Bridging the Gap Between Thyroidology & Pediatric Oncology

Chantal Anne Lebbink

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Colophon

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Bruggen bouwen op het gebied van de schildklier en kinderoncologie: op zoek naar verbetering van uitkomsten
(met een samenvatting in het Nederlands)

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Success consists of going from failure to failure without loss of enthusiasm.

-Winston Churchill-

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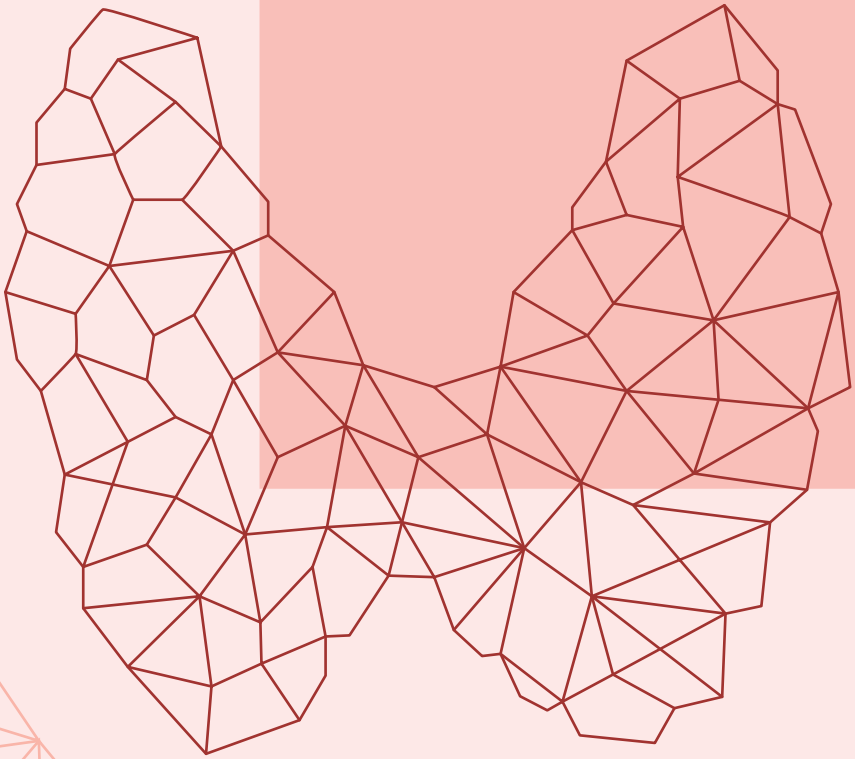

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General introduction

General introduction

In this chapter the principles and practices of pediatric thyroid disorders are described. Beginning with an overview of thyroid physiology, followed by a discussion on pediatric thyroid carcinoma and thyroid dysfunction during cancer treatment in children, and ending with the outline of this thesis.

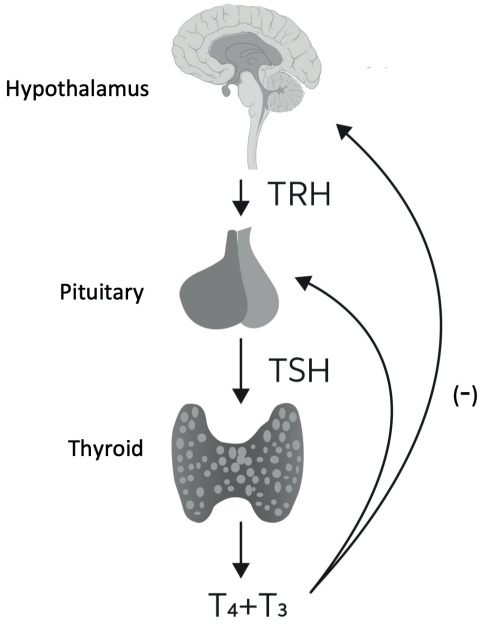
The thyroid gland

The thyroid is an endocrine organ, located in the lower part of the anterior neck. The thyroid consists of two lobes at both sides of the trachea connected through the isthmus. The thyroid is composed of two cell types: the follicular cells (thyrocytes) and parafollicular cells (C-cells) (1). The follicular cells aggregate into follicles, forming the basic structure of the thyroid. The follicles contain thyroglobulin, a large glycoprotein, that is important for the production of thyroid hormone. The follicles are also an important reservoir for thyroid hormone and iodine. The C-cells are calcitonin producing cells and are located between the follicles.

The follicular cells are polarized and have the apical membrane directed towards the lumen. The sodium (Na)-iodine symporter (NIS) is located at the basolateral membrane of the follicular cells and actively transports iodine into the follicular cell (2). The pendrin channel on the apical site of the follicular cell transports iodine into the lumen of the follicles, where organification of iodine and thyroid hormone production take place. Each thyroid hormone molecule consists of one thyroglobulin molecule and can bind to four iodine atoms.

The hypothalamic-pituitary-thyroid axis regulates the synthesis of thyroid hormones (figure 1). The hypothalamus releases thyrotropin-releasing hormone (TRH) which stimulates the anterior pituitary gland to secrete thyroid stimulating hormone (TSH). TSH stimulates the thyroid gland to produce thyroid hormones. The follicular cells produce T4 (thyroid hormone) and triiodothyronine (T3). T4 is produced solely by the thyroid gland whereas T3 is produced in thyroid gland as well as in the peripheral organs, by deiodination of T4. T3 and T4 provide negative feedback to the hypothalamus and the pituitary gland (1).

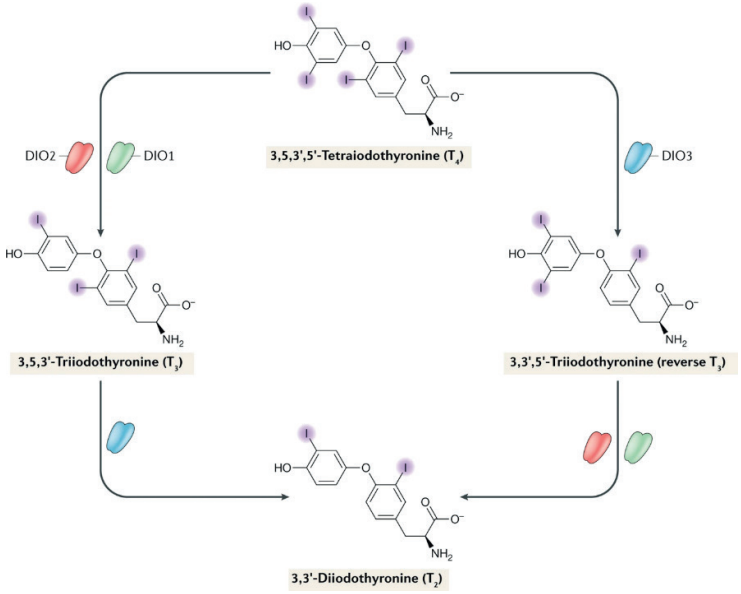
Figure 1. Hypothalamic-pituitary thyroid axis



Approximately 90% of the thyroid hormone output from the thyroid gland is produced as T4, whereas only 10% as T3. Thyroid hormone is mostly bound to serum proteins (thyroid-binding globulin (TBG), transthyretin, and albumin). T4 is the inactive form of thyroid hormone and must be metabolized to the active form T3. The conversion of T4 to T3 takes places in peripheral tissue by deiodinase enzymes. There are three different isoforms of the deiodinase enzyme, each with different functions: type 1 (D1), type 2 (D2) and type 3 (D3). D1 and D3 are located in the plasma membrane, whereas D2 is found in the endoplasmic reticulum (3). D1 and D2 have outer ring deiodinase activity and convert T4 to the active form T3 and degrade rT3 to 3,3'-T2 (figure 2). D3 has inner ring deiodinase activity and converts T4 to rT3 and T3 to 3,3'-T2. D1 is expressed in the thyroid, liver, and kidneys whereas D2 is expressed in the central nervous system, thyroid, brown adipose tissue, and muscles and D3 is expressed in the pancreas, placenta and in the adult brain tissue.

The activity of deiodinases is altered in case of critical illness and administration of several drugs (4,5).

Figure 2. Deiodinase thyroid hormone action
From Luongo, C. et al., Nat Rev Endocrinol, with permission



Thyroid disorders

Thyroid hormones are essential for cellular metabolism and are needed for normal longitudinal growth, maturation, and brain development during childhood (6,7). Insufficient thyroid hormone production (hypothyroidism) may result in, amongst other things, fatigue, weight gain, decreased growth velocity, mental retardation in the young, and constipation. An overactive thyroid gland (hyperthyroidism) may cause tiredness, tachycardia, weight loss and frequent stooling.

Hypothyroidism can be of thyroidal or central (hypothalamic or pituitary dysfunction) origin. Thyroidal hypothyroidism is diagnosed if free T4 (FT4) concentrations are low in combination with an increased TSH level. In case of central hypothyroidism, TSH concentrations remain low to normal in combination with low FT4 concentrations due to insufficient stimulation of an otherwise normal thyroid. Hyperthyroidism is diagnosed if TSH concentrations are suppressed in combination with increased FT4 concentrations.

Next to thyroid dysfunction, children may also present with an anatomical disorder of the thyroid gland such as an enlarged thyroid, a thyroid nodule or thyroid cancer. In these situations, the thyroid function can be completely normal. Thyroid nodules are described in 0.5-2% of all children (8,9). Although most thyroid nodules are benign, the risk for children of a thyroid nodule being malignant is 20-25%. Thyroid nodules can have autonomous thyroid hormone production resulting in thyrotoxicosis (autonomous thyroid nodule), however such nodules can be malignant as well.

Part I. Pediatric Thyroid Carcinoma

Thyroid carcinoma

Thyroid cancer comprises a wide spectrum of histological subtypes. There are two types of differentiated thyroid carcinoma (DTC) originating from follicular cells: papillary and follicular thyroid cancer (PTC and FTC, respectively). The papillary subtype is present in most pediatric cases. In contrast, poorly differentiated thyroid carcinoma, such as anaplastic thyroid carcinoma (ATC, arising from the follicular epithelium) and medullary thyroid carcinoma (MTC, deriving from parafollicular C-cells) are less common in children (10,11).

Differentiated thyroid carcinoma in children

DTC is a rare disease among children (0-19 years at diagnosis) but its worldwide incidence is rising (11). Age-standardized incidence rates of DTC in children vary between 0.5 to 20.0/million, depending on age group (11). Most children diagnosed with DTC are post-pubertal. Female sex is an important risk factor for developing thyroid nodules and DTC. It is suggested that the predominance of females may be induced by estrogen as estrogen is a potent growth factor for both benign and malignant thyroid cells (12). Other risk factors for DTC are exposure to neck irradiation, ^{131}I labeled meta-iodobenzylguanidine (MIBG), a positive family history for thyroid cancer or a thyroid cancer predisposition syndrome.

There are important differences between DTC in adults and children regarding clinical, molecular, and pathological characteristics. Children more often present with advanced disease at diagnosis, including more lymph node involvement, distant metastasis, and multifocal disease compared to adults with DTC (13). Although this more aggressive disease at diagnosis, DTC in children has an excellent prognosis (11,14). In addition, the genomic landscape of DTC in children differs from adults, dominated by diverse oncogenic fusions with a substantially smaller proportion of *BRAF* V600E driven tumors (15–17). Also, possible consequences of adverse (late) effects of treatment may be different for children because of their longer life span. These differences in between children and adults emphasize the need for specific recommendations for the pediatric population (18–20).

The American Thyroid Association (ATA) has developed specific recommendations for pediatric differentiated thyroid carcinoma (20). However, for the Netherlands and for Europe specific pediatric recommendations were lacking at the start of this thesis. Due to the fact that there are differences in regulations for medical care as well as cultural differences between the Unites States of America and the Netherlands and Europe, specific national and European recommendations on diagnostic work-up, management strategy and follow-up targets for children with DTC were envisioned.

Diagnosis of DTC in children

DTC in children most commonly presents with a palpable nodule of the thyroid gland. However, DTC may also be diagnosed after presentation with cervical lymphadenopathy or as an incidental finding on non-thyroid imaging exams (21). Less common are compressive symptoms such as dyspnea, hoarseness, dysphagia. Thyroid ultrasound is recommended to assess the risk of cancer in a thyroid nodule. Several specific ultrasound characteristics may increase the risk of a nodule to be malignant. An ultrasound scoring system can be used to help stratify for which thyroid nodules fine needle biopsy (FNB) is indicated (22–24). The Bethesda System for Reporting Thyroid Cytopathology is used in evaluating FNB results (25). The six different Bethesda categories determine the next steps in the diagnostic work-up or follow-up. When a FNB result confirms DTC (Bethesda 6 classification), a total thyroidectomy is generally advised. In case of uncertainty of the diagnosis, a diagnostic hemithyroidectomy may be advised.

Treatment for DTC

A total thyroidectomy is performed in all children diagnosed with DTC. If lymph nodes metastases are found pre- or perioperatively, a central and/or lateral lymph node dissection is also indicated. Subsequently, all children are treated with radioactive iodine; a targeted form of radiotherapy which is used in the treatment of DTC due to the unique characteristic of thyroid follicle cells to take up iodine. However, the role of post-operative radioactive iodine (^{131}I) therapy is a subject of debate, in terms of which children may benefit from ^{131}I therapy and which therapeutic goal (remnant ablation, adjuvant treatment or treatment of known disease) should be strived for.

Follow-up of children treated for DTC

After treatment for DTC, about 20% of the children experience recurrent disease (26). Recurrent disease is mostly located in the cervical lymph nodes (27). Factors associated with recurrent disease are lymph node metastases and distant metastases at diagnosis, preoperative elevated thyroglobulin (Tg) concentrations, the extent of resection (positive micro- or macroscopic margins ($R_{1/2}$)), ≥ 3 surgical interventions to achieve total thyroidectomy, capsular invasion, invasion of lymph vessels, infiltration of the surrounding soft tissues, multifocality and elevated postoperative stimulated thyroglobulin (26). Additionally, younger age has been shown to be a determinant for recurrent disease. Most recurrences occur in the first five years after diagnosis, although also late recurrences (>20 years after initial diagnosis) have been described (27). Therefore, long term follow-up has been advocated. The psychological impact of prolonged follow-up must be balanced with the decreasing risk of recurrent disease after a prolonged follow-up time.

Follow-up of DTC consists of clinical evaluation, neck palpation, measurement biochemical tumor markers (Tg and anti-thyroglobuline antibodies (TgAbs)), cervical ultrasound (US) and if indicated, FNB.

Thyroglobulin (Tg) and thyroglobulin antibodies (TgAbs)

Tg is a biochemical tumor marker for DTC. Tg has a high specificity, because it is only synthesized by thyroid cells (benign as well as malignant thyroid cells). Interpretation of Tg, however, needs to be in the context of TSH concentrations and previous therapy. Also, Tg concentrations raise due to thyroid trauma (e.g., FNB/surgery/^{131}I). In less differentiated tumors, Tg may be a less sensitive marker, however, less differentiated tumors are very rare in childhood. Circulating TgAbs are common in children (28) and affect Tg assays. Therefore, in the presence of clinically significant TgAb titres, Tg values are considered unreliable. In such cases, TgAb titres and imaging are the cornerstones of follow-up.

Cervical ultrasound (US)

Cervical US plays a central role in detection of recurrent disease (29). Cervical US include gray-scale studies with high-resolution linear-array transducers and assessment of lesion vascularity with color or power Doppler (30). A high-resolution cervical US enables detection of lesions as small as 2-3mm in the thyroid bed or cervical lymph nodes. Cervical US offers several practical advantages, including ubiquitous availability, absence of radiation exposure, no known adverse effects and low cost. However, US is highly equipment- and operator dependent and false-positive findings (lymphadenopathy while it is not DTC) are commonly seen. Additionally, the higher prevalence of enlarged inflammatory lymph nodes may reduce specificity of cervical US to detect recurrent disease, especially in children (31). Indeterminate or suspicious US findings may contribute to patient and provider worry and may lead to unnecessary investigations and/or interventions.

FDG PET/CT

18F-fluorodeoxyglucose (^{18}FDG) positron emissive tomography (FDG PET) is commonly used for many cancer types in evaluation and management. The tracer ^{18}FDG is a glucose analog that is taken up by benign as well as malignant cells, dependent on metabolic activity of the cell. The imaging modalities PET and computed tomography (CT) can be combined to acquire PET and CT images in a single session (FDG PET/CT). Several factors influence ^{18}FDG positivity in thyroid carcinoma: inflammation, primary tumor histology, the presence of radioactive iodine refractory disease, disease location, and TSH concentrations at time of the scan (30). Although, cervical US is the diagnostic imaging tool of first choice for detection of recurrent disease, FDG PET/CT can be useful in areas that are extremely difficult to explore using cervical US, such as the upper mediastinum or the retropharyngeal region (30).

Surveillance for DTC in children at increased risk for developing DTC

Children with a history of exposure to neck irradiation, ^{131}I-MIBG, a positive family history for thyroid cancer or a thyroid cancer predisposition syndrome are at increased risk to develop thyroid nodules and DTC. The risk of a nodule being malignant is increased in such children (32).

Surveillance programs for these high-risk patients aim to identify thyroid nodules suspicious of DTC at an early stage aiming to decrease overall morbidity and mortality (33). In contrast, a disadvantage of surveillance is the risk of a false-positive finding, which can engender undue anxiety and stress as well as higher health-care costs and may represent a risk for complications following unnecessary surgery. As for surveillance in general, the potential benefits must be balanced with the potential harms of surveillance.

Surveillance for DTC may be accomplished by either neck palpation or thyroid US. Both approaches have advantages and disadvantages that must be discussed with the patient and caregivers to drive a shared decision with respect to the preferred surveillance modality for each individual (34).

Several surveillance recommendations are available, such as the 2018 International Guideline Harmonization Group (IGHG) recommendations on thyroid cancer surveillance in survivors of childhood, adolescent, and young adult cancer (34), for children with thyroid cancer predisposition syndrome such as DICER-1 and *PTEN* hamartoma syndrome (PHTS) (35,36), and for children after nuclear accidents (37).

Subsequent differentiated thyroid carcinoma

Childhood cancer survivors (CCS) are at an increased risk of developing subsequent malignancies, of which approximately 10% are differentiated thyroid carcinoma (DTC) (38–41). The main risk factor for DTC after childhood cancer treatment is exposure to ionizing radiation that directly or indirectly involves the thyroid gland. Thyroid cancer in CCS is predominantly papillary thyroid carcinoma (PTC).

The increased risk for subsequent DTC ranges from 5- to 69-fold and increases linearly with the increasing estimated radiation dose to the thyroid gland (40). A plateau phase has been described around 10-30 Gy with a decline in occurrence after higher radiation doses, consistent with its cell-killing effect (42). In addition, younger age (<5 years) at exposure to radiation therapy is a risk factor for subsequent DTC. Patients treated for neuroblastoma with ^{131}I-MIBG may also be at increased risk for subsequent DTC (43). Moreover, in recent years, chemotherapeutic agents have been reported to play a possible role in the development of DTC after childhood cancer treatment (44,45).

The range of the latency period between treatment for childhood cancer and subsequent DTC is very broad, with a minimum latency time between radiation exposure and development of DTC of approximately 5-10 years (46).

Part II. Thyroid dysfunction during childhood cancer treatment

Thyroid hormone metabolism may change during childhood cancer treatment. Thyroid hormone metabolism may be disrupted due to direct damage to the hypothalamus, pituitary

or thyroid gland (caused by a tumor, chemotherapy, immunotherapy, or radiotherapy) leading to (central or thyroidal) hypothyroidism or thyroidal hyperthyroidism, due to supportive care drugs or as consequence of an adaptive mechanism during critically illness called 'euthyroid sick syndrome' (ESS).

