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Review

Differentiated thyroid cancer in children and adults: same or distinct disease?

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ABSTRACT

Differentiated thyroid cancer (DTC) is a rare disease, especially in children. Differences in the biology and clinical course of DTC in children, when compared with adults, may be related both to pathogenesis as well as to clinical outcome of the disease. In childhood, the thyroid gland exhibits higher susceptibility to the carcinogenetic effect of ionizating radiation than in adulthood. Papillary thyroid cancer (PTC) is more prevalent in children in comparison to adult patients. Among molecular events known to occur in papillary thyroid carcinoma, RET/PTC rearrangements exhibit higher prevalence in younger patients, while BRAF mutations are very rare in this age group. Cancer disease presents at a more advanced stage: 1) primary tumour at diagnosis is larger, especially in relation to the volume of the whole gland; 2) neck lymph node involvement is more commonly observed; 3) distant metastases are detected 3-4 times more frequently than in adults. The lungs are almost the sole distant metastatic site in children and pulmonary metastases are nearly always functional. Additionally, recurrence rates tend to be higher in children; nevertheless, cause-specific cancer mortality remains low. Up to now, thyroid cancer guidelines have been formulated on the basis of experience gained in the general population of patients. The peculiarities in childhood disease raise the question of whether it should be considered a distinct subtype, with specifically tailored therapy recommendations. A definitive answer to this question is not possible with the present state of knowledge. In the opinion of the authors, molecular analyses of childhood thyroid cancer may be crucial, as the clinical data have not satisfactorily answered this question.

Key words: Children, Differentiated thyroid cancer

Childhood cancer encompasses a spectrum of different malignancies varying by type of histopathology, site of disease origin, age and sex. In this age group, the vast majority of malignancies are due to non-epithelial malignant neoplasms: leukemias and lymphomas, central nervous system tumours, sarcomas or embryonal cancers such as neuroblastoma, retinoblastoma and Wilms' tumours. Carcinomas – malignant tumours of epithelial origin – are very rare, particularly before

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the second decade of life, and comprise only about 9% of all childhood cancers. Interestingly, differentiated thyroid cancer (DTC) contributes to a markedly higher morbidity in children than carcinoma in any other localization (only malignant melanomas exhibit similar incidence).[1] Additionally, the risk of malignancy in a thyroid nodule is distinctly higher in children than in adults.[2,3]

Incidence rates are practically negligible in very young children.[4-6] The average annual rate of DTC per million increases sharply in adolescence, being at that period additionally influenced by sex.[7] The age-specific incidence rates for males and females begin to diverge at age 10 years and from age 13 years the rates increase substantially for females.[1,8,9]

GENETIC PREDISPOSITION TO DIFFERENTIATED THYROID CANCER

Non-medullary thyroid cancer occurs rarely as an inherited disease. However, it is well known that PTC is diagnosed with a significantly higher incidence among the relatives of patients with this cancer histotype;[10-14] however, the genetic mutations underlying the predisposition to familial non-medullary thyroid cancer have been only poorly defined.[12,15-18] Non-medullary thyroid cancer in the course of familial adenomatous polyposis is well known but rarely diagnosed. It may also occur in Cowden syndrome due to inactivating PTEN mutations, Werner syndrome and some other rare monogenic diseases. Generally, it is considered to be inherited as an autosomal dominant trait with incomplete penetrance and variable clinical expression.[10] The existence of marked phenotypic differences indicates that there is a significant genetic heterogeneity and hence multigene contribution is probable. Recently, the CHEK2 polymorphism has been indicated as predisposing to PTC (with multiorgan involvement). Other single nucleotide polymorphism sites-based studies are ongoing and are expected to disclose additional contributing genes.[19-21] To our knowledge, there are no data indicating higher incidence of genetically determined disease among children diagnosed with DTC. In a population of 235 children and adolescents with DTC observed by us, only a few had a positive family history. On the other hand, it is well known that familial non-medullary thyroid cancer is more frequently multifocal and exhibits more advanced locoregional involvement, features considered to be characteristic for DTC in childhood. Thus, intensive studies of SNP polymorphisms in this subgroup are warranted.

