Differentiated Thyroid Carcinoma in Pediatric Age

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Epidemiology

Differentiated thyroid carcinoma (papillary and follicular thyroid carcinoma) is rare during childhood and adolescence. It comprises 90–95% of all pediatric thyroid cancers; medullary thyroid carcinoma is present in 5–8%, and undifferentiated anaplastic carcinoma is extremely rare. The annual incidence of differentiated thyroid carcinoma in children below 16 years of age is between 0.02 and 0.3 cases per 100,000, whereas the annual incidence per 100,000 in the general population ranges from 1.2 to 2.6 in men and from 2.0 to 3.8 in women [1]. In large retrospective surveys of differentiated thyroid carcinoma, 72 of 1,500 cases (4.8%) occurred in children of ≤16 years at the Institut Gustave-Roussy in Villejuif [2], and 140 of 1,599 cases (8.8%) in children of ≤19 years at the M.D. Anderson Cancer Center in Houston [3]. Most affected children are older than 10 years, and the occurrence of differentiated thyroid cancer below the age of 10 years is exceptional [1, 4]. Although juvenile thyroid cancer is rare, it accounts for about 35% of all carcinomas in children [5].

In the USA about 350 subjects younger than 20 years are diagnosed with thyroid carcinoma every year [5].

Differentiated thyroid carcinoma is in general 2–4 times more frequent in females than in males [1], but the sex difference in frequency is less marked in children below the age of 10 years [3, 4]. Age-specific incidence rates diverge for males and females starting at the age of 10 years, and increase substantially for females from age 13–14 years [5–7].

Over the past 60 years pediatric thyroid cancer incidence has had two distinct peaks [4]. The first occurred around the mid-20th century and was due to irradiation of benign conditions like tinea capitis, acne, chronic tonsillitis and
Thymus enlargement. Thyroid cancer incidence rates decreased when external neck irradiation for benign conditions was abandoned in view of its recognized causal relationship [8]. The second peak occurred in the early 1990s caused by environmental contamination with radioactive iodine from the 1986 Chernobyl nuclear power plant catastrophe, reaching its maximum in the mid 1990s [9]. Thyroid cancer developed mainly in children <5 years at exposure, with onset before the age of 14 years. Girls were at greater risk than boys, with a 30-fold increase of thyroid cancer. Others also observed that children under 5 years of age at the time of exposure are the most vulnerable to the effects of ionizing radiation, girls more so than boys [10]. This may be due to age- and sex-related differences in metabolic activity of the thyroid gland: follicles less than 100 μm in size are presumably active and more prevalent in children <12 years old, whereas follicles >200 μm considered to be hypofunctional are more frequent in adults up to the age of 40 years [11]. A comparative study on differentiated thyroid carcinoma among children and adolescents living in either Belarus or France/Italy demonstrated that the post-Chernobyl thyroid carcinomas in Belarussian children were less influenced by sex, occurred in younger children, had greater aggressiveness at presentation, were more frequently papillary, and were more frequently associated with thyroid autoimmunity than the naturally occurring thyroid carcinomas in French and Italian children [12].

Thyroïd cancer can occur after other childhood malignancies that involve radiation to the neck region, including tumors of the central nervous system, acute lymphoblastic leukemia, non-Hodgkin lymphoma, Ewing’s sarcoma and Wilms’ tumor [13]. The median latent interval between therapeutic irradiation for childhood malignancy and diagnosis of thyroid cancer is 13 years (range 6–30 years) [14]. Total body irradiation before allogeneic bone-marrow transplantation carries also a risk for thyroid cancer [15]. The risk of thyroid cancer after childhood exposure to thyroid irradiation increases with doses up to 20–29 Gy (odds ratio 9.8, 95% CI 3.2–34.8) [16]. At dose >30 Gy a fall in the dose-response relation is seen, consistent with a cell-killing effect. Both increased and decreased risks are more pronounced in children diagnosed with a first primary malignant disease before age 10 years than in those older than 10 years.