Drugs and thyroid function parameters

Drugs can affect thyroid function parameters at several levels of the thyroid hormone metabolism, including the hypothalamus (TRH secretion), the anterior pituitary gland (TSH production), the thyroid gland (synthesis and secretion of T4 and T3) and peripheral due to change in conversion of T4 to T3 by the liver deiodinases) (47). Additionally, thyroid function parameters can be affected by altering affinity for or concentrations of thyroxine-binding globulin (TBG). Lastly, the absorption of thyroid hormone (in patients using levothyroxine) can be affected by food or drugs. Table 1 gives an overview of drugs commonly used in oncology treatment that may affect thyroid function parameters.

Table 1. Drugs known to affect thyroid function parameters

1. Antineoplastic agents
- Mitotane
- L-asparaginase
- 5-fluorouracil
- Bexarotene
- Tyrosine kinase inhibitors

2. Immunoregulatory drugs
- IL-2
- IFN-α
- Alemtuzumab
- Immune checkpoint inhibitors
  Anti-CTLA4 monoclonal antibodies (ipilimumab, tremelimumab)
  Anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab, cemiplimab
  Anti-PD-L1 monoclonal antibodies (atezolizumab, avelumab, durvalumab)

3. Supportive drugs
- Glucocorticoids
- Dopamine, dopamine agonists and dopamine antagonists
- Retinoids
- Lithium
- Rifampin
- Aminoglutethimide
- Metformin
- Amiodarone
- Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)
- Anti-epileptics

4. Displacement from thyroxine binding globulin (laboratory artifact)
- Furosemide
- Phenytoin
- Probenecid
- Heparin

Table based on (47–59)

Antineoplastic drugs in pediatric oncology

Antineoplastic drugs may affect thyroid hormone function or its parameters. However, only a few studies have prospectively evaluated thyroid function parameters in oncology patients. Mitotane, an agent used against adrenocortical carcinoma, is known to give central hypothyroidism with a in decrease FT4 concentration, with no change in FT3 and TSH concentrations. However, the exact mechanism for this is yet unclear (48).

L-asparaginase has been shown to cause TBG-deficiency, resulting in a decline in total T4 concentrations (49). 5-fluorouracil (5-FU) induces an increase in total T4 and T3 concentrations, whereas FT4 and TSH remain unaffected (50). Additionally, combinations of antineoplastic drugs (e.g. alkylating agents and podophylline derivatives) have shown to alter thyroid function parameters (50). Bexarotene is used in treatment of cutaneous T-cell lymphomas and may induce central hypothyroidism due to its action as selective agonist of the retinoid X receptor.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) may result in hypothyroidism or transient hyperthyroidism, which is thought to be the result of a non-autoimmune destructive thyroiditis. Destructive thyroiditis may directly cause hypothyroidism or hypothyroidism may be preceded by a transient period of thyrotoxicosis. Hypothyroidism is commonly observed during treatment with sorafenib, sunitinib and imatinib (30).

Immunoregulatory drugs

Immunoregulatory drugs can disrupt the thyroid hormone axis in various ways. After administration of immunoregulatory drugs hyperthyroidism, hypothyroidism and thyroiditis have been described. Thyroid dysfunction occurs mostly in the first weeks to months after start of therapy (51). Thyroid dysfunction has been reported after treatment with various immunoregulatory drugs (52–54), such as interleukin-2, interferon-α (discussed below), alemtuzumab (binds to CD52) as well as after immune checkpoint inhibitors as ipilimumab, tremelimumab (anti CTLA-4); pembrolizumab, nivolumab, and cemiplimab (anti PD-1); atezolizumab, avelumab, and durvalumab (anti PD-L1).

Immunoregulatory drugs may induce auto-immune dysfunction, (non-autoimmune) destructive thyroiditis or secondary hypothyroidism resulting from hypophysitis (52). Destructive thyroiditis is characterized by rapid development of a thyrotoxic phase, followed by the development of hypothyroidism. These consequences on thyroid function have thus far mainly been described in adult cancer patients. However, with the increasing use of these drugs in pediatric oncology, thyroid dysfunction due to these etiologies may be encountered more often in children.

Interferon-α

Interferon-*α* is used in the treatment of viral, autoimmune, and neoplastic diseases. Prevalence of newly developed thyroid dysfunction (hypothyroidism, thyrotoxicosis) has been described in patients treated with interferon-α for hepatitis C in a range from 0.6 to 34.6% (55).

Supportive drugs

Glucocorticoids used as anti-emetic, anti-neoplastic or anti-inflammatory drug in pediatric cancer, influence TSH secretion due to TRH inhibition in the paraventricular nucleus of the hypothalamus, resulting in TSH decrease (56). Higher doses of glucocorticoids (4 mg of dexamethasone per day) may also inhibit deiodinase type 1, which results in a decrease of the T3 concentration within several days (47).

The hypothalamic-pituitary-thyroid (HPT) axis is, among other things, regulated by dopamine. Dopamine activates dopamine D2 receptors stimulating TRH secretion, but, in contrast, dopamine also appears to oppositely effects the anterior pituitary gland. This direct stimulating effect through the dopamine D2 receptors does not override the inhibitory effect of dopamine on the anterior pituitary gland, resulting in overall lower TSH concentrations. Dopamine antagonists (rarely used in children) increase TSH concentrations.

Rexinoids are derivates of vitamin A (retinol) that interact with the retinoid X receptor and regulate complex networks involved in differentiation, proliferation, and apoptosis of cells. Vitamin A deficiency induces central hyperthyroidism by increasing TSHβ mRNA in the pituitary gland resulting in increasing T4 and T3 concentrations. Administration of retinoids, e.g. used in treatment of neuroblastoma, can induce central hypothyroidism at the hypothalamic-pituitary level.

Other drugs that are used in pediatrics and that may influence the thyroid function are lithium, rifampin and aminoglutethimide, metformin, amiodarone, tricyclic antidepressants, selective serotonin reuptake inhibitors and antiepileptics (5). Administration of lithium, rifampin and aminoglutethimide are associated with hypothyroidism. Metformin has a suppressive effect on TSH concentrations, however, these suppressed TSH concentrations do not lead to decreased T4 or T3 concentrations. Amiodarone is an arrhythmic agent containing iodine, which can induce thyrotoxicosis. Additionally, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) may interfere with the HPT axis. Classical antipsychotics as phenothiazines may alter iodine uptake, although the exact mechanism remains unknown. Also, antiepileptics are associated with alterations in thyroid hormone concentrations and TBG concentrations. Of note, after administration of carbemazepine, oxcarbemazepine and valproic acid increased thyroid hormone metabolism through the hepatic P450 system has been described, but also central hypothyroidism due to alterations in responsiveness of the pituitary gland (57).

Displacement from thyroxine binding globulin (laboratory artefact)

Drugs as furosemide, phenytoin, probenecid and heparin may cause laboratory artefacts due to displacement from protein-binding sites by free acids resulting in false positive increased or decreased low FT4 and FT3 concentrations (58,59).

Effects of radiotherapy on thyroid function parameters

The effects of radiation to the thyroid gland have been studied extensively. For decades it has been recognized that radiation therapy is the major risk for developing primary (thyroidal) and central (hypothalamic pituitary) hypothyroidism (60,61). Additionally, primary hyperthyroidism may also occur after childhood cancer treatment, although the literature on hyperthyroidism children treated for cancer is scarce and inconsistent (62,63). As expected, the risk of developing thyroid dysfunction is greatest in children with tumor types in which radiotherapy to the neck or $^{131}I^-$ is routinely used, such as lymphoma and neuroblastoma.

External beam radiotherapy, using photons or protons, is the most frequently used form of radiotherapy. A different form of radiation therapy is internal radiotherapy, where a source of radiation, such as $^{131}I^-$ is introduced inside the body. Iodine-based cancer therapies, such as ^{131}I-tositumomab used in treatment of non-Hodgkin's lymphoma, act by delivering $^{131}I^-$ to target cells (64). Unwanted uptake of $^{131}I^-$ in the thyrocytes leads to destruction of thyroid cells due to β-radiation. Comparable to ^{131}I-tositumomab, thyroid dysfunction, nodules and even DTC have also been described after ^{131}I-MIBG used in the treatment of childhood neuroblastoma (65).

Primary (thyroidal) hypothyroidism

In CCS exposed to radiation including the thyroid gland, the risk of developing primary hypothyroidism directly correlates to the radiation dose (risk greatest with thyroid doses ≥ 25 Gy) (51). Twenty years after follow-up, primary hypothyroidism has been reported in up to 30% and 50% of children exposed to doses of 35-45 Gy and ≥45 Gy, respectively (66). Most CCS with radiation-induced primary hypothyroidism will be diagnosed within 5 years after radiation exposure. However, new cases continue to emerge >20 years after treatment (67). The reported time of onset of primary hypothyroidism (elevated TSH concentrations) varies between 0-47 years after radiotherapy (60).

Children treated for neuroblastoma and Hodgkin lymphoma have been reported to have the highest rates of primary hypothyroidism after exposure to ^{131}I-MIBG and external radiation, respectively, with prevalences up to 50% and 32%, respectively (65,68). Children treated for Hodgkin lymphoma were found to have a relative risk of 17.1 to develop hypothyroidism after exposure to irradiation (66). Confounding factors in these studies may be the very young age of the children during exposure to radiation and the absorbed radiation dose.

To prevent thyroidal uptake of free circulating radioiodine during treatment of neuroblastoma, most children are given potassium-iodide (KI) prophylaxis. However, despite the use of KI, primary hypothyroidism has been reported in up to 52.4% of patients after therapeutic doses of ^{131}I-MIBG (69–73). For this reason, an improved prophylaxis regimen was designed (dilute, block and replace (DBR) protection with levothyroxine, methimazole and potassium iodide) and found to decrease the rate of hypothyroidism (74). In some centers, the combination of KI with perchlorate has been preferred (70).

Central (hypothalamic-pituitary) hypothyroidism

The prevalence of central hypothyroidism after cranial irradiation is dose dependent and has been described in 11.1 to 55% (75), with highest risk following doses ≥ 30 Gy (75,76). In childhood brain tumor survivors, the median time between irradiation and onset of central hypothyroidism has been reported to be 2.8 years (0.02-10.3 years) after radiation exposure (61).

Primary hyperthyroidism

CCS treated for Hodgkin lymphoma, leukemia and central nervous (CNS) tumors seem to be at the highest risk of developing hyperthyroidism even after adjustment for thyroid radiation dose (62). This may be confounded by the closer surveillance for thyroid abnormalities in these patients, especially in those whose thyroid glands were included in the radiation field. No risk factor other than exposure to radiotherapy has been found in these patients (62).

In the general population, the most common cause of hyperthyroidism is Graves' disease, which is caused by autoantibodies to the TSH receptor that increase thyroid cell proliferation and stimulate thyroid hormone synthesis and release. In CCS, the exact mechanism that causes hyperthyroidism after radiation therapy remains unknown, but it is most likely caused by a destructive (non-autoimmune) or autoimmune reaction to thyroid antigens, as released after thyroid cell damage (77).

A latency time of 15.1 years between cancer diagnosis in irradiated children and the occurrence of hyperthyroidism has been reported, with a cumulative proportion of CCS diagnosed with hyperthyroidism after 30 years of 2.1% (CI 1.8-2.5%) and 1.5% (1.2-2.0%) for females and males, respectively (62).

Euthyroid sick syndrome (ESS)

Thyroid function parameters can be distorted in critically ill children due an adaptive mechanism called ESS (78). In case of ESS, concentrations of T4 and T3 decrease, due to down-regulation of the hypothalamic-pituitary axis (TRH) and due to changes in activity of the liver deiodinases (4). Circulating TSH concentrations may remain within the normal range or be slightly elevated. ESS has been described during critically illness (e.g. after cardiac surgery, admission to the intensive care unit, severe renal or liver disease) and during starvation (anorexia). Next to down-regulation of TRH and TSH, also other hypothalamic-

pituitary hormones can be down-regulated during ESS such as the gonadotrophins (leading to amenorrhea). Distortion of the GH axis is also seen with GH resistance and low insulin like growth factor (IGF-1) concentrations. ESS in critical ill patients is considered to be a physiological protective mechanism activated in response to oxidative stress.

Deiodinases in euthyroid sick syndrome

During critical illness the deiodinases D1 and D2 are downregulated and D3 is upregulated, resulting in decreased FT4 but increased rT3 concentrations (79). For this reason, during critical illness, rT3 can be used to distinguish between ESS and central hypothyroidism. High rT3 concentrations on admission have been associated with higher mortality and morbidity in children on the pediatric intensive care unit(80)

Clinical management of ESS

The possible benefits of thyroid hormone treatment in ESS has been investigated, but T4 treatment did not result in improvement of survival or improvement of hemodynamics in children undergoing cardiac surgery (81), although this remains a subject of debate (82) as some studies have shown small benefits (e.g. T4 supplementation in children undergoing cardiac surgery resulted in a decrease in the number of patients requiring inotropic drugs in the ICU, serum creatine kinase-MB activity, serum positive troponin I ratio, and myocardial expression of MHCβ mRNA (83).

Aims and outline of this thesis

In this thesis we aimed to improve the outcome of pediatric DTC by developing evidence based national and international harmonized recommendations for care and by performing new studies on imaging techniques and surveillance strategies for pediatric DTC (**part I**). In addition, we aimed to explore disturbances in thyroid function parameters during childhood cancer treatment (**part II**)

Part I. Differentiated thyroid carcinoma

Chapter 2 describes the national incidence trends and survival trends of thyroid malignancy in Dutch children, adolescents, and young adults in a 30-year period. In chapter 3, we provide recommendations for thyroid carcinoma surveillance in children with PHTS based on critical review of all reported DTC cases in pediatric PTEN hamarthoma tumor syndrome (PHTS) patients. In this chapter, we describe two pediatric cases to illustrate the pros and cons of thyroid carcinoma surveillance in PHTS. In chapter 4, the new national recommendations for treatment of DTC patients <18 years of age in the Netherlands are presented. These recommendations were a first step towards harmonized European guidelines. The first European guidelines for the management of pediatric thyroid nodules and DTC are presented in chapter 5. In chapter 6, we suggest a new “Tg first” approach for children with low grade thyroid cancer, using the results of a retrospective cohort study, in which we evaluated the

value of routine cervical ultrasound in follow-up of DTC. Chapter 7 describes a retrospective case series study focusing on the usefulness of FDG PET/CT in patients with low detectable Tg concentrations suspicious for persistent or recurrent DTC. In chapter 8, we describe the differences in presentation and outcomes of subsequent DTC compared to sporadic DTC.

Part II. Thyroid dysfunction during childhood cancer treatment

Chapter 9 includes a systematic review of all currently available studies on thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer. In chapter 10 and 11, we present the first results of a prospective cohort study in the Princess Máxima Center for pediatric oncology: the THYRO-Dynamics study. In chapter 10 the dynamics of thyroid function parameters in the first three months after starting treatment in children with newly diagnosed cancer are described. In chapter 11, we describe the changes in thyroid function parameters in children undergoing hematopoietic stem cell transplantation (SCT). Chapter 12 provides a summary and general discussion of this thesis and considers future perspectives.

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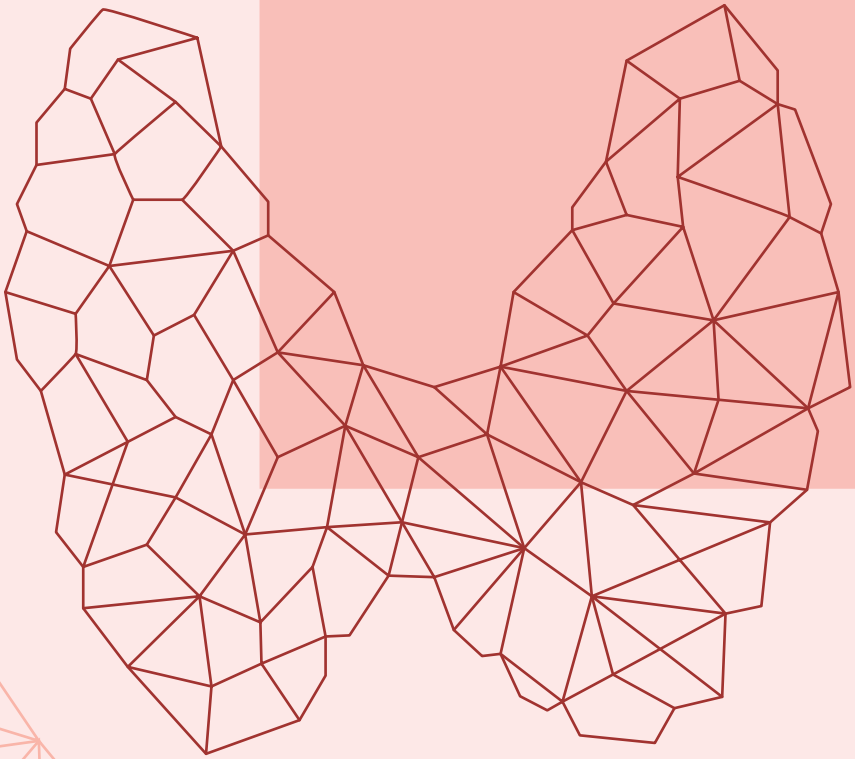

2

Opposite Incidence Trends for Differentiated and Medullary Thyroid Cancer in Young Dutch Patients over a 30-Year Time Span

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Simple Summary

Thyroid cancer is a rare disease in childhood; however, its incidence is rising. Thyroid cancer consists of three main types: Papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and medullary thyroid cancer (MTC). The aim of our retrospective study was to investigate the incidence and survival trends of these three thyroid cancer types in Dutch children, adolescents, and young adults over a 30-year life span. In total, 839 patients aged 0–24 years had been diagnosed with thyroid cancer between 1990 and 2019. The incidence of PTC increased significantly over time, the incidence of FTC showed a stable trend, while the incidence of MTC decreased significantly. Overall, the 10-year survival rates over the last decades were high (>95%) for PTC, FTC, and MTC in young individuals.

Abstract

Thyroid cancer is the most common endocrine malignancy in children. A rising incidence has been reported worldwide. Possible explanations include the increased use of enhanced imaging (leading to incidentalomas) and an increased prevalence of risk factors. We aimed to evaluate the incidence and survival trends of thyroid cancer in Dutch children, adolescents, and young adults (0–24 years) between 1990 and 2019. The age-standardized incidence rates of differentiated thyroid cancer (DTC, including papillary and follicular thyroid cancer (PTC and FTC, respectively) and medullary thyroid cancer (MTC), the average annual percentage changes (AAPC) in incidence rates, and 10-year overall survival (OS) were calculated based on data obtained from the nationwide cancer registry (Netherlands Cancer Registry). A total of 839 patients aged 0–24 years had been diagnosed with thyroid carcinoma (PTC: 594 (71%), FTC: 128 (15%), MTC: 114 (14%)) between 1990 and 2019. The incidence of PTC increased significantly over time (AAPC +3.6%; 95% confidence interval (CI) +2.3 to +4.8), the incidence rate of FTC showed a stable trend (AAPC -1.1%; 95%CI -3.4 to +1.1), while the incidence of MTC decreased significantly (AAPC: -4.4% (95%CI -7.3 to -1.5). The 10-year OS was 99.5% (1990–1999) and 98.6% (2000–2009) in patients with DTC and 92.4% (1990–1999) and 96.0% (2000–2009) in patients with MTC. In this nationwide study, a rising incidence of PTC and decreasing incidence of MTC were observed. For both groups, in spite of the high proportion of patients with lymph node involvement at diagnosis for DTC and the limited treatment options for MTC, 10-year OS was high.