RADIATION INDUCED THYROID CANCER

The increased risk of papillary thyroid cancer (PTC) in children exposed to ionizating radiation was documented for a wide range of doses, and a linear dose-response relation for doses from 0.1 Gy to up to 1-2 Gy has been described.[22,23] Two distinct peaks are known in the incidence of radiation-induced thyroid cancer in children and young adults. The first rise was observed in the middle of the 20th century and was due to previous irradiation of head, neck and upper thorax as a form of therapy for a variety of mostly benign conditions.[22-25] The risk of DTC was significantly elevated from 10-19 yr after exposure, peaking at 20-30 years and decreasing 40 years after exposure.[26] After such radiation ceased to be used for the treatment of benign disease, the peak of thyroid carcinomas declined by half.[27] Nevertheless, in some children radiation therapy for malignant disease is unavoidable and this subgroup constitutes an increased risk for later development of DTC if the radiation field encompasses the neck region.[28]

The second peak of thyroid cancer incidence in children, observed in some East European countries, was related to an uptake of radioiodine following the Chernobyl disaster in 1986.[25,29] The increased DTC incidence started 4–5 years after exposure, reaching its maximum in the mid-1990s, and the disease developed mainly in children <5 years old at exposure.[30,31] The accelerated onset, relative to external irradiation induced disease, is most probably related to radiation dose differences and to endemic iodine deficiency in Eastern Europe.[31] Though only papillary thyroid cancers were initially diagnosed, a trend to increased rates of follicular tumours – follicular adenomas and follicular thyroid cancer – has now been reported with a markedly longer latency time.

The mechanisms responsible for a higher risk of thyroid cancer after radiation exposure in childhood than in adulthood are not well defined. However, a correlation with the growth pattern of thyroid cells

seems the most probable mechanism. Thyroid cells proliferate actively only in early childhood and have very limited potential for proliferation during adult life. By using MIB-1 antibody that reacts with the Ki-67 nuclear antigen, found throughout the cell cycle but absent in resting (G0) cells, it was shown that the overall proliferative rate of normal adult thyroid cells is as low as 0.2%.[32] Comparable findings (0.6%) were observed when another proliferative marker, proliferating cell nuclear antigen (PCNA)/cyclin, was studied in several normal thyroid glands.[33] The recent analysis by Saad et al[34] of histologically normal thyroid glands aged from 11 weeks of gestation to age 60 years, based on the expression of the Ki-67 nuclear antigen, showed the highest indices of cell proliferation in early fetal life, particularly at 11-15 and 16-20 weeks of gestation, when 16% and 12% of cells were labelled, respectively. There was a steep decline in the proliferation index during the subsequent fetal period and the first few postnatal months. The proliferation index remained within the range of 0.2-0.3% throughout childhood and adolescence and further decreased in the adult population, where it was close to 0.1%.[34] There was an evidence of an overall trend for decreasing proliferative index with increasing age ($p<0.01$). The authors also compared the risks of radiation-related thyroid cancer and cell proliferation in the same age intervals and revealed a generally similar tendency for a decline in both parameters with age. However, a lack of correlation was noted between the slopes of risk and proliferative rate in the age group 0 to 9 years. This discrepancy suggests that additional and still unknown factors may further modify the risk of thyroid cancer in young children. One possibility would be a higher functional state of thyroid cells in early childhood. Indeed, Faggiano et al[35] revealed that small, metabolically active follicles with high expression of NIS and pendrin predominate in children <12 years of age, a finding indicating that iodide transport mechanisms are more active in the thyroids of younger individuals.

AGE-RELATED DIFFERENCES IN THE MECHANISM OF PAPILLARY THYROID CANCER INITIATION

Many studies have shown that the distribution of molecular events leading to malignant transformation of thyroid cells differs between children and adults. In papillary thyroid cancer, which constitutes the main histotype diagnosed in children, there are two major initiating events, RET/PTC rearrangements and BRAF point mutation, both activating the same down-stream pathway, the mitogen activated protein kinase (MAPK) signalling pathway, the crucial intracellular cascade regulating cell growth, differentiation and survival in response to growth factors, hormones and cytokines.[36] The other two mutations, NTRK1 rearrangements and RAS activating mutations, lie on the same pathway but occur rarely. Significantly, the frequency of RET/PTC and BRAF mutations show distinct age-related differences.[37-40]

