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Review

Differentiated thyroid cancer in childhood: a literature update

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ABSTRACT

Differentiated thyroid cancer in childhood is rare. Apart from family history, radiation exposure is a major risk factor. Although its clinical course is quite aggressive with higher rates of lymph node and pulmonary metastases as compared to adults, the final outcome tends to be favorable with mortality rates less than 2%. We herein review the clinical picture, genetic background response to treatment and recurrence rates of differentiated thyroid cancer in children and young adolescents are thoroughly reviewed and the main differences with adult differentiated thyroid cancer are highlighted.

Key words: Differentiated thyroid cancer, Mutations, Outcome, Radiation, Recurrence

EPIDEMIOLOGY

Differentiated thyroid cancer is quite rare in childhood with an annual incidence of 0.2 to 1 cases per million children. Its incidence increases after the age of 10 years and reaches a zenith in adolescence when it increases by 10-fold.[1] Specifically, the incidence rates increase from 0.43 (5-9 years) to 3.5 (10-14 years) and finally to 15.6 per million (15-19 years).[2,3] Prepubertally the rates are equal between males and females, whereas in adolescence there is a female predominence with a female to male ratio between 1-2.5 and 6, making thyroid cancer the second most common malignancy in adolescent girls[3-5] (Figure 1). In childhood, papillary thyroid cancer accounts for more than 90% of all cases[6,7] and follicular for 5-10% of cases occurring at slightly older ages.[1,5-8] Dominant histologic variants of papillary thyroid cancer in childhood are solid, follicular and diffuse

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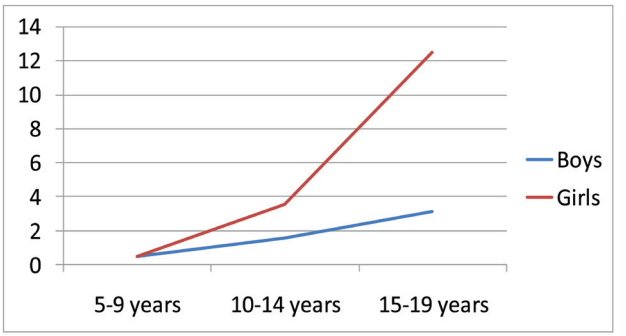

Figure 1. Incidence of thyroid cancer in childhood and adolescence.

sclerosing.[9] The incidence of NIFTP has not yet been widely investigated, although a recent study reported a rate of 1.9%, i.e. less frequent than in adults.[10] Medullary, poorly differentiated and anaplastic thyroid cancer are very rare in childhood.

RISK FACTORS

In approximately 5-10% of cases there is a family history of papillary thyroid carcinoma, comprising cases of adenomatous polyposis, DICER 1, PTEN hamartoma tumor syndrome, Carney complex or Cowden's disease.[11] However the main risk factor for PTC is radiation exposure[12,13] for children <5 years.[14,15] In particular, approximately 5 years after the 1986 Chernobyl Nuclear Power Plant accident the incidence of papillary thyroid cancer in the contaminated areas of Belarus, Ukraine and the Russian Federation increased from less than 1 case per million per year before the accident to more than 90 cases per million per year and the exposed children continued to carry an increased risk into adult life.[16] After 1996, the incidence declined progressively and after 2001 only sporadic cases, i.e. not through exposure to radiation, were reported in pediatric patients (<15 years old).[5,17-19] A non-significant increase in the prevalence of thyroid cancer was reported after the Fukushima Daiichi Nuclear Power Plant disaster where the radiation exposure was one tenth or less compared to the Chernobyl accident.[19]

MUTATIONAL STATUS

As shown in Table 1, a major difference between adult and pediatric PTC is that in children *RET/PTC* rearrangements are more common (30-70% of PTC in childhood), while activating point mutations in the signal transducing pathway, such as *RAS (NRAS* being the most frequent) and *BRAF* mutations, account for less than 10%.[20] *PET/PTC* rearrangements occur after radiation exposure or internal contamination, this being the case of the Chernobyl accident.[21] As radiation exposure induces DNA double-strand breaks, the RET gene and associated partners are highly vulnerable for recombination since they are juxtaposed in the nuclei of thyroid cells. To date, nearly 20 types of RET/PTC rearrangements have been identified.[21,22] The overall prevalence of RET/PTC diverges between sporadic and radiation-exposed pediatric PTC carcinomas (41% vs 58% respectively),[23,24] with RET/PTC3 being associated with more aggressive tumors and RET/PTC1 with classic PTC.[24,25] Due to interindividual variations in response to radiation, the role of genetic factors such as single nucleotide polymorphisms (SNPs) in the *ATM* and *FOXE1* genes in radiation-induced PTC has been documented, suggesting that its etiology may involve a DNA repair pathway, a thyroid morphogenesis pathway and/or dysregulation of the differentiated state in the thyroid.[26] In contrast to BRAF mutations, these RET/PTC rearrangements do not lead to genomic instability and dedifferentiation, which explains their better response to RAI and lower mortality rate.[7,27] Several studies have demonstrated that sodium iodine symporter expression is greater than in adults.[28,29] Moreover, a subsequent study showed that the expression of PDS, TPO and TSHR mRNA was higher in children compared to adults (22-59 years) and older patients (>60 years) as well.[30]

CLINICAL PRESENTATION

Thyroid cancer in children usually presents as a solitary nodule.[31,32] The incidence of clinically palpable thyroid nodules in children is estimated to be around 1-1.5% and in adolescents up to 13%.[33] Nodules in children carry a greater risk of malignancy compared to those in adults (22-26% versus 5-10% in most series).[34-36] It is noteworthy that even autonomously functioning hot nodules carry a higher risk of malignancy compared to those in adults, i.e. up to 30% in

Table 1. Differences of differentiated thyroid cancer in childhood compared to adults.