Introduction

Thyroid cancer is rare during early childhood (<10 years of age) (1,2); however, it is the eighth most frequently diagnosed cancer among adolescents (15–19 years) (3). Thyroid cancer accounts for 2–6% of all pediatric malignancies, making it the most common endocrine cancer in children (4,5). In addition, it is the second most common cancer in adolescent girls, due to a strong female predominance of differentiated thyroid carcinoma (DTC) which usually manifests during puberty (3,6). Thyroid cancer comprises a wide spectrum of histological subtypes; on the one hand, there are two types of DTC originating from follicular cells (papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)), while on the other hand, medullary thyroid carcinoma (MTC) derives from parafollicular C-cells. The papillary subtype represents the large majority of cases with pediatric thyroid cancer (83%), followed by FTC (10%) and MTC (5%) (1,7). In pediatric patients with DTC, lymph node involvement and distant metastases at the time of diagnosis occur more frequently than in adults (2). Nevertheless, pediatric DTC has an excellent prognosis (8). Pediatric MTC is not susceptible to radio-iodine treatment and is associated with worse survival (7,9). For this reason, in familiar cases such as the multiple endocrine neoplasia type 2 (MEN2) syndrome, prophylactic thyroidectomy is advised (10).

A rising incidence in pediatric thyroid cancer—especially PTC—over the last decades has been reported in several studies and matches epidemiological findings of thyroid malignancy in adults (8,11). In the United States of America, the incidence of thyroid cancer in patients aged 0–19 years showed a gradual annual percent change (APC) of +1.1% during 1973–2006, while it markedly increased thereafter (APC 2006–2013: +9.6%) (8). Studies in Europe and South Korea have demonstrated comparable results (12,13). There is an ongoing debate about the underlying mechanisms that may explain this phenomenon. Some suggest it is attributable to overdiagnosis, driven by the combination of the expanding usage of imaging studies, enhanced imaging techniques, in combination with the high prevalence of indolent differentiated thyroid tumors even in the juvenile population (14), while others argue that the concurrently increased incidence of large tumors and advanced-stage disease is proof of a 'true' rise in pediatric DTC (8,15). Suggested explanations for a true rise in children are the increased obesity prevalence and radiation exposure as a consequence of environmental radiation or after treatment for childhood cancer (16–18).

The Netherlands has a comprehensive national cancer registry (Netherlands Cancer Registry, NCR), which creates the opportunity to investigate the true incidence trends of thyroid malignancy with great accuracy. We aimed to retrospectively evaluate pediatric thyroid cancer incidence and survival trends from 1990 to 2019, based on patient and tumor characteristics among patients aged 0–17 years in the Netherlands using the population-based data of the NCR. Young adults (18–24 years) were also included as a (post-pubertal) comparative group, embodying the youngest patients treated in adult oncology centers.

Materials and Methods

Study Population

All Dutch patients below 25 years of age diagnosed with a malignant thyroid carcinoma from January 1990 to December 2019 were selected retrospectively from the NCR.

Definitions

Thyroid carcinoma cases were classified according to the International Classification of Diseases for Oncology, Third Edition (ICD-0-3) by topography (C73) and histology: Papillary (ICD-O-3 M8050, M8140, M8201, M8260, M8340-44, M8350, and M8504), follicular (ICD-O-3 M8290, M8330-32, M8335, and M8339), medullary (ICD-O-M8345, M8510-11) thyroid carcinoma, and others (ICD-O-3 M8000, M8337, and M8346) (19). Only thyroid carcinomas with malignant behavior (i.e., 5th digit of the morphology code/3) were included. No cases were diagnosed with an anaplastic thyroid carcinoma during our study period. Tumor staging was recorded according to the TNM (Tumor, Node, Metastasis) classification system of the Union for International Cancer Control (UICC) (20). The edition applicable at the time of diagnosis of thyroid carcinoma was used. In the case of a missing pathological TNM classification, the clinical TNM was used.

Patients were classified as treated in a university hospital if they received thyroidectomy and/or radio-iodine treatment in a university hospital.

The Netherlands Cancer Registry

The nationwide population-based NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has had national coverage since 1989 with a completeness value of at least 96% of all newly diagnosed malignancies in the Netherlands (21). The NCR relies on comprehensive case notification through the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharges. Retrospectively, data are extracted on patient, tumor, and treatment characteristics. Information on vital status (i.e., alive, dead, or emigration) was obtained by annual linkage of the NCR with the Personal Records Database (BRP) that holds vital statistics on all residents in the Netherlands. The last linkage was on 1st February 2021.

Statistical Analyses

Characteristics of the study population were described as percentages in relation to three periods of diagnosis: 1990–1999, 2000–2009, and 2010–2019. In addition, patient characteristics were analyzed for the following age groups: 0–17 (children and adolescents) and 18–24 years (young adults). Patients diagnosed with DTC and PTC were further divided into 0–9 (children), 10–14 (children), 15–17 (adolescents), and 18–24 years. This was not possible for FTC and MTC due to the low number of cases. Differences among categorical

variables were tested with the 2 tests or the Monte Carlo estimate for the Exact test in case of small numbers.

Annual incidence rates were calculated per million person-years, using the annual midyear population size as obtained from Statistics Netherlands (CBS). Rates were age-standardized according to the age structure of the World standard population for the age ranges 0–9, 0–17, and 0–24 years (22). Incidence rates were presented in the figures as three-year moving averages by taking the average of the rates of each given year and the rates on either side of it. Changes in incidence over time were evaluated by calculating the average annual percentage change (AAPC) along with the corresponding 95% confidence intervals (CI). AAPC was derived from linear regression modelling, using the calendar year as a continuous variable (22). The Joinpoint regression program (version 4.5.0.1; https://surveillance.cancer.gov/joinpoint/, accessed on 24 June 2021) was used to check for trend transitions during the study period (23). The null hypothesis assumed that the AAPC was constant throughout the study period. The permutation test was used to determine the number of joinpoints by default set to a maximum of four (24).

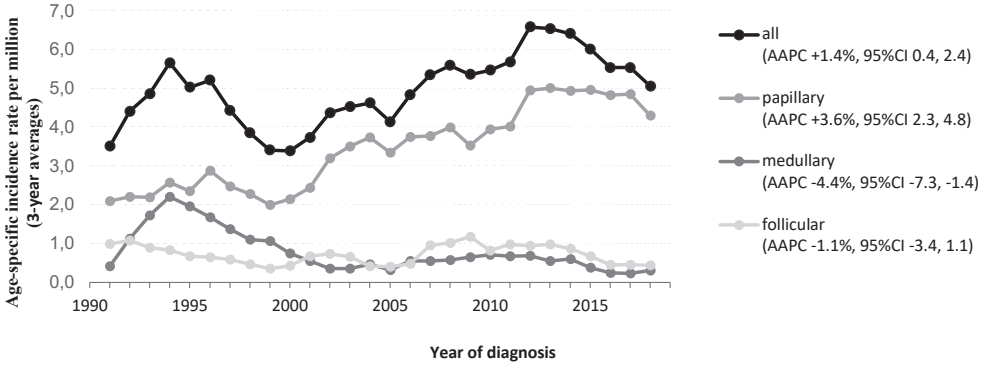
Survival time was calculated as the time elapsed between the date of diagnosis and the date of death due to any cause (event) or censoring (i.e., loss to follow-up, emigration before 1 February 2021), whichever came first. Traditional actuarial survival analysis was used to calculate overall survival (OS) at 10 years after diagnosis. OS was used instead of relative OS, which is an estimation of the disease-specific survival, because competing causes of death are rare among young cancer patients in developed countries such as the Netherlands (25). Kaplan–Meier curves and the logrank test were used for visualization and comparison of survival between DTC and MTC, respectively. Additional survival analysis to evaluate changes in survival over time was not possible due to the low number of events.

Incidence analyses were performed using SAS software (SAS system 9.4, SAS Institute, Cary, NC, USA), whereas STATA/SE 16.1 (StataCorp LP, College Station, TX, USA) was used for survival analyses. A p-value < 0.05 was considered statistically significant.

Results

A total of 839 children, adolescents, and young adults aged 0–24 years (Table S1) had been diagnosed with thyroid carcinoma between 1990 and 2019. The most common histopathological tumor subtype was PTC, accounting for 71% of the cases (n=594). FTC and MTC were found in 15% (n=128) and 14% (n=114) of the cases, respectively. Three patients had been diagnosed with a mixed/other histologic tumor type. Overall, the incidence of thyroid carcinoma increased in children/adolescents/young adults between 1990 and 2019 with an AAPC of +1.4% (95%CI 0.4 to 2.4) (figure 1). Further results are described by subgroup: DTC (consisting of PTC and FTC) and MTC.

Figure 1. Time trends in incidence of patients aged 0–24 years with thyroid carcinoma in the Netherlands, 1990–2019



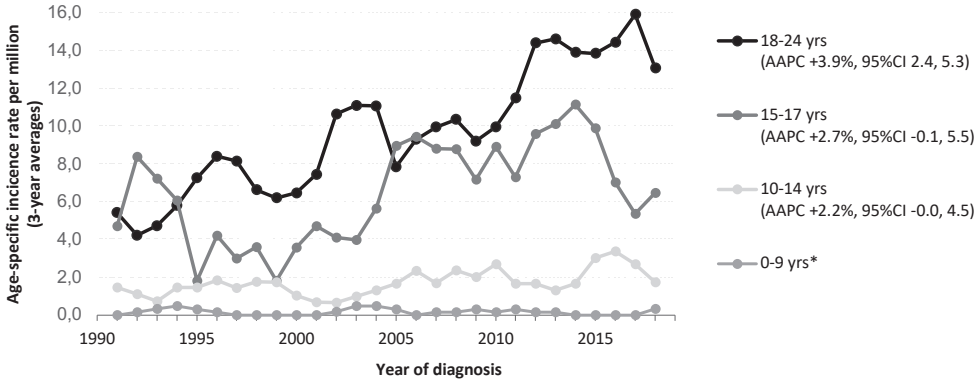
Abbreviations: AAPC, average annual percent change; CI, confidence interval. Three-year moving averages of the age-standardized incidence rate of thyroid carcinoma (standardized according to the World Standard Population) are shown. AAPC was estimated from a regression line, which was fitted to the natural logarithm of the rates using the year of diagnosis as a regressor variable.

Differentiated Thyroid Carcinoma

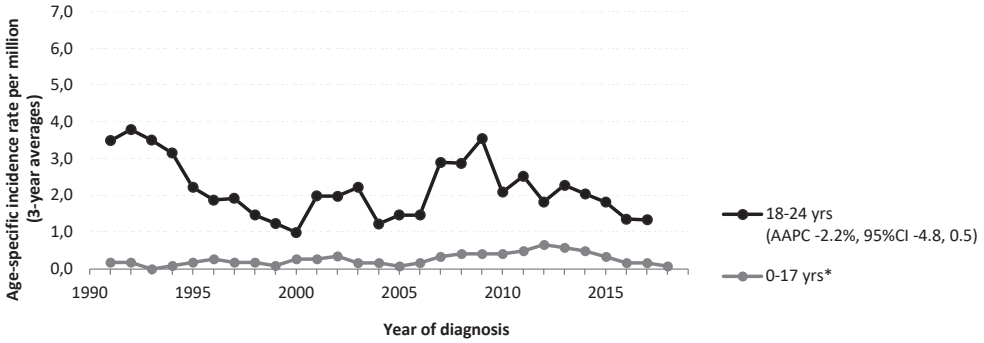
In a 30-year time span, 722 children, adolescents, and young adults had been diagnosed with DTC. The incidence of DTC in children/adolescents/young adults increased significantly over time, from 3.1 per million person-years (1990–1999) to 5.3 per million person-years (2010–2019), with an AAPC of +2.6% (95%CI +1.6 to +3.7) (figure 1). No join points were identified, which implicates a steady increase in incidence over time. Similar shifts in incidence were found, when specifically looking into PTC; the incidence of PTC increased significantly over time (AAPC +3.6%; 95%CI +2.3 to +4.8). In contrast, the incidence rates among FTC showed a stable trend, although the number of patients diagnosed with FTC was very low. The age-specific incidence rates are presented in figure 2A,B. The incidence of DTC among boys as well as girls increased significantly over time (Table S2). When focusing on age subgroups, the increasing incidence of PTC was seen in all age groups 10 years; however, this was only significant in young adults ($p < 0.001$).

Figure 2. Time trends in incidence of patients aged 0–24 years with thyroid carcinoma by histology and age in the Netherlands, 1990 2019

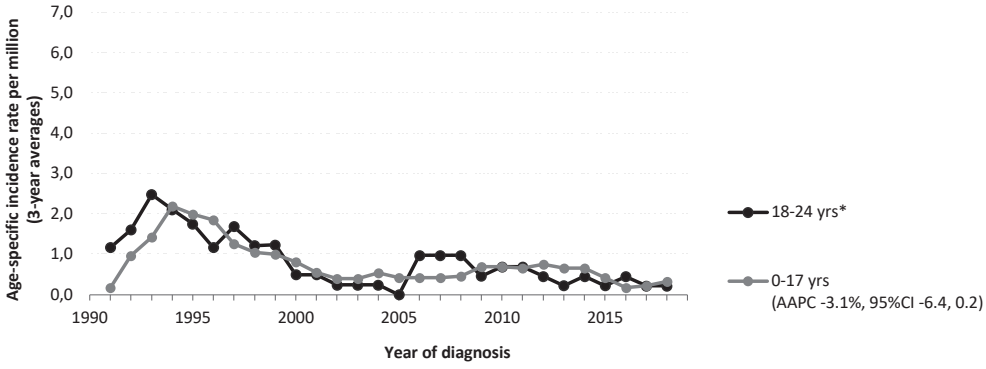
A. Papillary carcinomas by age group



B. Follicular carcinomas by age group



C. Medullary carcinomas by age group



(**A**) Papillary thyroid carcinoma. (**B**) Follicular thyroid carcinoma. (**C**) Medullary thyroid carcinoma. Abbreviations: AAPC, average annual percent change; CI, confidence interval. Three-year moving averages of the age-specific incidence rate of thyroid carcinoma are shown. The incidence rates of the patients 0–9 and 0–17 years are age-standardized according to the World Standard Population. AAPC was estimated from a regression line, which was fitted to the natural logarithm of the rates using year of diagnosis as a regressor variable. *Estimation of a reliable average annual percentage change was not possible because of n = 0 in >5 incidence years.

Of all patients with DTC, 28% (n=204) were <18 years of age (Table 1A); only 2% (n=13) of the cohort was aged <10 years at diagnosis of DTC. The age distribution of DTC did not differ over time. Girls were more often affected than boys (78% vs. 22%, respectively) regardless of age (figure 3). DTC as second primary cancer was observed in 2% (n=18, all PTC) of the patients. Most patients with DTC (42%) were found to have a T2 stage tumor. The distribution of T-stage changed significantly over time (p<0.001), with a shift from T4 stage to T3 stage and from T2 stage to T1 stage. In more than 40% (n=300) of the patients with DTC, lymph node metastases were found in the pathological report. Children and adolescents were diagnosed with lymph node metastases more often compared to young adults (54% vs. 40%, p=0.001). Significantly more lymph node metastases were reported in the period 2000–2009 (52%, p<0.02). Distant metastases were reported in 3% of the patients with DTC in total and were more frequently found in children (15% vs. 2% in older patients, p<0.001). The characteristics of DTC by age group are presented in Table S3.

Table 1A. Characteristics of differentiated thyroid carcinoma patients aged 0-24 years in the Netherlands, 1990-2019

	Total		Average per year	Period of diagnosis						
				1990-1999		2000-2009		2010-2019		
	N	%	N	N	%	N	%	N	%	p-value
	722		24	186	26	223	31	313	43	
Age										.75
0-9	13	2	0	4	2	5	2	4	1	
10-14	61	8	2	16	9	18	8	27	9	
15-17	130	18	4	27	15	46	21	57	18	
18-24	518	72	17	139	75	154	69	225	72	
Median age (in years, p25-p75)	20	(17-23)		21	(17-23)	20	(17-23)	20	(17-23)	.23
Sex										.98
boys	162	22	5	42	23	49	22	71	23	
girls	560	78	19	144	77	174	78	242	77	
Histology										.002
papillary carcinoma	594	82	20	138	74	185	83	271	87	
follicular carcinoma	128	18	4	48	26	38	17	42	13	
T stage[a]										<.001
1	198	28	7	25	14	64	31	109	35	

	Total		Average per year	Period of diagnosis						
				1990-1999		2000-2009		2010-2019		
	N	%	N	N	%	N	%	N	%	p-value
2	292	42	10	101	57	82	39	109	35	
3	145	21	5	22	13	41	20	82	26	
4	62	9	2	28	16	22	11	12	4	
unknown (3% of total)	25		1	10		14		1		
N stage[a]										.02
0	379	56	13	98	59	99	48	182	59	
1	300	44	10	68	41	108	52	124	41	
unknown (6% of total)	43		1	20		16		7		
Metastases										.41
no	606	97	20	140	97	161	95	305	97	
yes	20	3	1	4	3	8	5	8	3	
unknown (13% of total)	96		3	42		54		0		
Thyroid carcinoma as second primary cancer										.65
yes	18	2	1	6	3	6	3	6	2	
no	704	98	23	180	97	217	97	307	98	

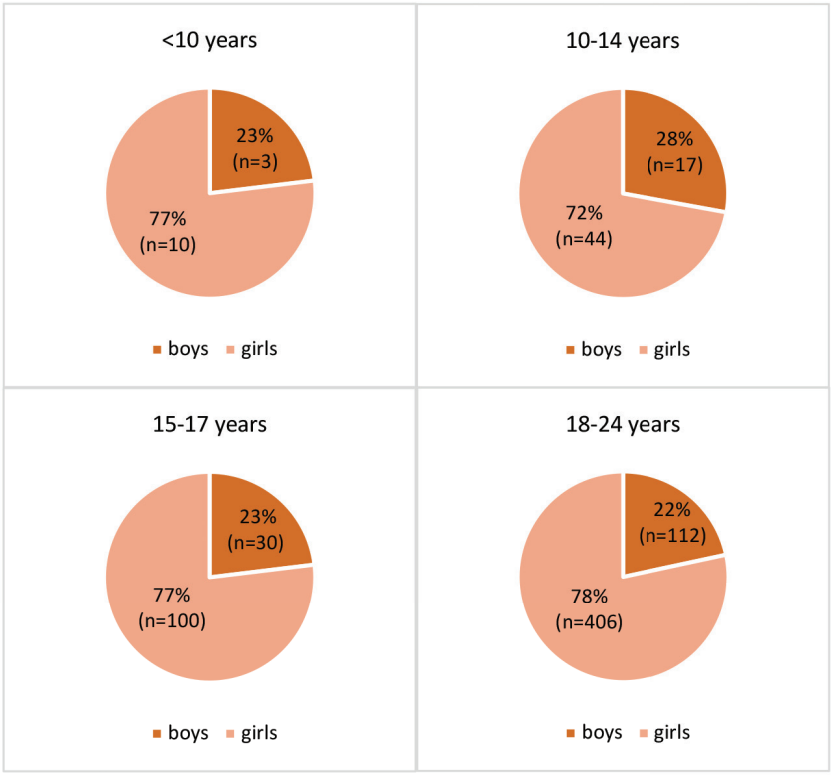
Abbreviations: *N*, number. Characteristics of the study population were described as percentages in relation to the three periods of diagnosis: 1990–1999, 2000–2009, and 2010–2019. Differences among categorical variables were tested with the χ^2 tests or the Monte Carlo estimate for the Exact test in case of small numbers. aTumor staging was recorded according to the TNM (Tumor, Node, Metastasis) classification system of the Union for International Cancer Control (UICC). The edition applicable at the time of diagnosis of thyroid carcinoma was used.