RET activation in follicular thyroid cell is due to inversion or translocation, known as RET/PTC rearrangement, which breaks the RET gene and results in the fusion of its 3' portion to the 5' portion of several unrelated genes.[41] Sixteen different types of RET/PTC have been reported to date with RET/PTC1 and RET/PTC3 accounting for the vast majority.[42] In the mutated gene, RET tyrosine kinase domain is fused with the regulatory domains of other genes. The most frequent rearrangements are: RET/PTC1 (results from the fusion of RET with the gene CCDC6, formerly called H4 or D10S170) and RET/PTC3 (fusion of RET to the gene NcoA4, formerly called RET fused gene (RFG) or ELE1 or ARA70).[36] Both of these genes are constitutively expressed in thyroid cells, contrary to the wild RET gene. Because mechanisms of transcription of their activation continue to operate, the transcription of the fusion gene is also activated and, in this way, a protein containing RET tyrosine kinase domain appears in the thyroid cell. The chimeric protein is found in cytoplasm (not in membrane, as the normal RET protein) and may be constitutively activated by dimerization (again, the regulatory domains of the gene fused with RET tyrosine kinase domain are responsible for this effect).[36] Thus, the RET kinase starts to phosphorylate down-stream proteins and the MAPK cascade becomes activated, leading to the increased transcription of proliferation genes.

Activation of cell proliferation by RET/PTC rearrangement is only the initial event. The subsequent steps, leading to malignant transformation and development of papillary thyroid cancer, are much

less known. Although it was observed that the rate of lymph node and distant metastases was higher in RET-positive papillary cancers, the overall prognosis is not affected or even considered more favourable in RET positive tumours.[39,43] RET/PTC rearrangement has only rarely been found in anaplastic thyroid cancer, which may indicate that cancers initiated by RET rearrangement are not prone to this unfavourable course of PTC natural history.[44] This view has recently been questioned by FISH studies showing the presence of RET/PTC in anaplastic cancer.[45]

The frequency of RET/PTC rearrangement differs substantially in various populations from less than 10% to more than 80% of cases.[36] Many factors are responsible for these differences and may include methodological and ethnic differences. However, one of the most important is age difference: RET/PTC rearrangements are much more frequent in younger patients with PTC and especially in children. They constitute 40-70% of sporadic papillary carcinomas diagnosed in children and young adults.[37-40,43] In fact, the highest frequencies of RET/PTC rearrangements in PTC, up to 87%, are encountered in the population of children with radiation-induced cancer developing after the Chernobyl catastrophe. This high detection rate was initially interpreted as the molecular fingerprint of radiation-induced cancer and only later was it related to the age of the patients.[37-39,46,47] It is probably the shorter latency of RET/PTC induced tumours, which explains the high frequency of this mutation in cancers appearing 5-10 years after the Chernobyl accident. The frequency of RET/PTC3 is the highest in the earliest Chernobyl-induced PTCs, while the incidence of RET/PTC1 starts to rise later. RET/PTC1 has also been reported to be more frequent in exogenous radiation-induced thyroid cancer.[48] The incidence of different RET rearrangements is age related, with RET/PTC3 being the most frequent in the youngest PTC patients.[37-39,49] The presence of RET/PTC3 rearrangement correlates with solid PTC morphology, while RET/PTC1 is seen more frequently in the classical PTC variant. Interestingly, recent FISH studies indicate multiclonality of RET rearrangements in PTC, which raises the possibility that RET rearrangements may be an early but not initiating event.[47]

An alternative way of MAPK signalling pathway activation is induced by a mutation of the BRAF gene. A thymine to adenine inversion in the nucleotide 1799 is the prevalent one, resulting in a substitution of a valine with a glutamic acid at residue 600 of the protein, leading to a constitutive activation of BRAF kinase.[50,51] To date, multiple studies have confirmed that BRAF mutation is the most common event in sporadic papillary carcinomas seen in adult patients. It occurs in approximately 40-60% of all cases.[51,52] In contrast to adult papillary carcinomas, paediatric tumours (both sporadic and radiation-induced) have a low prevalence of BRAF mutations (0-12%).[40,53-57] Kamagai et al[58] observed only one case of BRAF mutation in 46 PTC patients diagnosed under the age of 15 years, and this was a rare case of poorly differentiated cancer. Indeed, BRAF mutations are found in thyroid anaplastic and poorly differentiated carcinomas, typically in those tumours that also contain areas of well differentiated papillary carcinoma.[59] Mutant BRAF is detectable in both well differentiated and poorly differentiated or anaplastic tumour areas, providing evidence that it occurs early in tumorigenesis and predisposes to tumour dedifferentiation. Interestingly, BRAF mutations correlate with radiation dose in thyroid cancers occurring in atomic bomb survivors, which indicates that BRAF-positive PTCs may also be radiation-induced.[60] Some BRAF activating mutations are due to a rearrangement.[61]