Nodular disease	4-fold higher risk for malignancy (22-26% vs 5-10%)
Genetic background	PET/PTC rearrangements 30-70% vs 10-20% and BRAF mutations 10% vs 40-50%
Clinical course	LMN metastases 80% vs 20-50% of adults and pulmonary metastases in 9-30% vs 2-9% of adults
Outcome	Better *NIS* expression and better response to RAI

children[37] vs 3% in adults.[38] Thyrotropin >2.5mIU/L, suspicious ultrasonographic features i.e. microcalcifications or marked hypoechogenity, irregular margins, pathologic adenopathy or multinodular goiter were identified as independent predictors of malignancy together with FNA results.[39] US characteristics and clinical context should be used for pathologic evaluation via fine-needle aspiration (FNA)[40] rather than the size criterion alone, especially in a growing child whose thyroid may be half the size of an adult's. FNA is a useful modality in the evaluation of thyroid nodules in children, with 99% accuracy and overall sensitivity and specificity of 94% and 100%, respectively.[41] According to a recent study, the risk of malignancy, including papillary microcarcinoma, is 2% for benign aspirates, 26% for AUS, 57% for FN and 100% for suspicious or malignant aspirates,[41] which is much higher than in adults.[42] In the case of indeterminate cytology, given that data regarding molecular testing in children are insufficient they cannot be used in routine clinical practice.[40] Thus, when cytology is indeterminate, surgery (lobectomy plus isthmusectomy) is favored over repeat FNA.[40] Surgery is also a reasonable option for apparently benign growing nodules or those exceeding 4 cm and causing compressive symptoms.[40]

Compared to adult papillary carcinomas, the foci are often large, multifocal and bilateral. Multifocality and capsular invasion were significantly more frequent in patients less than 16 years of age.[43] The clinical course is quite aggressive, with lymph node metastases in up to 80% of cases[44] vs 20-50% of adults[45,46] and pulmonary metastases in approximately 9-30% of cases[47] vs 2-9% of adults[48,49] (Table 1), while bone and central nervous system metastases are very rare.[50-52] Children aged <10 years have higher rates of lymph node metastases compared to older children (92.59% vs 71.43%).[53] Distant metastases occur almost always in the lungs: they are diffuse, micronodular, not detected on standard chest X-rays and usually identified by I^{131}-WBS.[51,54-57]

According to TNM classification, pediatric DTC without distant metastases is defined as stage I and in the presence of distant metastases as stage II,[40] indicating a low risk of cancer-related death. Male gender, tumor stage and lymphadenopathy are risk factors for disease free survival in stage I pediatric DTC patients.[56] According to the recent pediatric DTC guidelines, children with DTC should be categorized into three risk groups for recurrence: i) ATA pediatric low-risk patients are those with disease confined to the thyroid or with microscopic metastases to a small number of central lymph nodes (N1a), ii) ATA pediatric intermediate-risk patients are those with extensive N1a or minimal N1b disease and iii) ATA pediatric high-risk patients are those with extensive N1b and locally invasive disease (T4) with or without distant metastases.[40]

TREATMENT

The indicated surgical approach is total or near-total thyroidectomy.[40] Recurrence rates are higher with lobectomy vs total thyroidectomy.[44,49] Central neck dissection should be performed when there is evidence of central and/or lateral neck metastasis or gross extrathyroidal invasion.[40] Routine prophylactic lateral neck dissection (levels III, IV, anterior V and II) is not recommended. However, lateral neck dissection should be performed on patients with cytologic evidence of metastases to the lateral neck. Measurement of Tg in the FNA washout can be considered if the cytological diagnosis is equivocal. RAI should be administered for treatment of locoregional/nodal disease not amenable to surgery and for the treatment of distant metastases.[40] There is no benefit of RAI remnant ablation in pediatric patients with intrathyroidal disease and no lymph node disease.[58] The postoperative activity of I^{131} administration is usually 37-74 MBq/kg (1-2 mCi/kg). An alternative to the fixed doses is a pretherapeutic dosimetry; I^{131} activities that are as high as safely administrable (AHASA) are at least 200 MBq/kg but in those patients with extensive pulmonary metastases a complete dosimetry including lung dose estimate is the only method to assess safe I^{131} activity.[59] An abbreviated 2-week levothyroxine withdrawal protocol is indicated for preparation for radioiodine administration[60] due to the more rapid T4 clearance and higher TSH to free T4 ratio in children.[61] A hypothesis that may account for this difference is that kidney function is much better retained in children. Because of the expected survival time for young DTC patients, the benefits