Table 1B. Characteristics of medullary thyroid carcinoma patients aged 0-24 years in the Netherlands, 1990-2019

	Total		Average per year	Period of diagnosis						
				1990-1999		2000-2009		2010-2019		
	N	%	N	N	%	N	%	N	%	p-value
	114		4	66	58	25	22	23	20	
Age										.67
0-17	78	68	3	43	65	18	72	17	74	
18-24	36	32	1	23	35	7	28	6	26	
Median age (in years, p25-p75)	13	(6-19)		13·5	(8-19)	11	(6-18)	11	(3-18)	.32
Sex										.18
boys	55	48	2	35	53	8	32	12	52	
girls	59	52	2	31	47	17	68	11	48	
T stage										.35
1	83	78	3	48	79	19	83	16	70	
2	12	11	0	7	11	1	4	4	17	
3	6	6	0	2	3	1	4	3	13	
4	6	6	0	4	7	2	9	0	0	
unknown (6% of total)	7		0	5		2		0		
N stage										.045
0	67	72	2	42	82	13	59	12	60	
1	26	28	1	9	18	9	41	8	40	
unknown (18% of total)	21		1	15		3		3		
Metastases										.84
yes	5	6	0	2	5	1	6	2	9	
no	75	94	3	37	95	17	94	21	91	
unknown (30% of total)	34		1	27		7		0		

Abbreviations: *N*, number. Characteristics of the study population were described as percentages in relation to the three periods of diagnosis: 1990–1999, 2000–2009, and 2010–2019. Differences among categorical variables were tested with the χ^2 tests or the Monte Carlo estimate for the Exact test in case of small numbers. [a]Tumor staging was recorded according to the TNM (Tumor, Node, Metastasis) classification system of the Union for International Cancer Control (UICC). The edition applicable at the time of diagnosis of thyroid carcinoma was used.

Figure 3. Sex distribution of differentiated thyroid carcinoma within different age groups in the Netherlands, 1990–2019.



Sex distribution of differentiated thyroid carcinoma of the age groups <10, 10–14 years, 15–17 years, and 18–24 years. Both percentage and the absolute number of patients are shown.

Over the years, patients with DTC were treated at an university hospital significantly more often (48% in 1990–1999, 67% in 2000–2009, and 73% in 2010–2019, p<0.001). This shift was especially noticeable in children and adolescents (0–17 years) (figure S1).

The median follow-up of all patients with DTC was 12.2 years. A total of 14 patients with DTC died during follow-up (12 PTC, 2 FTC, 5 of them within 10 years of follow-up), from which the cause of death was unknown. The 10-year overall survival was comparable between 1990–1999 and 2000–2009 (99.5% vs. 98.6%, respectively).

Medullary Thyroid Carcinoma

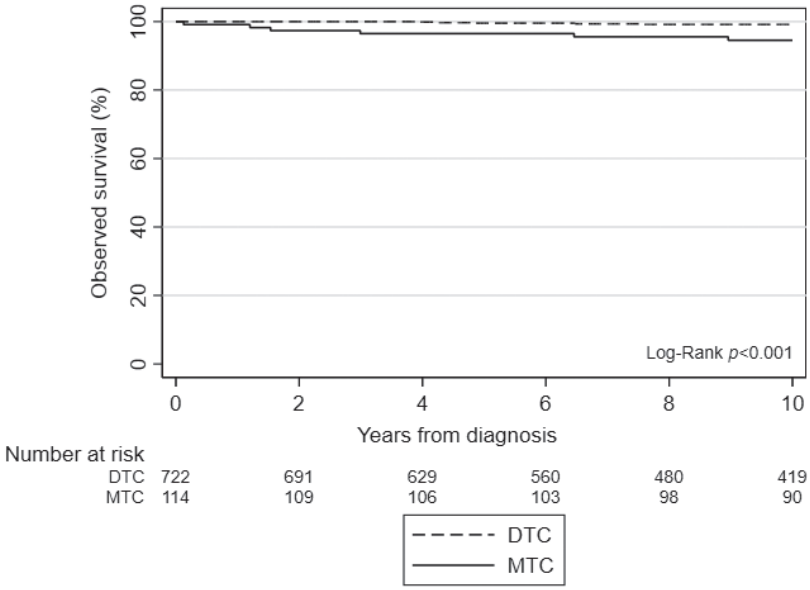
A total of 114 patients had been diagnosed with MTC during the study period. The incidence of MTC significantly decreased from 1.3 per million person-years in 1990–1999 to 0.5 per million person-years in 2010–2019 (AAPC: −4.4% (95%CI −7.3 to −1.5)) (figure 1). The incidence showed a downward near-significant trend for the younger age group (<18 years) (AAPC: −3.1% (95%CI −6.4 to +0.2), whereas estimation of a reliable AAPC was not possible for the young adults due to the low incidence in this group (figure 2C). The age at diagnosis and sex distribution did not change significantly over time. Tumor size distribution remained stable during 1990–2019, while the proportion of MTC with regional lymph node involvement showed a significant increase over time (p=0.045) (Table 1B). As shown in Figures 1 and 2C, the incidence rates of MTC showed a peak around 1994. Joinpoint analyses could not be performed due to the small number of events.

Boys and girls were equally affected (48% vs. 52%, respectively). In contrast to DTC, the majority of cases had been identified in childhood and adolescence (68% at age 0–17 years). Young adults diagnosed with MTC suffered from more advanced disease upon diagnosis than younger patients, illustrated by the significantly higher T-stage (p=0.01) and the higher proportion of patients with lymph node involvement (54% in young adults vs. 17% in patients <18 years, p<0.001, Table S2B). Likewise, young adults seemed to be diagnosed with a metastatic disease more often than children and adolescents (13% vs. 4% respectively), but this trend did not reach statistical significance (p=0.14).

Over the years, patients with MTC were treated at a university hospital significantly more often (68% in 1990–1999, 92% in 2000–2009, and 96% in 2010–2019, p=0.003). This shift in MTC care was detected in both children and adolescents and young adults (figure S1).

The median follow-up of all patients with MTC was 21.1 years. A total of 12 patients with MTC died during follow-up (six within 10 years after diagnosis), from which the cause of death was unknown. The 10-year overall survival was 92.4% for patients diagnosed in the period 1990–1999 and 96.0% for patients diagnosed in 2000–2009. Patients (all ages) with MTC experienced significantly worse survival than DTC (p<0.001) (figure 4).

Figure 4. Observed survival of patients, aged 0–24 years with thyroid carcinoma in the Netherlands, 1990–2019



Abbreviations: DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma. Survival time was calculated as the time elapsed between the date of diagnosis and the date of death due to any cause (event) or censoring (i.e., loss to follow-up, emigration, or 1 February 2021), whichever came first. The log rank test showed a significantly different 10-year survival between DTC and MTC: $p < 0.001$.

Discussion

This nationwide study, spanning three decades, shows opposite incidence trends for DTC and MTC in young individuals: Increasing incidence of DTC and decreasing incidence of MTC. In addition, the very good prognosis for both DTC as well as MTC in young patients (0–24 years) is confirmed, despite the frequent presence of advanced disease.

Differentiated Thyroid Carcinoma

The incidence rate of DTC in our cohort was comparable to previous studies (7,8,11,13,26), and the incidence of DTC seemed to increase in all age groups, with DTC being most frequently diagnosed in patients >18 years (13). This is mainly attributed to the increase in PTC over time. In accordance with two previous studies, stable incidence numbers of FTC over time were seen (8,13).

A preponderance of girls has been a persistent finding in previous studies reporting on pediatric DTC (11). It is suggested that this difference may be induced by estrogen as estrogen is a potent growth factor for both benign and malignant thyroid cells (27). With this in mind, the fact that a predominance of affected girls was also found in pre-pubertal

girls <10 years was surprising. Of these girls, six were <8 years and seven were aged 8–10. Possibly, the girls aged >8 years already had some activation of the gonadal axis contributing to this increased female/male ratio; unfortunately, data on the pubertal stage of the children could not be retrieved. The fact, however, that in the age group of 4–7 years the girls were also overrepresented may indeed confirm predominance also in pre-pubertal girls. This finding does not stand on its own (28,29). Lazar et al. described a male/female ratio of 3/7 in pre-pubertal children. Farahati et al. also described a male/female ratio of 1/7 in children <8 years (28). For the predominance of pre-pubertal and pubertal girls, several hypotheses may be suggested: In these young girls, estrogen exposure during mini-puberty may have been a trigger for the development of DTC at such young age. In addition, it may be considered that estrogen derived from adipose tissue may have contributed; for this reason, in future studies, body mass index should be taken into account. Of course, the small patient numbers make it impossible to draw conclusions and this must be further investigated in larger cohorts.

We found lymph node metastases in more than 40% of the patients with DTC, comparable to previous reports (51%) (26). However, relatively few patients with distant metastasis were found (3% versus 7.8–7.9% (1,26)). Possibly, this might be explained by a delay in diagnosis as a result of an overall poorer insurance status compared to our cohort (30). In line with previous studies, children and adolescents in our cohort were significantly more often diagnosed with more advanced disease, compared to young adults (2).

Over time, the T-stage of DTC patients at diagnosis shifted from T4 to T3 and from T2 to T1, suggesting that patients were diagnosed at an earlier stage. This shift in stage at diagnosis may be the result of improved quality and increased use of diagnostic imaging tools. Furthermore, the transition in the TNM classification system editions over time may have influenced our results since we based the TNM stage on the TNM edition applicable during the year of diagnosis. For example, the altered definition of T2 (tumor size >1 cm to ≤4 cm during 1990–2002 vs. >2 cm to ≤4 cm afterwards) could presumably explain the shift from T2 towards T1 tumors in recent years.

Medullary Thyroid Carcinoma

Contrary to DTC, the incidence of MTC decreased significantly during the study period. The literature on incidence trends of pediatric MTC is very limited. In 2018, Schmidt Jensen et al. described 27 patients aged 0–24 years with MTC and found no significant change in incidence over time (1980–2014) (13). A year later, Qian et al. reported an unchanged rate of MTC throughout the study period (1973–2013) in a cohort aged 0–19 years with MTC (cohort size unknown) (8). A possible explanation for the difference in incidence trends found in the Danish, American, and now Dutch populations are the small number of patients in the Danish and American cohorts. Another explanation for this could be a difference in approach to timely genetic counseling and, subsequently, preventive thyroidectomies at a young age in children diagnosed with MEN2. Also in contrast to DTC—but in line with

previous research—MTC was diagnosed most frequently in patients <18 (7). Patients >18 years more often presented with advanced disease, which may reflect late diagnosis in non-familiar or not-yet-recognized familiar cases. Genetic syndromes harboring an increased risk for MTC may be difficult to recognize, contributing to the delay in diagnosis of MTC (31).

The incidence of MTC peaked around 1994 and dropped afterwards. Synchronously, patients with MTC were found to have more advanced disease upon diagnosis in recent years. These findings can possibly be explained by the introduction of pre-symptomatic DNA screening in children from MEN2A families and prophylactic thyroidectomy in children with a high risk of MTC, which became common practice after the identification of germline mutations in the RET gene as the origin of MEN2 syndromes in the early 1990s (32,33). In the first years after the implementation of RET mutation screening, many children from MEN2A families were identified with local MTC, which resulted in the earlier mentioned peak incidence around 1994. After this first "wave", DNA screening

in early childhood prompted an early prophylactic thyroidectomy before the onset of MTC in the majority of children with MEN2A, explaining the declined incidence of MTC in the following years. On the contrary, children with MEN2B are unfortunately often not diagnosed until after the development of symptomatic (advanced) MTC, because RET mutations occur as de novo in 75–90% of MEN2B patients (10,34). Therefore, the implementation of DNA screening presumably did not affect the incidence of MEN2B- related MTC on a large scale. Together with the decrease in MEN2A-related MTC, this may have led to an increased proportion of (late-recognized) MTC in the context of MEN2B. This may also explain our finding of the higher percentage of MTC patients with lymph node involvement found in more recent years. In addition, MTC within the context of MEN2B is known to occur even earlier in life and with more aggressive behavior when compared to MEN2A.

Site of Treatment

Over the years, patients with thyroid carcinoma—both DTC and MTC—were more often treated in a university hospital, reflecting centralization of healthcare. Centralization of care is an important step in improving care for children, adolescents, and young adults with rare diseases such as thyroid carcinoma in order to optimize diagnostics, management, and outcomes while minimizing the long-term adverse consequences (35). We could not detect an improvement in 10-year OS over the years. Future studies will have to evaluate whether the number of adverse effects of treatment, such as hypoparathyroidism, have decreased with increasing centralization.

Strengths and Limitations

The major strengths of this study include its national coverage and standardized data collection. These elements resulted in the availability of generalizable and reliable data with a low risk of (information) bias. Furthermore, the long follow-up period allowed us to

analyze trends in incidence and outcome over a longer period of time, including the effect of the implementation of RET mutation analysis in MEN2A families.

Our study has several limitations. First, the exact causes of death were unknown. The causes-of-death database hosted by Statistics Netherlands (CBS) is not linked with the NCR on a routine basis. Therefore, we have checked the number of deceased patients in our study with the number of Dutch inhabitants who died from thyroid carcinoma at a young age derived from the independent causes-of-death statistics (source: Statistics Netherlands, CBS), and these numbers did not differ. Moreover, the absence of causes of death will have a limited effect on our survival outcomes as competing causes of death are rare among young cancer patients in developed countries such as the Netherlands (25). Second, the NCR used clinical (including ultrasound, computed tomography imaging, and functional imaging if available) and pathological data for stage registration until total thyroidectomy, which may have resulted in incorrect data about lymph node status, or the presence of distant metastases found at ^{131}I- scanning post-surgery. This may have led to an underestimation of the 'true' number of patients with positive lymph nodes or distant metastases. Furthermore, for DTC specifically, changes in the TNM system over time may have influenced the results. For MTC specifically, the low incidence and mortality numbers prevented us from performing further analyses into factors possibly related to the incidence or survival of MTC. Finally, information about germline RET mutations in patients with MTC, the family history of patients, and the incidence (trends) of premalignant C-cell hyperplasia would have helped to further elucidate the results of this study, but these data were not available.

Conclusions

In summary, the presently reported outcomes of the national Dutch cohort demonstrate an increasing incidence of pediatric PTC between 1990 and 2019, with a shift towards smaller tumors. This may be a reflection of a true rise, or, alternatively, it may reflect the increased usage and quality of diagnostics such as ultrasound of the neck. In contrast, the incidence of MTC decreased during this period, presumably explained by the implementation of pre-symptomatic DNA analysis in MEN2A families in the early 1990s. Furthermore, despite a more advanced disease in children and adolescents compared to adults, the overall survival rates over the last decades remain high for both DTC and MTC in young individuals.

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Supplementary materials

Figure S1. Proportion of patients with thyroid carcinoma aged <18 years and aged 18–24 years, treated at a university center

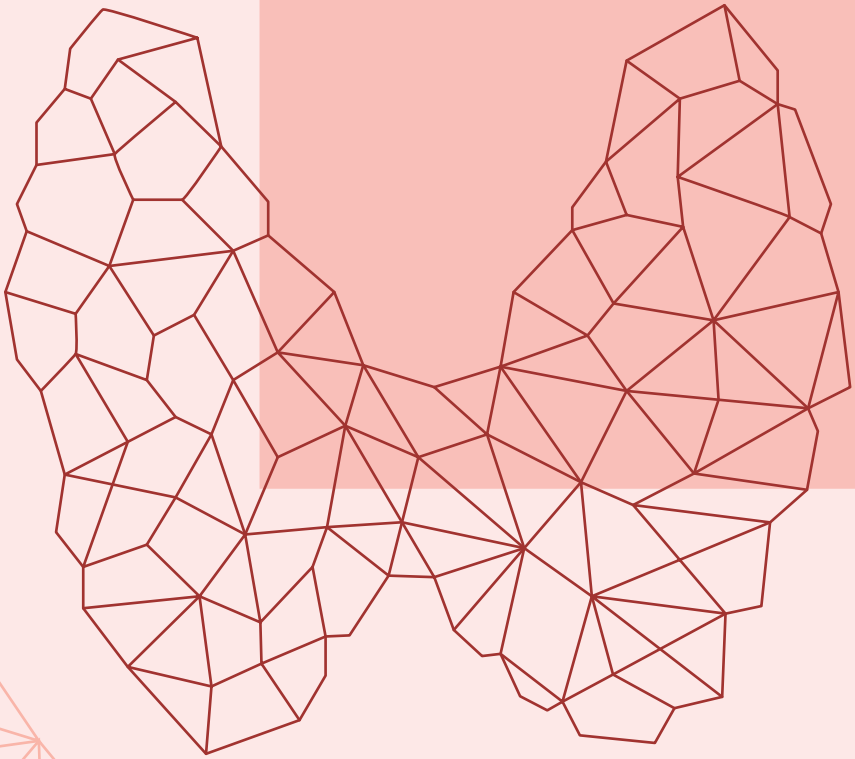
Table S1. Absolute number of cases thyroid cancer according to age in young Dutch patients over a 30-year time span

Table S2. Incidence of thyroid carcinoma in children, adolescents, and young adults aged 0–24 years in the Netherlands, 1990–2019

Table S3A. Characteristics of differentiated thyroid carcinoma patients aged 0–24 years in the Netherlands by age group, 1990–2019

Table S3B. Characteristics of medullary thyroid carcinoma patients aged 0–24 years in the Netherlands by age group, 1990–2019

Available online at: https://www.mdpi.com/2072-6694/13/20/5104/s1



3

Recommendations on Surveillance for Differentiated Thyroid Carcinoma in Children with PTEN Hamartoma Tumor Syndrome

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Abstract

Background

PTEN hamartoma tumor syndrome (PHTS) represents a group of syndromes caused by a mutation in the PTEN gene. Children with a germline PTEN mutation have an increased risk of developing differentiated thyroid carcinoma (DTC). Several guidelines have focused on thyroid surveillance in these children, but studies substantiating these recommendations are lacking.

Objective

The present study intends to provide the available evidence for a thyroid carcinoma surveillance program in children with PHTS.

Methods

An extensive literature search was performed to identify all studies on DTC in pediatric PHTS patients. Two pediatric cases are presented to illustrate the pros and cons of thyroid carcinoma surveillance. Recommendations for other patient groups at risk for DTC were evaluated. Consensus within the study team on recommendations for children with PHTS was reached by balancing the incidence and behavior of DTC with the pros and cons of thyroid surveillance, and the different surveillance methods.

Results

In 5 cohort studies the incidence of DTC in childhood ranged from 4 to 12%. In total 57 cases of DTC and/or benign nodular disease in pediatric PHTS patients were identified, of which 27 had proven DTC, with a median age of 12 years (range 4–17). Follicular thyroid carcinoma (FTC) was diagnosed in 52% of the pediatric DTC patients. No evidence was found for a different clinical behavior of DTC in PHTS patients compared to sporadic DTC.

Conclusions

Children with PHTS are at increased risk for developing DTC, with 4 years being the youngest age reported at presentation and FTC being overrepresented. DTC in pediatric PHTS patients does not seem to be more aggressive than sporadic DTC.

Recommendations

Surveillance for DTC in pediatric PHTS patients seems justified, as early diagnosis may decrease morbidity. Consensus within the study team was reached to recommend surveillance from the age of 10 years onwards, since at that age the incidence of DTC seems to reach 5%. Surveillance for DTC should consist of yearly neck palpation and triennial thyroid ultrasound. Surveillance in children with PHTS should be performed in a center of excellence for pediatric thyroid disease or PHTS.

Introduction

The PTEN hamartoma tumor syndrome (PHTS) is the encompassing name for the rare diseases Cowden syndrome, Bannyan-Riley-Ruvalcaba syndrome, and Proteus-like syndrome, and is caused by autosomal dominant mutations in the phosphatase and tensin homolog (PTEN) gene (1). PHTS is clinically characterized by macrocephaly, developmental delay and hamartomas. In addition, due to the pathogenic variant in PTEN, affected patients have a greatly increased risk to develop malignant neoplasms, including carcinomas of the breast, thyroid gland, endometrium, colon, and kidney (2).