In approximately 5% of children there is a family history of papillary thyroid carcinoma. In some families this is related to adenomatous polyposis or Cowden’s disease, but in other families there are no associated lesions.

**Pathology**

Combining three large surveys of differentiated thyroid carcinoma in children and adolescents, 107 of the 137 cases had papillary carcinoma (78%) and
30 had follicular carcinoma (22%) [1, 17, 18]; these figures are remarkably similar to 81% papillary and 19% follicular carcinomas among differentiated thyroid cancers in the general population [1, 3]. The data do not support a higher prevalence of papillary thyroid carcinoma in children than in adults, as stated by some authors [19].

Papillary thyroid carcinomas from children and adolescents contain more numerous lymphocytes than those from adults: nearly half contain CD4+ T helper cells, CD8+ killer cells or CD19+ B cells [20, 21]. This may be related to the more favorable prognosis of differentiated thyroid cancer in children and adolescents than in adults, in line with the notion that the immune response to thyroid cancer appears to be important in preventing metastasis and recurrence. Pediatric papillary thyroid carcinomas with the most numerous proliferating lymphocytes have indeed the longest disease-free survival [20]. Consistent with this effect is the greatest risk of recurrence in those pediatric papillary thyroid carcinomas which intensely express the B7–2 coactivator: B7–2 suppresses T cell growth by binding to the CTLA-4 receptor on T cells [22].

Differentiated thyroid carcinomas in general have a lower expression of the sodium iodide symporter (NIS) than normal thyrocytes, but this appears less so in childhood: NIS expression is absent or subnormal in about 90% of adult patients, in contrast to undetectable NIS expression in about 60% in patients <20 years of age [11, 23]. The greater NIS expression in juvenile than in adult cancer implies greater differentiation and radiiodine responsiveness at a younger age; indeed recurrence risk in young patients is lower in NIS-positive than in NIS-negative tumors [23].

Tumorigenesis of thyroid carcinomas is explained mainly by two mechanisms: activation of proto-oncogenes (e.g. the RET gene in papillary thyroid carcinoma) and inactivation of tumour suppressor genes (e.g. p53 and PTEN in follicular thyroid carcinoma). Pediatric differentiated thyroid carcinoma differs in many aspects from carcinomas in adults: in children, the cancer has a larger size and is already more widespread at presentation than in adults (vide infra). The difference calls for a biologic explanation. RET mutations can initiate papillary thyroid carcinoma, and they occur nearly always already in childhood; these mutations are less likely to be transmitted to later generations of cells after puberty in view of the early expiration of the potency of thyrocytes to divide [4]. Thus the papillary carcinomas with the fastest onset become detectable in children.

Many studies have looked after molecular-biologic differences between pediatric and adult thyroid cancers. In papillary thyroid carcinoma, mutations in RET, NTRK, BRAF (and rarely RAS) activate the MAP kinase cascade, resulting in increased transcription of growth and proliferation genes and thereby initiating tumorigenesis. RET rearrangements result from the fusion of the RET tyrosine
kinase domain with the N-terminus part of different proteins, creating chimeric oncogenes with constitutive activity, named \textit{RET/PTC}. At least 15 different \textit{RET/PTC} variants have been described so far involving rearrangements with 10 different genes. A higher frequency of rearrangement of the \textit{RET/PTC} oncogenes [24–26] and lower frequency of \textit{BRAF} mutations [27] have been observed in childhood than in adult papillary thyroid cancer, but these data have not been confirmed by others [28, 29]. The higher frequency of \textit{RET} rearrangements in radiation-induced cancer may be linked to the particular effectiveness of radiation in causing double-strand breaks (and thereby in gene rearrangements) rather than point mutations [30]. \textit{RET-PTC} and \textit{BRAF} mutations are mutually exclusive in papillary carcinomas, both activating constitutively the \textit{RET/PTC-RAS-BRAF-MAP} pathway. Gene expression in post-Chernobyl cancer is similar to that in sporadic papillary carcinoma as analysed by cDNA and Affymetric microarrays [30]. Radiation-induced thyroid cancers and sporadic papillary carcinomas thus most likely represent the same disease. A relationship between \textit{RET} and \textit{NTRK} positive cases and more advanced disease or worse prognosis is found in some [24] but not all studies [26, 29]. Likewise, increased expression of the tyrosine kinase receptor \textit{cMET} and its ligand hepatocyte growth factor/scatter factor in papillary thyroid carcinoma in children and young adults is associated with a high risk for metastasis and recurrence [31], but later studies observed overexpression of \textit{MET} in the majority of papillary thyroid carcinomas [4, 32]. \textit{RAS} and \textit{PPARG} are involved in follicular thyroid carcinogenesis, and it has been claimed that \textit{PPARG} rearrangement is more frequent in cancers at a younger age [33]. Taken together, it is clear that much still has to be learned on the biology of these tumors in order to fully understand differences in the clinical course of these tumors between pediatric and adult age.

