4 cm, gross extrathyroidal extension, and extensive regional nodal involvement as indicators for adjuvant RAI [86]. The guidelines for children recommend an individualized approach using post-operative thyroid-stimulating hormone (TSH)-stimulated thyroglobulin levels to determine who should receive adjuvant RAI [21]. There is no consensus in the calculation of the appropriate dose of iodine-131 (^{131}I) for pediatric patients, since both body weight and body surface area methods are used. Whole body ^{131}I dosimetry can also be used in patients with extensive metastases [87]. The success rate of ablation is significantly lower in patients who have undergone less extensive surgery, whether they are children or adults [22][78][84].

Successful ablation is usually defined as the absence of uptake or uptake of less than 0.1–1%, as detected by means of a total body scintigraphy performed 6–12 months after the procedure [85][88][89], accompanied by markedly decreased or undetectable serum thyroglobulin, and suboptimal TSH stimulus, all happening at the same time [77][78][88]. In most cases, one dose of radiodine therapy is able to achieve these goals [85], if not, the procedure may be repeated no earlier than 12 months after the first attempt [88][89]. The ablation should also be followed by a total body scintigraphy (post-therapeutic whole-body scan), performed ~5–7 days after the administration of the radioiodine, in order to detect or confirm the presence of functional metastases.

Lastly, thyroid hormone replacement, the third treatment modality, involves the oral use of levothyroxine. This modality is called suppressive therapy with thyroid hormone when a supraphysiological dose is used in order to keep serum TSH levels below the lower reference limit, reducing the risk of TSH-induced tumor growth or proliferation [90]. In children and adolescents, there are several studies guaranteeing the effectiveness and safety of this type of replacement, as long as it is carefully controlled, particularly regarding the patient's final height [66][77][91]. The actual recommendation is to keep TSH suppressed as needed [21]. Possible side effects of long-term suppressive therapy, documented in adults, include osteoporosis [82] and cardiovascular diseases, especially left ventricular hypertrophy [92][93]. Regarding fertility, some studies suggest that radioiodine may affect testicular and ovarian function, at least temporarily [94][95][96].

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