Differentiated thyroid carcinoma (DTC) is one of the common cancer types in patients with PHTS, with a lifetime risk of 35–38% (2). This increased risk is already present during childhood, whereas the risk of developing other types of cancer during childhood appears to be equal to that of the general population (2). This may warrant periodic surveillance for DTC in affected children, and currently several thyroid surveillance recommendations for PHTS patients have been proposed (3-7).

The National Comprehensive Cancer Network (NCCN) in the Unites States of America recommends that pediatric PHTS patients receive an annual thyroid ultrasound from the age of diagnosis onwards (3). In contrast, the American Thyroid Association advises to perform annual physical examinations of the thyroid gland in children from the age of diagnosis of PHTS onwards with additional thyroid ultrasound in case of palpable nodule(s), thyroid asymmetry, or abnormal cervical lymph node(s) (4). The Dutch association for clinical geneticists (VKGN) proposes annual surveillance of the thyroid gland in children, by means of palpation or thyroid ultrasound. The Dutch VKGN guideline for adult PHTS patients recommends yearly neck palpation, thyroid ultrasound yearly or once every 2 years, and annual serum thyroid-stimulating hormone concentration (6). The UK Cancer Genetic Group advises to perform annual ultrasound surveillance from the age of 16 years onwards, or earlier in case of a family history for DTC or after informed discussion with the patient and its family (5).

Although these guidelines agree on once a year surveillance frequency, they are discordant with regard to the age at start and the method of surveillance. It may be questioned on which evidence these guidelines are based, considering the scarcity of studies in pediatric PHTS patients.

Consensus within the study team has been reached that surveillance for any childhood cancer may be justified when its incidence reaches 5%, also for tumors with a good prognosis (8, 9). For this reason, the first question that needs to be answered is about the incidence of DTC in children with PHTS.

The second question that needs to be addressed is whether there is evidence that DTC in PHTS behaves differently than sporadic DTC.

Thirdly, surveillance is only justified if its benefit outweighs any possible harm; in other words, surveillance should improve disease outcome. Therefore, the third question that should be answered before formulating recommendations on surveillance is whether detecting DTC in an early stage is beneficial for a child with PHTS.

In addition to a literature search, review, and consensus discussion, we present 2 cases to illustrate the pros and cons of surveillance for DTC in children with PHTS. We aimed to formulate optimal recommendations for surveillance of DTC in children with PHTS based on the best available evidence that also meet the (clinical) needs of young patients.

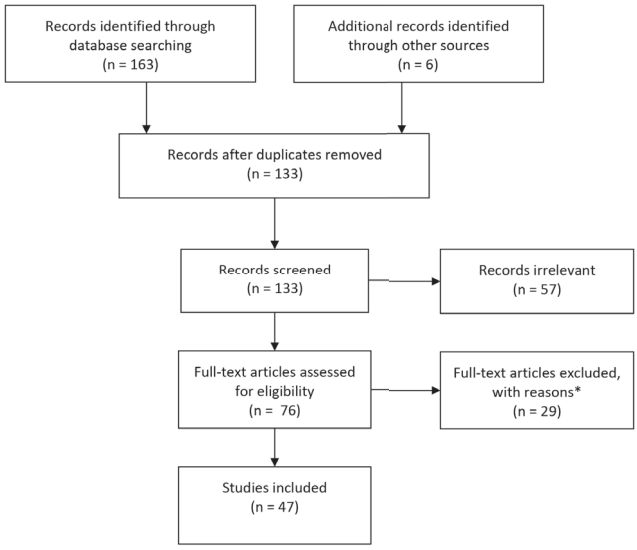
Methods

An extensive literature search was done using PubMed and Embase for the age of onset of thyroid abnormalities and benefits of surveillance for DTC in pediatric PHTS patients (figure 1). There was no date limit. Articles written in English, German, Dutch, and French were included. Data on children with a clinical diagnosis based on the PHTS criteria as well as on children with a proven PTEN mutation were included in our analysis. We set no minimum threshold for the number of patients in a cohort for studies to be included. Additionally, the references of all qualifying articles were meticulously screened to identify articles that were missed in the initial search.

To illustrate the pros and cons of surveillance for DTC in children with PHTS, 2 cases are presented. Informed consent was obtained from both patients and their parents for publication.

Results of the literature search were discussed within the national expert panel, including pediatric endocrinologists, endocrinologists, a pediatric radiologist, a pediatric oncologist, a pediatric surgeon, and a clinical geneticist. All panel members have special expertise in pediatric thyroid carcinoma and/or PHTS. Recommendations for surveillance were formulated.

Figure 1. Flow diagram of extensive literature results.



*Reasons for full-text article exclusion:
- No child data available
- No full text available
- No thyroid data available

Search strategy, Pubmed, search terms: (Cowden syndrome OR Cowden disease OR Bannayan Riley Ruvalcaba syndrome OR PTEN hamartoma syndrome) AND (thyroid cancer OR thyroid carcinoma OR thyroid nodule OR thyroid disease). To specify the search for childhood data, the terms (child OR pediatrics) were added. In total, 169 papers were found by the search of which 47 were included in this recommendation.

Results

Question 1: Incidence and Age of Onset of DTC in Children with PHTS

Incidence Studies

Five studies were found describing the incidence of DTC in pediatric patients with PHTS (table 1). Bubien et al. (10) calculated the cumulative risk for developing DTC in PHTS to be 5% for patients under 20 years of age. Tan et al. (11) confirmed this cumulative risk in a similar study: of the 105 patients with a PTEN mutation, with an age distribution ranging from 3 to 78 years, 5 developed DTC under the age of 20 years (4.8%). The results of Riegert-Johnson et al. (12) were concordant: in their cohort of 211 PHTS patients, 4% developed DTC before the age of 20, of which the youngest DTC patient was 10 years old. These studies included patients from academic hospitals and beyond in Western countries. In 2 other studies with child-only cohorts, the risk of developing DTC at the pediatric age was estimated to be around 12%, and the risk for developing benign nodular disease (BND) was estimated to be around 50% (13, 14). These studies included the patients from academic

hospitals. Nieuwenhuis et al. (15) reported that females had a higher risk of developing DTC than males, and this seems to be true for children as well. Ngeow et al. (16) reported that DTC was overrepresented in PHTS patients who carry a mutation in exon 5 of the PTEN gene. Frame shift PTEN mutations were also common amongst PHTS patients diagnosed with DTC, especially in the pediatric age group (17).

Table 1. Studies describing DTC childhood PHTS patients

Study	Risk, %	Sample size, n	Youngest age at diagnosis, years
Adult/child cohort (10-78 years)[a]			
Bubien et al. (10)	5	140	16
Tan et al. (11)	4.8	105	not reported
Riegert-Johnson et al. (12)	4	211	10
Child/adolescent cohort (<21 years)			
Smpokou et al. (14)	12	34	7
Plamper et al. (13)	12	16	6

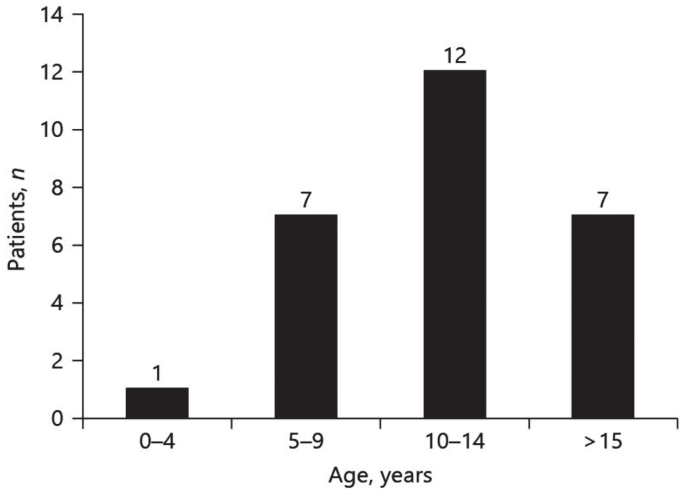
[a]Risk analysis for DTC (%) of the child cohort shown.

Cases

Age at Onset

Fifty-five children with PHTS with DTC and/or BND were identified in the literature. Adding to our 2 cases, 27 out of 57 children had proven DTC, 27 had proven BND, and in a number of cases histology was not reported (several children had both DTC and BND). Six children had thyroiditis (online suppl. Appendix A; see online Supplementary Materials). By combining all cases reported in the literature, the median age at diagnosis of DTC in the pediatric PHTS population was 12 years (range 4–17); the median age for developing BND was also 12 years (range 5–17). The youngest age at which DTC had been diagnosed was 4 years (follicular thyroid carcinoma (FTC)), with most cases of DTC diagnosed between the ages of 10 and 14 years (figure 2).

Figure 2. Age distribution of pediatric patients with PHTS diagnosed with DTC.



In total, 27 children (<18 years) with PHTS were identified with DTC. These patients were divided into 4 age categories: 0–4 years (n=1), 5–9 years (n=7), 10–14 years (n=12), >15 years (n=7).

Mode of Discovery.

The way in which DTC and BND had been detected was reported in some, but not in all cases (online suppl. Appendix B). Of the pediatric DTC patients, 7 were identified by physical examination, 4 by thyroid ultrasound, 1 due to observation by an attentive family member, 1 in preoperative evaluation for tonsillectomy, and DTC in 1 patient was found by evaluation of histology results. Of the proven BND patients, 4 were identified by physical examination, 8 by thyroid ultrasound, and 3 by attentive family members.

Question 2: Cancer Type and Behavior

In 52% of the cases identified in the literature with reported histology, FTC was diagnosed, as compared to a prevalence of 10% FTC in children without a PTEN mutation (18). This overrepresentation of FTC in pediatric PHTS patients is in agreement with the recognition of FTC being a major clinical characteristic by the NCCN.

No reports of more aggressive behavior of DTC, defined as increased risk for metastasized disease at diagnosis, recurrence, or increased morbidity or mortality when compared to children with sporadic DTC, could be found. The one study reporting on this topic showed low metastases and recurrence rates in children with PHTS; of the 32 PTEN mutation-positive patients diagnosed with DTC, 2 presented with cervical metastases and 1 with distant metastases at the time of diagnosis. With an average follow-up time of 3.3 years, no recurrences of DTC were identified (19). The cases identified by our literature study confirmed the relatively mild course of disease; of the 27 DTC cases, only 2 had reported metastatic DTC, and in 2 cases a recurrence was mentioned.

Question 3: Does Early Detection of DTC in Children with PHTS Improve Outcome?
No evidence was found for children with PHTS. In an extensive expert evaluation using the GRADE system by the International Guideline Harmonization Group, some evidence was found to answer this question in non-PHTS patients (20). For adults, level A evidence was found that detection of DTC in an early stage may lead to a lower mortality rate and a decreased risk of hypoparathyroidism (20), and level B evidence was found that it leads to lower recurrence rates (20). In addition, level B evidence was found that lower $^{131}I^-$ activity will decrease the risk for second primary malignancies caused by radiation exposure (20). For children, only level C evidence could be found that finding DTC in an early stage results in a lower risk for recurrence and lower mortality (20). Conflicting evidence was found for the effect of diagnosing DTC in an early stage and the risk for morbidity.

Formulating Recommendations with the Current Available Evidence

Question 1: Incidence of DTC in Children with PHTS
The data suggest that the prevalence of DTC at the pediatric age is approximately 4–12%. In concordance with the recommendations for other low-grade childhood tumors with excellent prognosis (such as Wilms' tumor), surveillance was deemed worthwhile when the risk of disease exceeds 5% (8, 9). Considering the data gathered for this study, it is expected that only in teenage children (>age 10) does the risk for DTC exceed 5%. With these facts in mind, the study team recommends surveillance for DTC in PHTS from the age of 10 years onwards.

Question 2: Does DTC in PHTS Behave Differently than Sporadic DTC?
Sporadic childhood DTC, although it generally presents with a more advanced disease stage when compared to adults, has a very good prognosis. The 10-year survival rate for papillary thyroid carcinoma (PTC) varies between 93 and 99%, and the 10-year survival rate for childhood FTC varies between 96 and 100% (18, 21, 22).

DTC in children with PHTS might have a different clinical behavior than sporadic DTC since differences in oncogenic pathways involved can lead to differences in cancer phenotype (1). For this reason, it may be valuable to identify the cancer phenotype (such as disease progression) caused by PTEN protein inactivation, as it may help to understand the behavior of DTC in PHTS patients. In animal models, evidence exists that PTEN mutations are more common in the highly malignant anaplastic thyroid carcinoma and that loss of heterozygosity results in higher levels of invasion and loss of differentiation (21-25). This may suggest that PTEN mutations potentially contribute towards a thyroid carcinoma type that is more aggressive in nature, and more prone to becoming poorly differentiated (26, 27).

No reports could, however, be found on PTEN mutations causing pediatric DTC with a more aggressive phenotype compared to pediatric DTC without a PTEN mutation. In fact, PTEN mutations in sporadic adult DTC were not associated with tumor invasiveness, metastases, and recurrence, and the low metastatic and recurrence rates we found in this review of the literature may even suggest that DTC in pediatric PHTS patients has a possibly milder disease progression (28, 29).

The national expert panel concluded that, due to lack of reports of more aggressive behavior of DTC in PHTS compared to sporadic DTC, data about advantages and disadvantages of surveillance for DTC in other populations such as childhood cancer survivors (CCS) may be applied, due to the fact that similar principles with regard to surveillance of DTC exist (30).

Question 3: Does Early Detection of DTC in Children with PHTS Improve Outcome?

If early detection of DTC improved outcome, this would be an argument for an active surveillance program. No evidence for improved outcome was found for PHTS children and for children in the International Guideline Harmonization Group initiative, only level C or conflicting evidence was found. Consensus within the study team for the PTEN hamartoma population was therefore reached based on the opinion of the national expert panel.

For children with PHTS, the national expert panel recommends that, although DTC in children has a good prognosis, surveillance for DTC is desirable aiming to detect DTC in an early stage. This may lead to improved disease outcome, mainly due to less complicated surgery. Advanced disease, such as invasive growth and metastases, requires more extensive surgery, thereby increasing the chance of complications such as recurrent laryngeal nerve injury and hypoparathyroidism. Moreover, advanced disease requires a higher cumulative $^{131}I^-$ activity which is undesirable in young patients and in patients at risk for secondary malignancies (20).

Based on these arguments, the national expert panel recommends surveillance for DTC in children with PHTS to enable detection of DTC in an early stage.

Cases

Two cases are presented that illustrate the potential disadvantage of surveillance and that of nonsurveillance.

Case 1: An Example of a Potential Disadvantage of Surveillance

A boy, diagnosed with PHTS, received routine thyroid ultrasound at the age of 8 years which revealed multiple thyroid nodules without calcifications. The largest nodule had a diameter of 5 mm, without suspicious cervical lymph nodes. Six months later, a follow-up ultrasound showed unchanged thyroid nodules and, again, no suspicious lymph nodes. Another 6 months later, a third ultrasound showed multiple hypoechogenic nodules of which the largest was still 5 mm, but now multiple bilateral nonenlarged prominent lymph nodes were seen with several hyperechogenic foci; additionally, enlarged inhomogeneous salivary glands were noted. These prominent lymph nodes were interpreted as suspicious for malignancy among others because of the boy's PHTS. Because the prominent lymph nodes persisted over the following weeks, one node was removed (surgical approach chosen over fine-needle aspiration cytology on surgeon's preference) for pathological examination, which demonstrated a reactive lymph node without signs of malignancy. Despite this reassuring result, later on the boy and his parents reported that they had been very distressed during and after this period. They wondered if all these investigations had really been necessary.

Currently, after a follow-up time of 5 years, the boy is doing well with no palpable nodules. In agreement with the boy and his parents, the future thyroid surveillance strategy consists of annual thyroid ultrasound examination.

Case 2: An Example of a Potential Disadvantage of Not Performing Surveillance

A girl presented at the age of 4 years with Graves' disease. At the age of 5 years, genetic testing was performed for the combination of tall stature, hypertelorism, and macrocephaly. A c.517 C>T mutation in the PTEN gene was found, confirming the diagnosis of PHTS.

Because of her young age, with persisting Graves' disease, total thyroidectomy was preferred over radioactive iodine and was performed at the age of 9 years. Ultrasound surveillance for DTC had not been performed. During surgery, the thyroid gland felt "hardened", and regional lymph involvement was suspected, for which several suspicious lymph nodes were removed. Pathological examination of the thyroid gland proved lymphocytic thyroiditis (Graves' disease) and PTC in the left thyroid lobe (1.4 cm in diameter) as well as in all of the 18 removed lymph nodes. A therapy of $^{131}I^-$ (5,516 MBq) was administered, and on the postablation scan additional metastatic lymph nodes in the left supraclavicular region and bilateral in level II were seen.

After 6 months, follow-up neck ultrasound revealed multiple enlarged lymph nodes with calcifications, and biopsy again demonstrated PTC. Additional lymph node resection was performed, which was complicated by thoracic duct injury necessitating drainage. This was complicated by a wound abscess, requiring surgery.

After recovery, 1 year after the first $^{131}I^-$ treatment, a second $^{131}I^-$ (5,500 MBq) treatment was given. Another 6 months later, no suspicious lesions were seen on follow-up ultrasound examination of the neck.

Currently, the girl is under observation by means of annual neck palpation and ultrasound examination, and measurement of the serum thyroglobulin concentration. At the last follow-up, the girl is doing reasonably well. Because of permanent hypothyroidism and hypoparathyroidism, she is treated with thyroxine, calcitriol, and calcium. After this experience, the parents requested active surveillance for any other malignancy that the girl has an increased risk for, regardless of the fact that the girl is not yet fulfilling the starting age for these types of surveillance.

Discussion

We summarized the available evidence on the incidence and behavior of DTC and BND and its prognosis in children diagnosed with PHTS. Unfortunately, no studies could be found evaluating long-term DTC surveillance in PHTS patients. Our study confirms that children with PHTS are at increased risk of developing DTC and BND, with an incidence of 5% from

the age of 10 onwards. DTC in PHTS does not seem to behave differently from sporadic DTC. DTC detection at an early stage seems to be beneficial to improve morbidity. The national expert panel recommends surveillance for DTC in children with PHTS from the age of 10 years onwards.

The optimal mode of surveillance for detecting DTC at an early stage is debated. Surveillance for DTC can be done either by neck palpation or by thyroid ultrasound. Thyroid ultrasound is most sensitive but not specific, neck palpation on the other hand has a very low sensitivity and specificity. Both ways of surveillance have their advantages and disadvantages (30).

Recently, a surveillance recommendation has been formulated for CCS at increased risk for DTC (30). The pros and cons of thyroid surveillance as identified by this study are shown in table 2. Due to the fact that behavior of DTC in CCS and in PHTS does not seem to differ from sporadic DTC, data on DTC surveillance in CCS were used to form recommendations for DTC surveillance in children with PHTS, based on similar principles. However, although there are similarities between thyroid cancer surveillance in CCS after neck irradiation and children with PHTS, there are also some important differences that must be mentioned. Children with PTEN have a higher prevalence of benign nodular disease than when compared to CCS, which makes the interpretation of the ultrasound images much more difficult. In the irradiated thyroid gland, often a solitary nodule is found. Due to the fact that the interpretation of a thyroid nodule, possibly being malignant, in the thyroid gland of a child with the PHTS is challenging, radiological surveillance should only be performed in centers with high-volume thyroid imaging.