Apart from older age in several studies, the presence of BRAF mutation has been found to correlate with more frequent extrathyroidal extension, advanced tumour stage at presentation and tumour recurrence.[42] BRAF mutation is an independent predictor of tumour recurrence, even in patients with stage I and II of the disease.[62] Importantly, BRAF mutations have also been associated with a decreased ability of tumours to trap I-131 and with the treatment failure of the recurrent disease.[62,63] However, the association between BRAF mutation and more aggressive tumour behaviour has not been found in some other studies.[64] No multivariate analyses have thus far been performed, and hence it is not clear whether BRAF mutations are primarily related to poor prognosis or only occur in older patients, in whom other factors are primarily responsible for the poor outcome. It is a matter of future investigations to answer the question whether differences in mutations as a function

of age account for the well documented but as yet poorly understood observation that age is a relevant prognostic indicator for patients with papillary thyroid carcinoma.

BRAF and RET mutations are related to very prominent differences in the gene expression profile of PTC.[65] This suggests that the differences in the clinical course of BRAF- and RET-positive PTCs may be mediated by the induction of different molecular down-stream pathways.[66] No data on the possible interaction with age are available. BRAF and RET mutations are believed to be alternative initiating events in PTC. In a general population of PTC patients, BRAF and RET mutations covered nearly all cases and those patients without any mutation identified constituted less than 20%. The last group was recently related to PDGFB amplification.[67] However, in childhood PTC up to 40% of tumours might be caused by events other than RET/PTC and BRAF mutation, as neither one of these mutations can be found.[38-41,50,55-58] Thus, it cannot be excluded that another molecular mechanism, characteristic for early onset of PTC, will be discovered in future studies.

ARE THERE OTHER DIFFERENCES IN THE MOLECULAR PROFILE OF THYROID CANCER IN CHILDREN?

Molecular studies in thyroid cancer are oriented on mutations initiating the process while further steps of tumorigenesis remain less known.[68-70] Microarray-based gene expression profiling has documented that expression of several thousands of genes is changed in papillary thyroid cancer, when compared to the normal thyroid tissue.[71] A distinct part of them is related to the immune response. Indeed, it is well known that many PTC tumours exhibit lymphocytic infiltration, well demonstrated in younger patients.[72-76] Thus, it is conceivable that the better outcome in children's DTC is related not only to differences in the molecular profile of cancer cells but additionally to the host anti-tumour immunity.[75,76] Functional genomic studies may help to evaluate this hypothesis.

In the context of the molecular profiling of PTC, it is noteworthy that no major differences in the gene expression profile of radiation-induced cancer have thus far been detected compared to those unrelated to radiation.[77]

CLINICAL PRESENTATION AND OUTCOME

The age at diagnosis is preponderantly included in the clinical scoring system of differentiated thyroid carcinoma patients with distant metastases. Patients younger than 45 years are considered to be in stage II of disease, while those older than 45 are in stage IV. In fact, however, metastases are rare at diagnosis of DTC in patients between 21 and 45 years of age, while they are present in a significant number of younger patients, 20% in our experience in patients up to 18 years of age.[78] The very favourable outcome in patients diagnosed in their first two decades of life is based on low mortality rate, with the specific overall survival approaching 100%.[9,78] Cancer deaths nevertheless do occur in this age group.[1]

Although mortality rates in children and adolescents are much lower than in adults, DTC in childhood is often more advanced at presentation and there is a higher risk of disease recurrence.[5,9,79-81] Papillary microcarcinoma, defined as a tumour less than 1-1.5 cm, is a rare diagnosis in children and in most studies accounts for less than 3% of sporadic PTC,[82] while in adults up to 36% of thyroid cancers are below 1 cm.[83] Zimmerman et al[79] described 9% of tumours under 1 cm in children in comparison to 22% in adults. Nevertheless, Demidchik et al[84] in their recent study of radiation-induced thyroid cancer reported that in 73% of children the thyroid cancer size was less than 2 cm in diameter.