of RAI administration should be balanced against the risks, specifically, mainly the risk of second primary malignancy which at any site corresponds to 4.4 excess cases per 10,000 person-years at risk.[62] The risk of development of a salivary malignancy is 1.7 excess cases per 10,000 person-years at risk, while the risk of developing leukemia, though slightly elevated, does not reach statistical significance.[63] The risk of pulmonary fibrosis is 1% in children with diffuse pulmonary lesions, especially when the retained I^{131} activity exceeds 80 mCi.[64] Permanent infertility does not occur in women with doses up to 300mCi I^{131} and happen in less than 10% of men with this same dose. With doses of 800mCi or more, infertility would go up to 60% of women and more than 90% of men.[65]

There is no role for external beam radiation therapy in children because usually tumor foci in the neck concentrate radioiodine and thus subsequent I^{131} therapy remission is achieved. Following thyroidectomy, levothyroxine is given at higher doses per kg of body weight compared to adults in order that TSH may be decreased to 0.1μU/ml and free T3/free T4 not exceed the above limit of normal range. The usual dose for children <10 years is 3-4μg/kg/day, while adolescents 16-18 years require 2.4-2.8μg/kg/day.[66] In children who achieve complete remission, suppressive doses are no longer mandatory and the daily levothyroxine dose may be lowered in order to maintain TSH level in the low normal range (around 0.5μU/ml).[40,67]

PROGNOSIS

Pediatric thyroid carcinoma carries an excellent prognosis. In fact, despite its aggressive presentation in childhood, often with nodular involvement and pulmonary metastases, its prognosis is more favorable than in adults,[68] showing long-term cause-specific mortality of less than 2%.[1,6,31,44,69] A systematic review demonstrated that following I^{131} treatment for pulmonary metastases complete remission is not achieved; however, disease-specific morbidity and mortality remain low (2.68%),[47] while the 10-year survival rate approaches 98%.[2] The risk of recurrence should be estimated according to the ATA risk stratification,[42] which is also valid for pediatric PTC.[70] Children <10 years in contrast to adolescents present with large[71] multifocal tumors with a solid/follicular growth pattern, extrathyroidal extension, lymph node and lung metastases and have higher recurrence rates.[70] The risk of recurrence correlates only with the extent of ETE and not with histologic subtype.[72]

Even in the case of radiation-induced thyroid cancer, an observational study of this high-risk pediatric population in the most contaminated regions near Chernobyl demonstrated that complete response [negative I^{131} whole-body scan and TSH-stimulated serum thyroglobulin (Tg) <1μg/L] was achieved in 64.2%, nearly complete remission (complete response, except stimulated Tg 1-10μg/L) in 30.1% and partial remission (Tg >10μg/L, decrease from baseline in radioiodine uptake intensity in >1 focus, in tumor volume or in Tg) in 4.8%.[73]

FOLLOW-UP STRATEGIES

Follow-up is accomplished by clinical examination, measurement of serum Tg levels, neck ultrasonography and whole body radioiodine diagnostic scans. Tg is a sensitive marker for residual or recurrent disease and should be measured along with TgAb since the presence of TgAb renders Tg results uninterpretable.[74-76] The magnitude of TSH-stimulated Tg elevation in the absence of TgAb distinguishes between patients in remission and those with recurrence. If undetectable, there is a high probability of long-term remission and the patient is mainly monitored by TSH-suppressed Tg levels, TSH is maintained in the low-normal range and the intensity of follow-up is relaxed.[40] A low-level TSH-stimulated Tg <10ng/ml indicates persistent disease requiring serial TSH-supressed measurements and radiological imaging, although this value may decline over time without additional treatment.[77] A clearly elevated TSH-stimulated Tg >10ng/ml indicates structural disease necessitating localization and intervention.[40] Cervical ultrasonography should be performed 6 months postoperatively, then annually for 5 years and thereafter for low-risk patients individualized according to the patient's risk of recurrence.[40]

In children previously treated with I^{131} a diagnostic RAI scan should be performed 12 months afterwards to confirm the absence of disease. If negative there is no need for a repeat diagnostic WBS. In contrast, for high-risk pediatric patients known to have RAI-avid metastases, a diagnostic scan is beneficial and

should be performed after at least 12 months of clinical follow-up and deferred even longer in children who continue to demonstrate a clinical response to previous treatment.[78] Low-dose diagnostic I^{123} scans are preferred over I^{131} scans due to decreased radiation exposure and avoidance of stunning.[79] However, metastatic pulmonary foci may not always be visualized through these scans.[79] Suspicious lymph nodes should be submitted to FNA and Tg measurement in the fluid aspirate. Surgery is favored for macroscopic (>1 cm) nodular disease, especially if located in a lymph node compartment not previously operated upon.[80] As previously mentioned, I^{131} is the treatment of choice for RAI-avid pulmonary metastases visualized with a diagnostic WBS.[40]

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