Table 2. Pros and cons of screening for DTC

Arguments for and against DTC surveillance patients at risk (independent of surveillance modality)

Advantages

- Patients at risk whose DTC is detected by surveillance are likely to have it detected at an earlier stage. This may reduce the extent of surgery and/or additional radioiodine therapy, which could decrease overall morbidity, recurrence as well as morbidity.
- Patients at risk who are shown not to have a DTC after surveillance benefit by being reassured that they do not have cancer

Disadvantages

- There is uncertainty about the benefit of early treatment since most DTC can be cured. There are no randomized studies that demonstrate a clear benefit of DTC surveillance.
- Detection of a benign nodule with surveillance (false positive results for DTC) can lead to repeated ultrasounds, fine needle aspiration biopsies or thyroid surgery. These patients may experience unnecessary stress and anxiety in the process of ruling out DTC, as well as inconvenience and complications of unnecessary biopsies or surgery.
- There is a risk for detection of an indolent DTC which might have a less aggressive natural course which can lead to overtreatment.
- False negative results of surveillance may lead to some patients being falsely reassured that they do not have DTC, when in fact they do.

Arguments for and against DTC surveillance with neck palpation.

Advantages

- Quick, inexpensive and non-invasive.
- High specificity (96-100%) for detecting a thyroid nodule that might represent DTC (many true negatives and few false positives for nodules).

Disadvantages

- Low sensitivity (17-43%) for detecting a thyroid nodule that might represent DTC (few true positives and many false negatives for nodules).
- Increase in unnecessary invasive procedures due to false positive screening results.
- Detection of DTC at a more advanced stage (compared to thyroid ultrasonography), possibly leading to increased morbidity, recurrence and mortality rate.
- Diagnostic value depending on experience of the physician (high-interobserver variation).

Arguments for and against DTC surveillance with thyroid ultrasonography.

Advantages

- Non-invasive.
- High sensitivity (~95-100%) for detecting a thyroid nodule that might represent DTC (many true positives and few false negatives for nodules).
- High specificity (~95-100%) for detecting a thyroid nodule that might represent DTC (many true negatives and few false positives for nodules).
- Detection of DTC at an earlier stage (compared to neck palpation).

Disadvantages

- Poor diagnostic value of ultrasound for predicting whether a detected nodule is a DTC: detection of a high number of benign thyroid nodules and indolent DTC.
- Increase in unnecessary invasive procedures due to false positive screening results.
- Diagnostic value depended on experience of the ultrasonographer (high-interobserver variation).

DTC: differentiated thyroid carcinoma. Adapted from Clement et al. (30)

Active surveillance is likely to identify all DTCs; however, this may have disadvantages. The most important argument to advocate active surveillance is that early detection of DTC is associated with better disease outcome (20). Our case No. 2 is illustrative of the possible natural course of DTC in PHTS with no active thyroid surveillance.

The disadvantage of intensive surveillance with thyroid ultrasound is however the increase in the number of incidental findings, with the inherent risks of unnecessary fine-needle

aspirations and even (hemi)thyroidectomies (31). Additionally, thyroid surgery may inflict unwanted complications. Also, there is currently no evidence that DTC in children with PHTS behaves more aggressively making exhaustive surveillance unnecessary. Case No. 1 is a good example of the clinical and psychological uproar that DTC surveillance may cause, when surveillance results in a false-positive outcome.

By combining the available data in the literature with both its limitations and advantages of surveillance possibilities, and the study team's opinion, consensus was reached to recommend surveillance for DTC in all children with PHTS by means of annual neck palpation and triennial thyroid ultrasound from the age of 10 years onwards. Surveillance from 10 years onwards may be justified by the fact that DTC in PHTS seems to have a relatively mild disease progression and is very rare before the age of 10 years.

Acknowledging its low sensitivity, we recommend yearly neck palpation as surveillance tool, which may be done by the treating physician of the child (this will mostly be a general pediatrician). Despite its low sensitivity (17–43%), neck palpation has high specificity (96–100%) and low false-positive rates for detecting thyroid nodules (30). It is a quick, noninvasive strategy for detecting nodules, without a high risk of finding an incidentaloma requiring additional investigations.

If the initial ultrasound of the thyroid gland, performed in a thyroid or PHTS expertise center, did not reveal any thyroid nodule, we recommend ultrasound of the thyroid gland and neck lymph nodes not more than once every 3 years. This time interval was chosen as this will lead to fewer incidental findings compared to annual surveillance but will detect DTC in an early stage. In case of a thyroid nodule larger than 10 mm, or a smaller nodule with a combination of several suspicious characteristics (solid components, hypoechogenicity, microlobulations or irregular margins, calcifications, and taller-than-wider shape), or when suspicious lymph nodes are detected, fine-needle aspiration cytology is indicated. If a nodule is smaller than 10 mm without suspicious characteristics, follow-up ultrasound examination 6 months later is indicated to assess whether the nodule has acquired any new features of malignancy. It is essential that an experienced thyroid radiologist performs the ultrasound. Reports upon the use of the ACR TIRADS classification as reporting system in children show contradictory results about its adequacy in children (32, 33), and no studies exist that evaluate this classification system in children with a germline PTEN mutation. For this reason, no recommendation for using this reporting system can be made.

The strength of our study is that it summarizes all available literature on DTC and BND in children diagnosed with PHTS, and that consensus for recommendation was reached with a national multidisciplinary expert team. Limitations are the lack of studies published on DTC in PTEN mutation-positive children influencing the applicability of our results to the general pediatric PHTS population. The results obtained from the literature-derived cases must be interpreted with caution. The clinical information provided about these cases varied greatly,

such as great variability in follow-up time, rendering it impossible to generalize them into a homogeneous sample. The reported risk can be an overestimation due to publication bias, and due to the fact that studies often recruited their patients in academic centers. Moreover, if a child develops DTC this can lead to the diagnosis of PHTS earlier, thereby enriching the childhood PHTS population with DTC cases. On the other hand, the reported risk for developing DTC might be an underestimation. In 3 retrospective studies the investigators based the diagnoses on available clinical information obtained from referring physicians or primary clinical records, in which it was not specifically stated whether all patients were screened for the presence or absence of DTC. Despite this low level of evidence, by linking incidence and behavior of DTC in PHTS to previously formed recommendations for childhood tumor predisposition syndromes and for CCS at risk for DTC, we tried to augment the evidence underlying this recommendation. These recommendations provide guidance for surveillance of DTC in children with PHTS. However, the importance of individual considerations evaluated by experts in this field and shared decision making with the patient and parents should be emphasized. The present surveillance strategy should be evaluated in time in order to prove its efficacy or be adjusted in case of new upcoming evidence.

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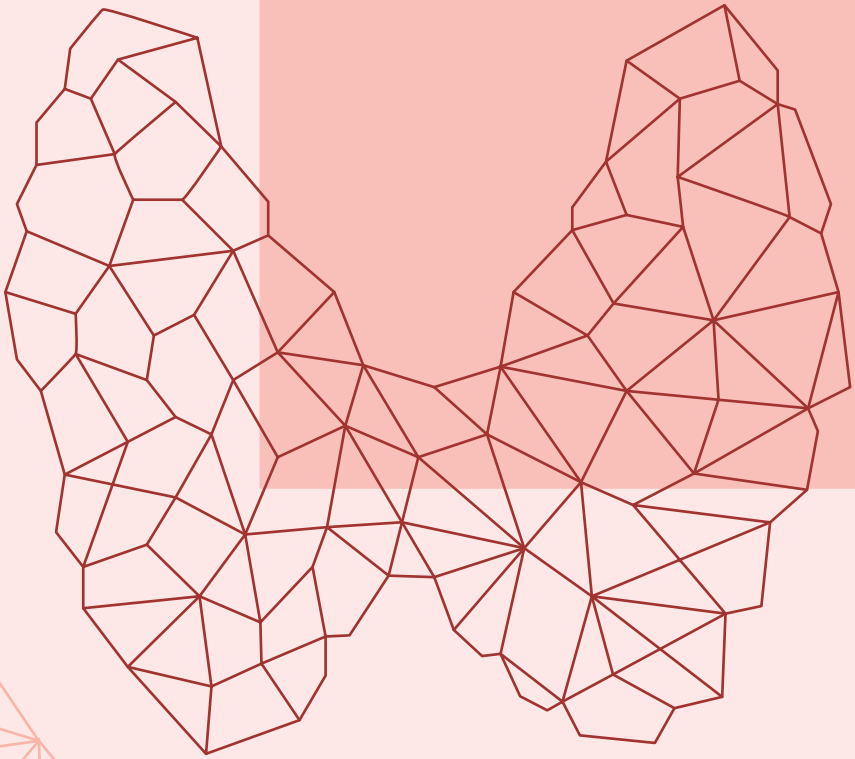
Supplementary material

Appendix A. Patients with PHTS who present with thyroid benign nodular disease or differentiated thyroid carcinoma before the age of 18

Available online at: https://etj.bioscientifica.com/view/journals/etj/9/5/ETJ508872.xml?alreadyAuthRedirecting&body=supplementarymaterials-49140



4

New national recommendations for the treatment of pediatric differentiated thyroid carcinoma in the Netherlands

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Abstract

Background

Currently, there are no European recommendations for the management of pediatric thyroid cancer. Other current international guidelines are not completely concordant. In addition, medical regulations differ between, for instance, the US and Europe. We aimed to develop new, easily accessible national recommendations for differentiated thyroid carcinoma (DTC) patients <18 years of age in the Netherlands as a first step toward a harmonized European Recommendation.

Methods

A multidisciplinary working group was formed including pediatric and adult endocrinologists, a pediatric radiologist, a pathologist, endocrine surgeons, pediatric surgeons, pediatric oncologists, nuclear medicine physicians, a clinical geneticist, and a patient representative. A systematic literature search was conducted for all existing guidelines and review articles for pediatric DTC from 2000 until February 2019. The Appraisal of Guidelines, Research and Evaluation (AGREE) instrument was used for assessing quality of the articles. All were compared to determine dis- and concordances. The American Thyroid Association (ATA) pediatric guideline 2015 was used as framework to develop specific Dutch recommendations. Discussion points based upon expert opinion and current treatment management of DTC in children in the Netherlands were identified and elaborated.

Results

Based on the most recent evidence combined with expert opinion, a 2020 Dutch recommendation for pediatric DTC was written and published as an online interactive decision tree (www.oncoguide.nl).

Conclusion

Pediatric DTC requires a multidisciplinary approach. The 2020 Dutch Pediatric DTC Recommendation can be used as a starting point for the development of a collaborative European recommendation for treatment of pediatric DTC.

Background

Pediatric thyroid cancer is a rare disease; however, its worldwide incidence rate is increasing (1, 2). Differentiated thyroid carcinoma (DTC) is the most common form of this disease and comprises 3% of all pediatric tumors, with 0.2 to 3 cases per million children per year (3, 4). In the Netherlands, in a 43-year period, 170 children with DTC were identified (5). In 2015, the American Thyroid Association developed a special recommendation for pediatric nodules and thyroid cancer (6), but in Europe, such a recommendation is not yet available. Because regulations for medical care differ between the US and Europe, next to possible cultural differences, specific European and national recommendations are required.

Compared to adult DTC, pediatric DTC presents with more advanced disease, expressed as more frequent lymph node involvement at diagnosis, distant metastases and multifocal disease. Despite this more aggressive presentation, pediatric DTC has an excellent prognosis in terms of survival rates (1). Also, differences exist between adult and pediatric DTC with regard to histology and molecular characteristics (7, 8). For children, treatment-related late effects may be more important than for adults, because of the longer life span. The rareness of the disease, in combination with the aforementioned clinical, histological and molecular differences, differences in intercontinental medical regulations, and the importance of minimizing late effects, emphasizes the need for a national and European pediatric DTC recommendation.

As in many other countries, also in the Netherlands centralization of care is seen as the best way forward to improve care for rare diseases. For children with thyroid cancer, there was need for harmonization of diagnostic work-up, management strategy and follow-up targets. To achieve optimal care for the Dutch population, a national multidisciplinary working group was formed aiming at the development of harmonized Dutch recommendations for DTC patients <18 years of age. Secondly, this work may be used as first step to develop a harmonized European recommendation.

Methods

To develop Dutch recommendations, a committee of experts was composed, including pediatric and adult endocrinologists, a pediatric radiologist, a pathologist, endocrine surgeons, pediatric surgeons, nuclear medicine physicians, an epidemiologist, a clinical geneticist, a pediatric oncologist, and a patient representative.

The working group agreed to write the new Dutch recommendation using a guideline adaptation process instead of producing a de novo Dutch DTC recommendation. Given the existence of several pediatric DTC guidelines and reviews, this was considered to be the most efficient way.

Next to the committee of experts, three co-chairs and two PhD students were assigned to the project. For efficiency, three working groups were formed: (1) diagnostics and follow-up, (2) surgery and (3) nuclear medical treatment and imaging. All experts represented their own discipline in the working group.

Guideline search

A systematic literature search was conducted in Pubmed to find all existing recommendations and review articles. The complete search terms can be found in Appendix A (see section on supplementary materials given at the end of this article). In total, 813 studies were found, and abstracts were screened using the following inclusion criteria: (1) studies describing the management of DTC in patients <18 years, (2) studies written in English or Dutch and (3)

studies published after 2000 or an updated elder original article. In total, six guidelines or review articles on treatment of pediatric DTC were retrieved for further evaluation of their quality with the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument (6, 9, 10, 11, 12, 13, 14). The six included guidelines were scored in six domains of a seven-point scale (1 = strongly disagree, 7 = strongly agree; Appendix A). According to this system, the recommendation of the American Thyroid Association (ATA) for pediatric thyroid nodules and DTC was reviewed as the highest quality guideline (6). Therefore, it was agreed to use this recommendation as the cornerstone to develop recommendations for the Dutch population.

The next step was identifying discussion points in the current ATA recommendations based on the current Dutch diagnostics, treatment and follow-up policy, expert opinion and new available evidence. To answer additional research questions resulting from this process, new systematic literature searches were performed in Pubmed (Appendix A).

Results

Based on the most recent evidence in combination with expert opinion, recommendations for management of pediatric DTC were developed. The new Dutch recommendations can be found in the Appendix and online (www.oncoguide.nl).

Recommendations

Organization of patient care

A child with suspicion of DTC, proven DTC or (suspicion of) MEN syndrome should be referred to a hospital with an experienced multidisciplinary thyroid team (defined as level four hospital; Appendix 1, Fig. 1), including at least a pediatric and adult endocrinologist, pediatric radiologist, endocrine surgeon (a 'high volume' thyroid surgeon), pediatric surgeon experienced in thyroid surgery, pathologist, nuclear medicine physician, clinical geneticist, pediatric psychologist and a pediatric oncologist.

Diagnostics

- Fine needle aspiration cytology (FNAC) is recommended for thyroid nodules ≥1 cm or increased suspicion of DTC because of the presence of suspicious ultrasound (US) characteristics (taller than wide, microcalcifications, irregular margins, hypoechogenicity, solid pattern, intranodular vascularity, shape and halo sign absence) or clinical context (15).
- Next to molecular gene analysis on cytological material of suspicious nodules (Bethesda 5) for the presence of BRAF mutations, it may be considered to analyze the presence of other oncogenic drivers and gene-fusions such as RET/PTC and NTRK-fusions due to the fact that these may also be associated with presence of PTC. These results should always be discussed in the (national) multidisciplinary team to stratify care.

- The recommended surgical intervention in case of Bethesda 1–4 depends on the likelihood of the thyroid nodule(s) being malignant (e.g. size ≥4 cm, trachea compression, and sonographic features-like microcalcifications, irregular margins, hypoechogenicity, solid pattern, intranodular vascularity, shape and halo sign absence) (15), and patient preference (e.g. cosmetic reasons).
- The absence of BRAF in FNAC specimen does not rule out presence of PTC, as BRAF is only identified in 40% of pediatric PTC. For this reason, diagnostic hemithyroidectomy is advised.
- In case of FNAC result with Bethesda 5 in a nodule positive for a BRAF mutation or in Bethesda 6, total thyroidectomy is advised after preoperative evaluation.

Preoperative management

- A comprehensive US of all neck regions by an experienced pediatric radiologist should be performed.
- In case of substantial cervical lymphadenopathy, a low dose CT thorax without contrast should be considered.
- In case of large or fixed thyroid masses, vocal cord paralysis, bulky metastatic lymphadenopathy or tumor invasion in the esophagus or trachea determined by physical examination or US, preoperative MRI should be considered.
- FNAC is recommended for suspicious lateral lymph nodes (size, aspect or US characteristics), but refraining from cytological confirmation is possible in case of an evident (pathological) lateral lymph node.
- Prophylactic vitamin D (and possibly calcium) treatment is recommended for reducing the risk of (possible) post-thyroidectomy hypocalcemia.

Operative management

- Total thyroidectomy is strongly recommended for all children with DTC.
- For some selected pediatric patients, there could be an indication for lobectomy or hemithyroidectomy. Such children (all children with microcarcinoma (tumor <1 cm, limited to the thyroid gland and no signs of cervical lymphadenopathy)) should be discussed in the national multidisciplinary (tumor board) consultation to decide whether one could refrain from total thyroidectomy and choose for lobectomy or hemithyroidectomy.
- Routine prophylactic central or lateral neck dissection is not recommended.
- Lateral lymph node dissection should be performed in all children with preoperative proven lymph node metastases or in case of evident (pathological) lateral lymph node(s).

Postoperative therapy

- Postoperative restaging with a $^{123}I^-$ whole-body scan (WBS) is not recommended.
- It is recommended that all pediatric DTC patients are treated postoperatively with $^{131}I^-$. An exception can be made for children with microcarcinoma (tumor <1 cm, limited to the thyroid gland). This individual treatment policy should be discussed in the national multidisciplinary meeting.
- Before the administration of $^{131I^-}$ therapy, semen preservation should be discussed with all (post)pubertal boys (Tanner stage III and higher and able to produce semen).
- The $^{131}I^-$ activity depends on extent of surgery, tumor size, presence of metastases, body weight and pubertal stage (Table 1).
- After $^{131}I^-$ treatment, a WBS 4 to 7 days post-treatment is advised.
- All patients should be discussed in the national multidisciplinary (tumor board) consultation.

Table 1. $^{131}I^-$ activity postoperative additional therapy DTC in children.

Clinical status	**Activity $^{131}I^-$**
Radical resection, T1-T3a tumor, no lymph node or distant metastases	1100 MBq
Irradical surgery*, T3b, N1	
Pre-puberty	100 MBq/kg (max 5550 MBq)
Post-puberty	5550 MBq
T4/M1 tumor	
Pre-puberty	100 MBq/kg (max 7400 MBq)
Post-puberty	7400 MBq Discuss in multidisciplinary local and national tumor board

The TNM classification edition 8 (2016) should be used in staging.*Irradical surgery is defined as macroscopically or microscopically tumor in the resection margin on pathology evaluation.

Follow-up

- Stratification of pediatric patients based on the risk of persistent cervical disease and/or distant metastases is recommended.
- Neck ultrasound should be performed in the follow-up of all patients, independent of the ATA pediatric risk level.
- The desired thyroid-stimulating hormone (TSH) suppression level should be determined by current disease status and ATA risk levels.
- Serum thyroglobulin (Tg) concentrations should be measured 3, 6, (ON), and 12 months (OFF) after $^{131}I^-$ therapy; thereafter, timing and frequency should be guided by the ATA pediatric risk level.
- In patients with visible thyroid tissue or suspect lymph nodes on neck US during follow-up, surgical consultation, FNAC and additional nuclear imaging are advised.

- In case of detectable Tg and negative neck US, additional imaging with FDG-PET is recommended. In these cases, $^{131}I^-$ treatment without preceding nuclear imaging may be considered dependent on Tg concentration, previous lymph node dissections or presence of distant metastases.
- It is recommended to have an interval of at least 12 months between the first and a subsequent $^{131}I^-$ treatment.