Not only larger primary tumour but also a higher propensity for lymph node and distant metastases characterises childhood DTC.[79,80] In sporadic PTC in children, the incidence of node metastases ranges from 40% to 60%. An extremely high propensity for lymph node metastases is seen in radiation induced PTC (>80%). In our study, where clinical outcome of DTC in children and adolescents younger than 18 years of age was compared with the outcome of young adults up to 30 years of age, we found that the incidence of lymph node and distant metastases was, respectively, two and four times higher in children than in young adults.[80]

The rate of distant metastases at diagnosis of PTC shows two peaks, the first in childhood and the second in patients older than 60 years.[85] In children, distant metastases outside the lungs are very rare.[86] Unlike adult lesions, pediatric pulmonary DTC metastases are overwhelmingly miliary and seldom nodular, and almost always functional.[87-89] Among 95 Byelorussian children with radiation-induced DTC and lung metastases, 92 (97%) had disseminated and only 3 (3.15%) had nodular pulmonary radioiodine uptake.[88] This type of lung metastases – disseminated involvement of miliary type – was also seen by other groups.[90,91] In our group of 47 children and adolescents with primary (40 patients) or recurrent (7 patients) distant metastases, 44 had functional metastases.

The high prevalence of functional metastases in pediatric DTC may be related to differences in sodium iodide symporter (NIS) expression. While NIS expression is reduced in cancer cells, childhood tumours appear to have greater and more frequently detectable expression than adult tumours.[92,93] In the absence of TSH stimulation, NIS expression is undetectable in ~65% of papillary and ~56% of follicular cancers in patients aged <20 years.[93] In contrast, NIS expression is absent or reduced in ~90% of adult DTC, as assessed by reverse transcription polymerase chain reaction.[92] Expression of other iodine transport-related molecules, pendrin and apical iodide transporter (AIT), has been found to be reduced in pediatric (Wiench, manuscript in preparation) as well as in adult DTC,[94,95] but there are no data as to whether or not expression is greater in childhood DTC.

The greater NIS expression in pediatric than in adult DTC implies greater differentiation and radioiodine responsiveness in the former, which may be relevant to outcome. In young patients, recurrence risk was increased in NIS-negative versus NIS-positive tumours, even when TNM status and treatment were similar.[93] The degree of NIS expression in primary DTC lesions correlated with subsequent radioiodine uptake in metastastases[96] and the clinical response of recurrences to therapy.[97]

The net major characteristic of DTC diagnosed in children versus adults is a generally higher recurrence rate. With 16.6 years' follow-up, this rate approaches 40% in patients with PTC diagnosed in subjects aged <20 years, versus ~20% in patients diagnosed at age 20-50 years.[98] With more frequent application of radical surgery and adjuvant radioiodine therapy, we have observed recurrence in 14% of our more than 200 DTC patients diagnosed prior to age 18 years and a median follow-up of 82.2 months.[78]

Overall survival is distinctly better in children than in adults, despite the more advanced disease at diagnosis and the frequent recurrences. Not more than 35 cause-specific deaths occurred among 2000 recently reported children and young adults.[9] Despite the good overall survival prognosis, our own experience favours total thyroidectomy, modified lymphadenectomy in patients with lymph node metastases and adjuvant radioiodine treatment after radical surgery. We demonstrated in the multivariate analysis that all of these measures independently reduced the risk of thyroid and lymph node recurrence in young patients.[78] Thus, in respect to the recommended treatment, we do not see any difference in comparison to older patients. However, in this age group special attention must be paid to avoid long-term complications related to therapeutic procedures applied.

CONCLUSIONS

While thyroid cancer guidelines are formulated on the basis of experience gained in the general population of patients,[99,100] the peculiarities in childhood disease raise the question as to whether it should be considered a distinct subtype with specifically tailored therapy recommendations. In the opinion of the authors, molecular analysis of childhood thyroid cancer may be crucial as the clinical experience has not produced a satisfactory solution to pertinent questions.[9,101,102] Future research directed towards a better understanding of the molecular mechanisms underlying pathogenesis of thyroid cancer will likely lead to molecularly oriented diagnosis, prognosis and therapy in children.

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