Personalising treatment for childhood thyroid carcinoma

This recent European collaboration on paediatric differentiated thyroid carcinoma seeks to enable personalised treatment.

Although rare, paediatric differentiated thyroid carcinoma (ped-DTC) is the most common endocrine malignancy in children, accounting for 2–4% of all paediatric malignancies.[1] The incidence of thyroid cancer is increasing worldwide, most likely as a result of (a) earlier and better detection of small and early stage papillary tumours, probably due to improved diagnostic tools and clinical awareness, and (b) changes in environmental risk factors resulting in an absolute increase in paediatric thyroid carcinoma.

Of all ped-DTC, the papillary form is most common (80–90%). There are important differences between adult and ped-DTC in terms of clinical, molecular and pathological characteristics. Compared to adult DTC, patients with ped-DTC are more likely to present with advanced disease at diagnosis, with larger tumour sizes, more frequent lymph node involvement, distant metastases and multifocal disease. Despite this more aggressive presentation, ped-DTC has an excellent prognosis in terms of survival (overall 10-year mortality rate <2%), although tumour recurrence/persistence is not uncommon.

Unmet medical needs

The therapeutic approach for adult and ped-DTC is classically based on surgery (i.e. total thyroidectomy, with or without lymph node dissection), followed by postoperative treatment with ^{131}I.[2,3] The 2022 European Thyroid Association guideline for ped-DTC recommends total thyroidectomy and ^{131}I treatment in nearly all patients.[2]

The consequences of total thyroidectomy include the need for lifelong thyroid hormone replacement therapy, and the risk of endocrine and non-endocrine complications of surgery (i.e. hypoparathyroidism and recurrent laryngeal injury). Adverse effects of ^{131}I treatment have been widely reported in survivors of ped-DTC, affecting up to 35% of treated patients, probably depending on the cumulative activity/dose administered. Late complications of ^{131}I treatment include permanent salivary gland dysfunction, permanent nasolacrimal duct obstruction, permanent bone marrow suppression, pulmonary fibrosis, and possibly secondary primary malignancies (SPM).[4]

Although the overall disease-free survival of ped-DTC patients is excellent with the current treatment strategies described above, there is ongoing controversy about the necessity of the treatments applied. Central to this debate is the question of whether ped-DTC is currently over-treated, potentially leading to unnecessary adverse effects, particularly in the management of patients at low-risk of recurrence.

The current 'one-size-fits-all' approach could be improved by moving towards more personalised treatment. This may include less extensive surgery (lobectomy versus total thyroidectomy), more limited use of postoperative ^{131}I, and less intensive follow-up protocols. We hypothesise that modification of current treatment protocols will not affect disease-specific morbidity and mortality, yet may reduce treatment-related adverse outcome.

The ped-DTC registry: a unique European collaboration

Due to the rarity of the disease in childhood and adolescence, current treatment guidelines are based mainly on the results of small retrospective observational studies. However, such results should be interpreted with caution, due to their inherent limitations and potential bias. Given the important differences in the behaviour of DTC in children compared with adults, evidence from large studies conducted in adults cannot be directly extrapolated to children and, therefore, ideally should not be. To improve the management and outcomes of patients with ped-DTC, there is thus an unmet need for consistent prospective data collection from larger cohorts and randomised-controlled clinical trials.

As ped-DTC is a rare disease, no single study site is able to generate clinical data in sufficient quantities to conduct conclusive studies. So, in January 2024, we launched the European ped-DTC registry, in collaboration with the European Registries for Rare Endocrine Conditions (EuRRECa).[5,6] To date, at least 30 clinical sites in 13 different European countries are participating in this unique project. This collaborative effort will provide clinical datasets that are large enough to answer questions conclusively through well powered studies. The registry will provide detailed demographic information on each patient and will serve as an umbrella for linked studies.

First linked study: ped-DTC STRATIFY

With the support of the Dutch Cancer Society (KWF; who have provided a Young Investigator Grant), we started the first linked study in October 2024. In this prospective cohort study (n= 200), we aim to investigate prognostic factors of persistent/recurrent disease in children with DTC, and to establish prediction models based on these prognostic factors.

We believe that the first step towards personalised treatment protocols will be the development of accurate pre- and post-surgical prognostic stratification tools. We hypothesise that (a) a preoperative model consisting of a combination of patient characteristics, ultrasound and cytology/biopsy features will be able to predict the behaviour of ped-DTC and thus help to guide the extent of surgery, and (b) the addition of clinical, pathological and genetic features to the current American Thyroid Association risk stratification will lead to a more accurate postoperative prediction of recurrent/persistent disease in children with DTC and thus guide the need for adjuvant ^{131}I treatment. A more personalised approach to staging and treatment may reduce unnecessary exposure to extensive surgery or to ^{131}I in patients with ped-DTC, potentially reducing short and long term complications and toxicity.

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