Distant metastases

- All patients with distant metastases should be discussed in the national multidisciplinary (tumor board) with regards to follow-up and possible additional therapy.

Discussion

Harmonization of care for children with rare diseases is necessary to improve the outcome of disease. Differences between Dutch pediatric DTC patients and American pediatric DTC patients may exist (16). For this reason specific Dutch recommendations were aimed for. These new Dutch recommendations for the treatment of pediatric DTC have been formulated based on current international recommendations (the ATA pediatric DTC guideline) and the most recent available evidence in combination with expert opinion. Next to harmonization of care, organization of care was also addressed with the intention to centralize care (Appendix A Fig. 1), and to improve the outcome of disease. To enable European collaborative studies and registration, a next step should be to develop European harmonized recommendations.

The recommendations in this manuscript provide guidance for physicians and other health care providers to make well-considered decisions together with patients and parents in diagnostics, treatment, and follow-up of DTC in children. It is recommended that all children with DTC should only be treated in specialized expert thyroid teams with special expertise in childhood. All steps in this process should be discussed with the patient and parents to provide personalized individual medicine.

In the Netherlands, each year about eight to ten children are diagnosed with DTC. This low number in combination with the required multidisciplinary knowledge and skills is a strong incentive for centralizing the care for these patients in highly experienced hospitals (level four) (17). In addition, to ensure high management quality, a national three-monthly, multidisciplinary tumor board has been implemented, in which all new and complex Dutch patients are anonymously discussed among the involved thyroid experts across the country. Next to this national three-monthly consultation, the level four hospitals also have a local weekly multidisciplinary tumor board (17).

Survival rates in children with DTC are favorable. Morbidity caused by treatment remains substantial, however, mainly as a consequence of surgical complications (permanent

hypoparathyroidism and recurrent laryngeal nerve injury present in up to 32%) (18). Other late effects of childhood DTC treatment include dry mouth (19) or dry eyes that may have been caused by $^{131}I^-$ treatment or side effects induced by TSH suppression therapy, such as altered diastolic function (20). Awareness of these late effects of given treatment in childhood is important. By aiming to reduce these complications, steps can be made toward improving the quality of life for these children.

At this moment, evidence for the benefit of performing molecular testing in pediatric DTC, in terms of, clear clinical implications, is limited, however, it is a rapid changing area with new publications coming soon. Molecular testing may be useful to understand the tumor etiology, behavior, predict prognosis and possibly guide the development of novel treatment strategies. In pediatric DTC, up to 50% of tumors show a genetic alteration (21). BRAF mutations are less common in children compared to adults. However, in adult DTC these mutations are associated with aggressive tumors and in FNA samples the finding of BRAF is 100% specific for PTC presence (22, 23). For this reason, performing a total thyroidectomy when a BRAF mutation is found in a Bethesda 5 FNA sample is recommended. For the future, discussion whether a BRAF mutation in an atypical nodule (Bethesda 3 or 4) has treatment consequences may be indicated. In addition, it may be considered to analyze the presence of other oncogenic drivers and gene-fusions (e.g. RET/PTC and NTRK-fusions) due to the fact of increasing awareness that these are also associated with the presence of PTC. At this moment, however, the committee has stated that the current evidence to incorporate this as standard care for all children with thyroid nodules suspect for DTC is not sufficient. If possible, the committee does support the analysis of other oncogenic drivers and gene-fusions (e.g. RET/PTC and NTRK-fusions) in the FNA specimen. The results of these tests should always be discussed in the national multidisciplinary team to decide the treatment consequences in combination with other clinical determinants. The committee is very much aware of the fact that this is a rapid changing field and will update these specific recommendations each year. Possibly, in non-iodine-avid DTC, finding a genetic alteration may enable targeted therapy. Also, perhaps in the future, if targeted therapies were to give fewer side effects compared to current therapy strategies standard testing of genetic alterations could be useful.

Preoperative evaluation in pediatric DTC is needed for optimal surgical planning and additional treatment. The working group agreed with a comprehensive US of all neck regions by an experienced head and neck orientated radiologist (ATA recommendation 10), however with a footnote; the sensitivity of US investigation to detect central lymph nodes (level VI–VII) when compared to lateral nodes is lower, however the specificity may be comparable. Also, not all single suggestive findings are 100% specific (Research question C1, Appendix A) (24, 25, 26, 27, 28).

The working group recommends a low dose CT thorax without contrast as the gold standard to detect pulmonary metastases. In contrast to the ATA recommendation, a chest X-ray in case of substantial cervical lymph node disease is not advised because of lack of sensitivity

in this setting. In case of large or fixed thyroid masses, vocal cord paralysis, bulky metastatic lymphadenopathy or tumor invasion in the esophagus or trachea, MRI should be considered because of the higher spatial resolution and excellent soft tissue contrast, especially when minimal fat tissue in the neck is present.

The main argument for treating all DTC children with $^{131}I^-$ postoperatively is that children are much more likely to initially present with lymph nodes metastases, as well as with distant metastases (29). Based on expert opinion, recommendations for $^{131}I^-$ activity were proposed dependent on the individual clinical situation (Table 1). In addition, direct postoperative restaging with a $^{123}I^-$ or $^{124}I^-$ WBS is not recommended due to the fact that all children will have a WBS 4 to 7 days after initial $^{131}I^-$ treatment. The main arguments (for the recommendation) to wait for a minimum of 12 months for retreatment with $^{131}I^-$ after initial $^{131}I^-$ therapy (if necessary), is that decline of Tg has been reported for a prolonged time after $^{131}I^-$ treatment. Also longer recovery time in between $^{131}I^-$ therapy may lower the risk for late adverse effects (30, 31).

In contrast to the ATA recommendation to perform diagnostic WBS routinely during follow-up in intermediate and high-risk patients, the Dutch committee of experts found no indication to adopt this strategy because of the high sensitivity of neck US combined with Tg measurement to detect recurrent DTC (expert opinion).

Since 2015 the term 'noninvasive follicular thyroid neoplasm with papillary-like nuclear features' (NIFTP) is used. NIFTP has a prevalence of less than 5% in the pediatric PTC population (32). Further studies are needed regarding the role of this new entity, management strategies and follow-up targets.

Our recommendation has several limitations. First of all, the method by which these recommendations were developed has a limitation. The AGREE-II instrument that was used (9) is intended to assess the quality of guidelines and is not valid to evaluate the quality of review articles.

Transition of care from pediatric to adult medicine is an important aspect in follow-up care for pediatric DTC but has not been addressed in the current recommendation. This aspect in care should receive separate attention because it is an important aspect in the care and support of the young adult DTC patient.

Similar to the ATA pediatric guideline, these recommendations have been developed for patients ≤18 years of age. However, there is a spectrum of childhood and adult DTC changing in the age group of 16–25 years (expert opinion). There are some young adults who may present with childhood DTC and who might benefit from treatment along the pediatric guideline, and vice versa. This aspect should be studied in the coming years, aiming to develop an adolescent DTC recommendation.

These new Dutch recommendations have been formulated based on the best available high-quality evidence. However, new evidence may necessitate quick adaption of the recommendations. For this reason, a dynamic flowchart was developed on Oncoguide in which the recommendations can easily be updated (www.oncoguide.nl) (33). In this way, if upcoming literature makes it necessary to update the recommendation, this can easily be done. In general it is advised to update clinical guidelines every 3 years (34, 35).

Recently a survey on organization and management of pediatric DTC in Europe was carried out, showing a scattering of care in Europe with limited centralization and different protocols being used (36). Collaboration between countries is needed to optimize treatment and minimize adverse long-term effects. In the absence of a European pediatric DTC guideline, these Dutch recommendations may be used as starting point for the development of a European guideline.

Conclusion

Treatment of pediatric DTC is challenging, given that children more often present with extensive and aggressive disease and have a longer life-span, making the long-term outcome of the given treatment of special importance. The optimal treatment approach of pediatric DTC is complex and cannot be captured in a one-size-fits-all model. It requires a multidisciplinary approach in thyroid cancer expertise centers. These new Dutch recommendations provide guidance. However, the importance of individual considerations evaluated by an expert national multidisciplinary meeting and shared decision making with the patient and parents should be emphasized. Besides, to optimize diagnostics, management and outcomes while minimizing the long-term adverse consequences for patients with pediatric thyroid cancer, we have to cross borders and collaborate. Development of a European guideline for management of pediatric DTC would be an essential step to achieve this. These Dutch recommendations may be used as starting point for the development of a collaborative European recommendation.

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Supplementary materials

Appendix A. Methods and Detailed Description of the New National Recommendations for the Treatment of Pediatric Differentiated Thyroid Carcinoma in the Netherlands

Table 1. AGREE instrument - Guidelines and review articles management of DTC in children

Table 2. Research questions working groups

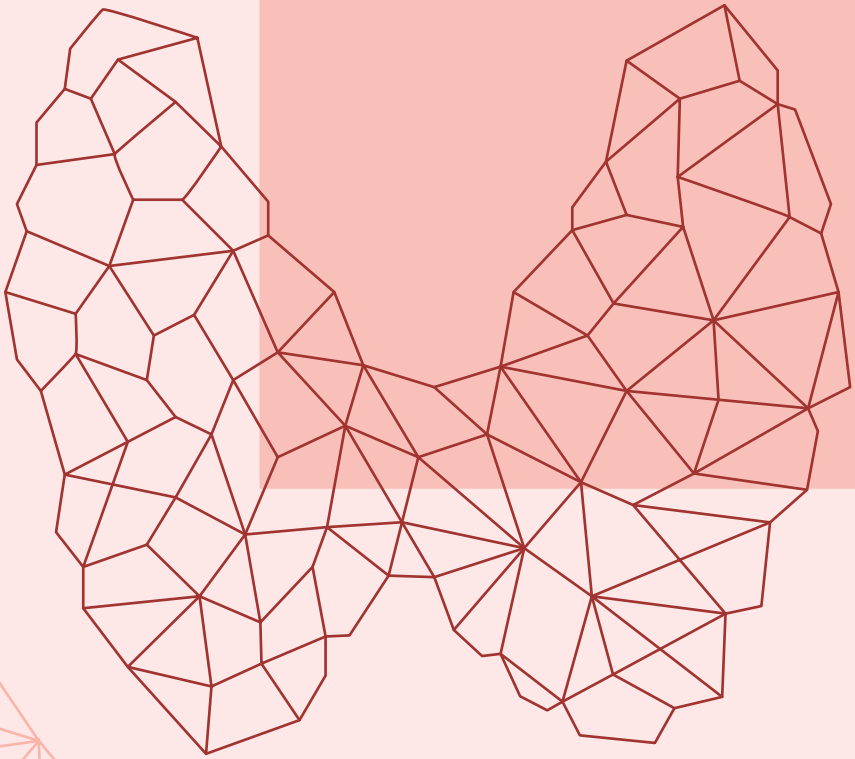
Table 3. $^{131}I^-$ Activity Postoperative Additional Therapy DTC in Children

Table 4. American Joint Committee on Cancer TNM Classification System for Differentiated Thyroid Carcinoma

Table 5. Pediatric Thyroid Cancer Risk Levels and Recommendations Postoperative Management in Children with Differentiated Thyroid Carcinoma; table adapted from the ATA pediatric guideline

Available online version at: https://eje.bioscientifica.com/view/journals/eje/183/4/EJE-20-0191.xml?alreadyAuthRedirecting&body=supplementarymaterials-48939

The national recommendations for pediatric DTC are also published as an online interactive decision tree (www.oncoguide.nl).



5

2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma

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Abstract

At present, no European recommendations for the management of pediatric thyroid nodules and differentiated thyroid carcinoma (DTC) exist. Differences in clinical, molecular, and pathological characteristics between pediatric and adult DTC emphasize the need for specific recommendations for the pediatric population. An expert panel was instituted by the executive committee of the European Thyroid Association including an international community of experts from a variety of disciplines including pediatric and adult endocrinology, pathology, endocrine surgery, nuclear medicine, clinical genetics, and oncology. The 2015 American Thyroid Association Pediatric Guideline was used as framework for the present guideline. Areas of discordance were identified, and clinical questions were formulated. The expert panel members discussed the evidence and formulated recommendations based on the latest evidence and expert opinion. Children with a thyroid nodule or DTC require expert care in an experienced center. The present guideline provides guidance for healthcare professionals to make well-considered decisions together with patients and parents regarding diagnosis, treatment, and follow-up of pediatric thyroid nodules and DTC.

Introduction

Pediatric differentiated thyroid carcinoma (DTC) is a rare disease; however, its worldwide incidence is rising (1, 2). DTC comprises several histological subtypes, with papillary thyroid carcinoma (PTC) accounting for the vast majority of thyroid carcinoma cases. Other tumor subtypes such as follicular thyroid cancer and non-invasive follicular thyroid neoplasm with papillary-like nuclear features are extremely rare in the pediatric population and will therefore not be discussed separately.

There are important differences between adult and pediatric DTC regarding clinical, molecular, and pathological characteristics. Compared to adults with DTC, pediatric patients more often present with advanced disease at diagnosis, including more lymph node involvement, distant metastasis, and multifocal disease (3). Despite this more aggressive presentation, pediatric DTC has an excellent prognosis (1, 2). Also, the most common genetic alterations in pediatric DTC are RET-PTC and NTRK fusions, while mutations in *BRAF,* V600E, and RAS point mutations are less frequent (4, 5). Due to these genomic differences, the utility of molecular testing on biopsies of thyroid nodules and on thyroid tissue in children may be different from that in adults. In addition, the consequences of possible adverse effects of treatment may be different for children because of their longer life expectancy.

These differences emphasize the need for specific recommendations for the pediatric population (6, 7, 8). The American Thyroid Association (ATA) has developed recommendations for pediatric nodules and thyroid carcinoma (8); however, in Europe, such recommendations are not yet available. Regulations for medical care differ between the United States of America and Europe, and there are potential cultural differences. Therefore, specific European recommendations are required.

The present guideline will provide guidance for healthcare professionals to make well-considered decisions together with patients and parents regarding diagnostics, treatment, and follow-up of DTC in children.

Methods

The expert panel for this guideline was instituted by the executive committee of the European Thyroid Association (ETA). The panel represents an international community of experts from a variety of disciplines including pediatric and adult endocrinology, pathology, endocrine surgery, nuclear medicine, clinical genetics, and oncology. All experts were divided into three panels: (i) diagnostics and staging, (ii) treatment, and (iii) follow-up. All experts represented their own discipline in the panel. The three panels were chaired by a pediatric endocrinologist (HvS), and the project was coordinated by a PhD student (CL).

Consensus was achieved to use the 2015 ATA Pediatric Guideline 2015 as framework for the 2022 ETA Pediatric Guideline (8). Based on the 2015 ATA Pediatric Guideline, the expert

panel identified areas of discordance and clinical questions were formulated. For each clinical question, a systematic literature search was performed using Pubmed (last search date: May 2020) (Appendix B).

In total, 3251 studies were identified. All abstracts were screened by two reviewers following the general inclusion criteria: (i) English language, (ii) children and adolescents (<21 years of age), and (iii) study population of at least n=20. All studies with an age limit of <21 years were included, to avoid excluding important pediatric literature in which the age limit of <21 years was used instead of <18 years. For some clinical questions, specific inclusion criteria were defined (shown in each section). After abstract selection, 45 full papers were included. Each full paper was summarized and graded by two independent reviewers. The modified Grading of Recommendations Assessment, Development, and Evaluation system was used to grade the quality of evidence (9, 10). Quality of evidence was scored as level 1: high (randomized controlled trial (RCT) evidence/meta-analysis – high-quality evidence (⨁⨁⨁⨁)); level 2: moderate (intervention short of RCT or large observational studies – moderate-quality (⨁⨁⨁⊖)); level 3: low quality (case–control studies, case series – low quality (⨁⨁⊖⊖)); level 4: very low quality (case reports, expert opinion – very low quality (⨁⊖⊖⊖)) (9).

If all expert panel members agreed on a recommendation of the 2015 ATA Pediatric Guideline (8), no specific search was performed. The grade of quality of evidence, as had been assigned by the ATA working group, was assumed. The statements based on recommendations of the 2015 ATA Pediatric Guideline are considered as 'expert opinion' (level 4).

The expert panel members discussed the evidence and formulated statements based on the best available evidence and expert opinion (Table 1). The expert panel identified several significant gaps in current knowledge that require further research to improve management of pediatric thyroid nodules and DTC (Table 2). The final statements were formed by consensus of the expert panel members. The strength of each statement was scored as strong (S, a recommendation) or weak (W, a suggestion – not a recommendation), depending on the clinical significance and weight of opinion favoring the statement. Strong recommendations are clinically important best practice and should be applied to most patients in most circumstances. In contrast, weak statements should be considered by the clinician and will be applicable to best practice only to certain patients or under certain circumstances. Strong statements are associated with the phrase 'we recommend', and weak statements are associated with the phrase 'we suggest' (10).