\textbf{Clinical Presentation}

The most common clinical presentation of childhood thyroid cancer is a palpable thyroid nodule; it is the first sign of the disease in 73–87\% of the cases [8, 18]. Most thyroid cancers in children are asymptomatic, but palpable thyroid nodules are more frequently malignant in children than in adults [19, 34]. As with adults, hoarseness, dysphagia or a hard fixed nodule may be indicative of an underlying thyroid malignancy. Fine-needle aspiration cytology of the nodule should confirm the diagnosis. The size of newly diagnosed papillary thyroid tumors in childhood is larger than in adulthood: a size of >4 cm is found in 36\% of children vs. 15\% of adults, and a size of <1 cm occurs in 9\% of children vs. 22\% of adults [35]. Invasion of contiguous structures in papillary thyroid carcinoma is also more frequent in children than in adults (24 vs. 16\%) [35].
Neck node involvement is quite common in childhood papillary thyroid carcinoma, in the order of 60–90% [2–4, 8, 35]; palpable cervical lymphadenopathy occurs usually in the presence of a palpable thyroid nodule, whereas palpable lymph nodes in the absence of a palpable thyroid nodule is uncommon [18]. Neck node involvement is much more frequent in children than in adults. Among 1,039 consecutive patients with papillary thyroid carcinoma treated in the Mayo Clinics, nodal metastases were present in 90% of children vs. 35% in adults, and the same was true for distant metastases (7% in children vs. 2% in adults) [34, 35]. Similar findings have been reported in other large series [2, 3]. The distant metastases occur almost always in the lungs; they are rare outside the lungs. In contrast to adult lesions, pediatric pulmonary metastases are overwhelmingly miliary and seldom nodular; they may not be detected on standard chest radiographs or even on spiral computed tomography scans, becoming visible only at postablation 131I whole-body scans [36–39]; they are almost always functional [4].

It might well be that children with differentiated thyroid carcinoma nowadays present with less advanced disease than in the past, possibly reflecting increased awareness on the part of pediatricians and family physicians [34]. Nevertheless, one must conclude that differentiated thyroid carcinoma in children and adolescents is associated with a much higher frequency of cervical lymph node and distant (pulmonary) metastases at clinical presentation than in adults. The paradox of this more widespread disease in children is its association with a better prognosis than in adults (vide infra).

**Management**

The goals of primary treatment of differentiated thyroid carcinoma are to eradicate disease and extend recurrence-free survival [4]. Childhood differentiated thyroid carcinoma is, however, a rare disease, and it may take decades even at large referral centers to accumulate large series from which meaningful conclusions on the most appropriate treatment regimen can be derived. No randomized controlled trials are available. Guidelines consequently rely on adult and more specifically pediatric outcomes literature, which has been summarized in two recent publications [4, 34].

**Thyroidectomy**

The general consensus is that total or near-total thyroidectomy is the best operation in experienced hands. Reasons to perform a complete thyroidectomy are first the high prevalence of multifocality and bilaterality in papillary thyroid carcinoma, due to intrathyroidal lymphatic spread or de novo tumors