Table 1 Research questions and conclusions of evidence

Research questions, conclusions of evidence		Quality of evidence
Diagnostics and staging		
1. What is the sensitivity and specificity of thyroid US for distinction of thyroid cancer from a benign thyroid nodule of a child?		
Conclusion	The expert panel concludes that specificity and sensitivity of thyroid US for distinction of thyroid cancer from a benign thyroid nodule in children depends on multiple US characteristics.	⊕⊕⊕⊖
2. What is the sensitivity/specificity of different suspicious US findings for presence of DTC metastasis to a lymph node?		
Conclusion	*No evidence was found on suspicious US findings specific to DTC in childhood.* The expert panel concludes that the sensitivity/specificity of different suspicious US findings for presence of DTC metastasis to a lymph node may be referred to adult literature.	⊕⊖⊖⊖
3. Will molecular testing in an FNB specimen of a thyroid nodule in a child help you to distinguish it from a benign nodule?		
Conclusion	*No evidence was found.* The expert panel concludes that prospective studies are needed to determine if molecular testing in an FNB specimen of a thyroid nodule in a child helps to distinguish DTC from a benign nodule	⊕⊖⊖⊖
4. Does molecular testing in thyroid carcinoma tissue in a child alter its management?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient to conclude that molecular testing in pediatric thyroid carcinoma tissue has consequences for pediatric DTC management and prospective studies are needed.	⊕⊖⊖⊖
5. What is sensitivity of the different imaging modalities for presence of pre-operative metastasis?		
Conclusion	*No evidence was found.* The expert panel concludes that the sensitivity for neck palpation, comprehensive neck ultrasonography, or laboratory work-up to predict DTC, could not be determined.	⊕⊖⊖⊖
6. Are histopathological criteria related to distant/any metastases?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient to relate histopathological criteria to distant/any metastases and prospective studies are needed.	⊕⊖⊖⊖
7. Which imaging modality is most sensitive for the presence of DTC, post-operatively?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient to state which imaging modality is most sensitive for the presence of DTC, post-operatively.	⊕⊖⊖⊖
8. What is the diagnostic value of serum calcitonin in a child with a thyroid nodule?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient to determine the diagnostic value of serum calcitonin in a child with a thyroid nodule	⊕⊖⊖⊖
9. What is the prevalence of non-clinically relevant thyroid nodules in a child?		
Conclusion	The prevalence non-clinically relevant thyroid nodules in a non-childhood cancer survivor cohort of children seem to vary between 0.6 and 2%.	⊕⊕⊕⊖

Research questions, conclusions of evidence		Quality of evidence
Treatment		
10. What is the difference in outcome of DTC in children treated with a total thyroidectomy vs hemithyroidectomy or vs subtotal thyroidectomy?		
Conclusion	Total thyroidectomy may be associated with more recurrence-free survival and disease-free survival.	⊕⊕⊖⊖
11. What is the difference in outcome of DTC in children with microcarcinoma (<1 cm) treated with nodule excision/resection vs subtotal resection or vs hemithyroidectomy?		
Conclusion	No studies investigated differences in outcome of patients with TMC treated with total thyroidectomy vs hemi or subtotal thyroidectomy. No differences in disease-specific survival and overall survival between patients with TMC and patients with DTC > 1 cm, although patients with TMC were more often treated with partial thyroidectomy/ lobectomies/isthmusectomies and not followed by RAI.	⊕⊖⊖⊖
12. What is the difference in outcome of DTC in children treated with a (prophylactic) central lymph node dissection vs no central lymph node dissection?		
Conclusion	Conflicting results were found. One study suggests that an aggressive surgical approach may both simultaneously decrease the risk of recurrence and improve prognostication in patients with more advanced or aggressive disease. Another study showed no difference in recurrence-free survival between patients treated with LND compared to limited node excision of no LND. However, location of LND was not specified. It remains unclear if these patients underwent prophylactic central lymph node dissection.	⊕⊖⊖⊖
13. Is outcome of microcarcinoma worse in children treated with I-131 vs those not treated with I-131?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient and prospective studies are needed to evaluate outcome of small pediatric DTC not treated with I-131 vs those treated with I-131.	⊕⊖⊖⊖
14. Is the most optimal dose-effect curve of radioiodine with least side effects calculated by body weight/fixed-dose dosimetry?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient and agreed that individual patient-based approach should be used to calculate the most optimal activity of I-131 taking into account the potential side effects of I-131 with an increasing activity. The preferred individual administered activity should be discussed in the multidisciplinary tumor board taking the individuality of the patient into account.	⊕⊖⊖⊖
15. Is rhTSH effective and safe in children during treatment with I-131?		
Conclusion	All studies reported TSH levels after rhTSH stimulation of >50mIU. No significant side effects were reported. No studies reported on iodine uptake after rhTSH injection.	⊕⊕⊖⊖
16. What is the difference in outcome in children with measurable but not rising Tg after treatment for DTC? (incomplete biochemical response with I-131 vs a wait-and-see approach)		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient and prospective studies are needed to evaluate outcome in children with an incomplete biochemical response treated with I-131 compared to a wait-and-see approach.	⊕⊖⊖⊖

Research questions, conclusions of evidence		Quality of evidence
17. What is the difference in outcome in children with recurrent disease/progressive thyroid cancer treated with additional I-131/surgery/other vs a wait-and-see approach?		
Conclusion	*No evidence was found.* The expert panel concludes that current evidence is insufficient and prospective studies are needed to evaluate outcome in children with recurrent disease/progressive thyroid cancer treated with additional I-131/surgery/other vs a wait-and-see approach.	⊕⊖⊖⊖
18. What is the difference in outcome of DTC in children treated with different treatment than surgery and I-131?		
Conclusion	Based on case reports, targeted therapy may play a role in the management of disease in very rare cases of the pediatric patient with progressive I-131-refractory PTC, for which no standard therapy exists.	⊕⊖⊖⊖
Follow-up		
19. What is the sensitivity/specificity of neck US for recurrent DTC in follow-up of children who have been treated for DTC?		
Conclusion	The sensitivity and specificity of thyroid US for recurrent DTC in follow-up of children who have been treated with total thyroidectomy and radioiodine therapy for DTC are 85.7 and 89.4% respectively.	⊕⊕⊕⊖
20. What is the sensitivity of I-124, I-123, as well as FDG PET/CT for DTC/thyroid rest or recurrent disease in follow-up of children who have been treated for DTC?		
Conclusion	*No evidence was found.* Prospective studies are needed to determine the sensitivity of radioiodine imaging and FDG PET/CT for the detection of persistent or recurrent disease in children who have been treated for DTC.	⊕⊖⊖⊖
21. What are the late effects of treatment of DTC? (cardiac late effects, salivary glands, psychosocial, bone, female fertility)		
Conclusion	*Cardiac dysfunction:* in 21.2% of asymptomatic survivors, diastolic dysfunction was found. Salivary gland dysfunction: in 1.9–47.6 and 35.5% of the DTC survivors, salivary dysfunction and xerostomia were found, respectively. *Quality of life:* no differences were found in the course of life questionnaire between DTC survivors and two non-affected groups (non-affected with cancer and other CCS). Also, on most quality-of-life subscales, score of DTC survivors and controls did not differ significantly. However, more physical problems, more role limitations due to physical problems, and more mental fatigue were described by DTC survivors. *Bone mineral density:* no differences were found with respect to BMD and Z scores at any site evaluated by DXA and in bone microstructure parameters between DTC survivors and controls. However, calcium-D3 medication has a beneficial effect on BMD. TSH-suppressive therapy does not affect BMD in women treated for DTC at young age, at least after 10 years of follow-up. *Female fertility:* no major abnormalities in reproductive characteristics and in predictors of ovarian failure in female survivors of DTC who received I-131 treatment during childhood were reported.	⊕⊕⊕⊖
22. Is presentation, outcome, and/or disease course of DTC in children with genetic syndromes different than in children without genetic syndromes for which treatment and/or follow-up should be adjusted?		
Conclusion	In children DICER1 or PTHS, DTC does not seem to have a more aggressive presentation, outcome, and disease course.	⊕⊖⊖⊖

Research questions, conclusions of evidence		Quality of evidence
23. Is presentation, outcome, and/or disease course of DTC in children with a history of radiation exposure different than in children without a history of radiation exposure for which treatment and/or follow-up should be adjusted?		
Conclusion	*Presentation:* CCS with subsequent DTC tended to have on average smaller tumors and might have more often bilateral disease. *Disease course:* inconsistent findings about difference in tumor characteristics (ETE and LNM) were reported. ETE and LMN might be more frequently found in radiation-induced thyroid tumors in children diagnosed in the Chernobyl region. *Outcome:* no significant differences were found between CCS with subsequent DTC and controls in the occurrence of surgical complications, recurrence rate or disease-related death.	⊕⊖⊖⊖

CCS, childhood cancer survivors; DTC, differentiated thyroid carcinoma; LND, lymph node dissection; PTC, papillary thyroid carcinoma; PTHS, *PTEN* hamartoma tumor syndrome; rhTSH, recombinant TSH; TSH, thyroid stimulating hormone; US, ultrasound; BMD, bone mineral density; ETE, extra thyroidal extension; LNM, lymph node metastases. The modified GRADE system was used to grade the quality of evidence: high (RCT evidence/meta-analysis – high-quality evidence (⊕⊕⊕⊕)); level 2: moderate (intervention short of RCT or large observational studies – moderate-quality (⊕⊕⊕⊖)); level 3: low quality (case–control studies, case series – low-quality (⊕⊕⊖⊖)); levels 4: very-low quality (case reports, expert opinion – very-low-quality (⊕⊖⊖⊖)) (9).

Table 2. Research goals for future studies on pediatric DTC based on current gaps in literature

Research goals in pediatric DTC
Pediatric thyroid nodules **To upgrade the level of evidence and to (more certainly) determine the prevalence of non-clinically relevant thyroid nodules in childhood.**
Pre-operative management • To determine the state of evidence upon measurement of calcitonin in the diagnostic work-up of a thyroid nodule. • To determine the positive and negative predictive value of molecular testing in an FNB specimen of a thyroid nodule in a child for presence of DTC in a thyroid nodule. • To determine the predictive value of suspicious neck US findings in a lymph for presence of a DTC metastasis. • To determine whether other imaging modalities than neck US contribute to evaluating the presence of lymph node and or distant metastases pre-operatively.
Post-operative management **To determine which histopathological criteria are related to distant/any metastases in childhood DTC.** • To determine if molecular testing in pediatric thyroid carcinoma tissue alters its management. • To compare the difference in outcome of DTC in children treated with a prophylactic central and/or lateral lymph node dissection vs no prophylactic central and/ or lateral neck dissection. • To evaluate the outcome of pediatric DTC patients with a small thyroid carcinoma and no suspicious lymph nodes, treated with partial thyroidectomy/lobectomies/isthmusectomies vs total thyroidectomy. • To evaluate outcome of small pediatric DTC not treated with I-131 vs those treated with I-131. • To determine the most optimal I-131 activity effect curve in treatment of pediatric DTC with least side effects. • To determine the beneficial effect of upfront systemic therapy vs surgery.

Research goals in pediatric DTC

Follow-up

To determine the benefit of neck US in addition to measurement of serum Tg in the follow-up of pediatric DTC.

- To evaluate outcome in children with measurable but not rising Tg (incomplete biochemical response) treated with I-131 vs a wait-and-see approach.
- To evaluate outcome in children with recurrent disease/progressive thyroid cancer treated with additional I-131/surgery/other vs a wait-and-see approach.
- To determine the sensitivity of I-124, I-123, and FDG PET/CT for DTC/thyroid rest or recurrent disease in follow-up of pediatric DTC.
- To define the risk factors for and clinical impact of adverse effects of treatment for pediatric DTC.

Table 3. Overview of recommendations and suggestions in the 2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma.

Location	#	Recommendation or suggestion
[A] Organization of care and goals for pediatric thyroid nodules and thyroid carcinoma		
[A2]		Thyroid expert team
	1	We recommend that a child with suspicion of thyroid cancer and proven DTC or MTC should be referred to an experienced multidisciplinary thyroid team, specifically with experience in pediatric thyroid cancer (4S).
[A3]		Goals of therapy for DTC in children
	2	We recommend that children with DTC are stratified according to those who may benefit from higher-intensity treatment vs those for whom lower-intensity treatment will suffice. By stratification, the goals of therapy for pediatric DTC (to maintain the high survival rate with low recurrence rate and to minimize adverse effects of treatment) will be reached (4S).
[B] Recommendations and suggestions for the pediatric thyroid nodule		
[B2]	3A	Risk of malignancy in thyroid nodule during childhood We recommend thyroid US to assess the risk of cancer in a thyroid nodule, based on multiple US characteristics. However, US alone cannot definitively distinguish a benign thyroid nodule from thyroid cancer. For this reason, in suspect nodules, FNB is recommended (figure 1) (2S).
	3B	The expert panel recommends, in children with thyroid nodule(s), a complete neck US to evaluate all cervical levels for the presence of lymph node enlargement (4S).
[B5]		Children at high risk for developing DTC
	4A	We recommend that patients with a high risk of developing DTC (history of radiation exposure to the thyroid or a thyroid cancer predisposition syndromes) should be counseled for surveillance (4S).
	4B	We suggest that initiation of surveillance and the decision regarding which surveillance modality (neck palpation and optionally neck US) to use are the result of shared decision-making between the physician and the high-risk patient (4W).
[B6]		Diagnostic value of serum calcitonin in a child with a thyroid nodule
	5	We suggest that, in selected cases (conditions which suggest MEN2, a positive family history of MEN2 or in case of bulky thyroid disease), measurement of calcitonin may be of additional value for early diagnosis of MTC (4W).
[B8]		Molecular testing in FNB specimen
	6	We suggest that molecular gene analysis for presence of *BRAF* V600E mutation in a FNB specimen may be helpful for diagnosis of PTC and therefore may be considered in the diagnostic work-up. The presence of PTC however must be confirmed cytologically or histologically before total thyroidectomy is performed (4W).

Location	#	Recommendation or suggestion
[B9]		Role of surgery for benign thyroid lesions
	7A	We recommend that benign nodules should be followed by serial US and undergo repeat FNB if suspicious features develop (4S).
	7B	We suggest hemithyroidectomy for benign nodules, performed by an experienced high-volume pediatric thyroid cancer surgeon, in patients with compressive symptoms, cosmetic concerns, or according to patient/parent preference after counseling of the possible benefits and risks of thyroid surgery (4W).
[B10]		Autonomous thyroid nodules in children
	8A	We suggest hemithyroidectomy for autonomous nodules during childhood, which must always be performed by an experienced high-volume pediatric thyroid cancer surgeon (4W).
	8B	We recommend discussion of the advantages and disadvantages of surgery vs radioiodine treatment using shared decision-making in each individual case (4S).
[C] Recommendations and suggestions for the management of pediatric differentiated thyroid carcinoma		
[C1]		Pre-operative evaluation
	9A	We recommend neck palpation, comprehensive neck ultrasonography, and laboratory work-up as minimal pre-operative evaluation measures in the pediatric population. The expert panel suggests further genetic or imaging diagnostics in case of suspicion of familial or
	9B	extensive disease (4S).
	9C	We suggest additional pre-operative investigations using MRI or low-dose non-contrast CT in case of bulky disease or suspicion of lung metastases (4W).
	9D	We recommend confirmation with FNB of suspicious lateral lymph nodes (size, aspect, or US characteristics) (4S).
		We suggest assessment of vocal cord function in children with bulky disease pre-operatively (4W).
[C2]		Surgical approach for DTC (figure 2)
	10A	We suggest total thyroidectomy as treatment for children with DTC (3W). *See*
	10B	*Recommendation 10C for exceptions.*
	10C	We recommend that future studies are conducted that evaluate the impact of limited surgery for pediatric DTC with respect to recurrence and remission rates (4S).
		We suggest that, in pediatric patients with incidentally found, very small thyroid carcinoma, and non-aggressive histological features, hemithyroidectomy may be considered as therapeutic option (4W).
[C3]		Therapeutic central and lateral lymph node dissection
	11A	We suggest that prophylactic central lymph node dissection should only be performed in advanced pediatric thyroid cancer (extracapsular extension, vascular invasion, distant metastases). It can be avoided or limited to ipsilateral lymphadenectomy in patients without
	11B	suspicious features for advanced thyroid cancer on neck US (4W).
	11C	We suggest that therapeutic central lymph node dissection is always recommended in pediatric DTC in case of suspicious central lymph nodes based on neck US or intraoperative assessment, or perioperative visible extracapsular tumor growth (4W).
		We recommend that therapeutic lateral lymph node dissection is performed in all children with pre-operatively proven lymph node metastases or in case of evident (pathological) lateral lymph node(s). The expert panel does not recommend prophylactic lateral lymph node dissection (4S).
[C4]		Surgical complications of thyroidectomy and neck dissection
	12	We recommend that all children with DTC should be operated on by high-volume pediatric thyroid cancer surgeons with experience in pediatric thyroid cancer and who are embedded in a center with expertise in the management of DTC (4S).
[C5]		Post-operative staging
	13A	We recommend that post-operative staging is done using the surgical report, histological report, measurement of Tg, and I-131 post-therapy scintigraphy (4S).
	13B	We suggest that the AJCC TNM classification system is used to describe the extent of disease in pediatric DTC (4W).

Location	#	Recommendation or suggestion
[C6]		I-131 therapy
	14A	We suggest that I-131 therapy is indicated for all children following total thyroidectomy, for the treatment of persistent locoregional, or nodal disease that cannot be resected for as well
	14B	as iodine avid distant metastases (M1) (4W).
		We suggest that, for patients with persistent disease following post-operative I-131 therapy,
	14C	the decision to pursue an additional course of I-131 therapy should be individualized according to previous response (4W).
		We suggest that the minimal interval between I-131 treatment in childhood for DTC be recommended to be around 1 year (4W).
[C7]		I-131 activity
	15	We suggest that an individual patient-based approach is used to calculate the optimal activity of I-131 taking into account the potential side effects of I-131 with increasing activity. The preferred individual administered activity should be discussed in the multidisciplinary tumor board taking the individual characteristics of the patient into account (4W).
[C8]		Preparation of the patient for treatment with I-131
	16A	We recommend that TSH stimulation (>30 mI/L) is induced before I-131 therapy in order to
	16B	facilitate I-131 uptake (4S).
		We suggest that stimulated TSH can be achieved either using thyroid hormone withdrawal or rhTSH. The expert panel did not reach consensus on the optimal way of preparation. The
	16C	decision for one against the other is up to the clinical experience of the treating team (3W).
		We suggest that a low iodine diet for at least 4 days before I-131 therapy may be favorable for iodine uptake (4W).
[C9]		Targeted therapy for pediatric DTC
	17	We suggest that, in specific cases, treatment with targeted therapy may be considered, but this should preferably only be given in the setting of clinical trials (4W).
[C10]		Somatic molecular testing (in thyroid carcinoma tissue)
	18A	We suggest that molecular testing in pediatric thyroid carcinoma tissue be recommended in research setting but that the result has currently no consequences for pediatric DTC
	18B	management (4W).
		We suggest that for cases with I-131 refractory DTC, molecular testing in pediatric thyroid carcinoma tissue be recommended as the result may have consequences for pediatric DTC management (4W).
[C11]		Treatment for pediatric radiation-induced DTC
	19A	We suggest that children with radiation-induced DTC undergo total thyroidectomy because of the increased risk for bilateral disease (3W).
	19B	We suggest that for CCS with DTC, specific medical and psychosocial considerations should be taken into account, requiring an individual treatment and follow-up plan (4W).
[C12]		Treatment for DTC in children with genetic syndromes
	20	We do not suggest adjustment of treatment or follow-up for children with DTC and DICER1 or PHTS or any other tumor predisposition syndrome (3W).
[D] Surveillance and follow-up of pediatric differentiated thyroid carcinoma		
[D1]		TSH levels during follow-up (figure 3)
	21A	We suggest that TSH levels should be kept suppressed with concomitant high-normal values of FT4 until full clinical remission, while a low-normal value of TSH (between 0.3 and 1.0
	21B	mU/L)) should be advised thereafter (4W).
		We suggest measurement of TSH and FT4 to monitor the level of suppression or substitution of the LT4 therapy every 3–6 months during growth and puberty and thereafter once a year (4W).

Location	#	Recommendation or suggestion
[D2]		Tg measurement during follow-up
	22A	We recommend that serum Tg is a reliable marker in the follow-up after treatment for DTC in childhood. The expert panel suggests that serum Tg should be assessed every 6 months during
	22B	the first 3 years and annually thereafter (4S).
	22C	We suggest that, in case of circulating TgAbs, these may be measured as 'alternative' tumor marker (4W).
		We suggest that a highly sensitive Tg assay should preferably be used in the follow-up of pediatric DTC patients (4W).
[D3]		US during follow-up
	23A	We recommend follow-up with neck US in combination with serum Tg measurement for detection of recurrent DTC (2S).
	23B	We recommend that neck US is performed by a professional with experience in neck US in childhood (4S).
	23C	We suggest that annual neck US is performed in the first 5 years of follow-up. In low-risk patients, the expert panel suggests, after the first year of follow-up, to only perform neck US in cases with rising Tg or TgAbs or suspicion of recurrence of disease to avoid false-positive findings (4W).
[D4]		Other imaging modalities (I-131, I-124, I-123, or FDG PET/CT scans) during follow-up
	24A	We suggest that children with undetectable Tg on LT4 during follow-up after treatment for DTC should not undergo other imaging modalities (I-131, I-124, I-123, or FDG PET/CT scans)
	24B	(4W).
		We suggest that, in children with detectable (but not rising) Tg on LT4 and no focus on neck US, in individual cases, I-123 scanning may be considered. If no source of Tg is found, serum Tg and serum TgAbs must be followed every 3–6 months. In case of further rising Tg or TgAbs, further imaging is indicated (4W)
[D5]		Persistent/recurrent cervical disease
	25A	We suggest performing neck US in children with consistently rising Tg on LT4 or TgAbs. In these cases, additional I-123 and/or FDG PET scanning may be considered. Surgery or I-131 therapy is indicated depending on the size, tumor load, and degree of progression (4W).
	25B	We suggest that empiric I-131 iodine treatment be only recommended if the abovementioned diagnostic modalities have failed to identify a source of rising Tg on LT4 or rising TgAbs (4W).
[D6]		Pulmonary metastases and follow-up
	26A	We recommend that I-131 is the first-line therapy for patients with pulmonary metastases
	26B	(4S).
		We suggest that a pulmonary function test should be performed, before repeated I-131
	26C	treatment of patients with diffuse lung metastases (4W).
		We recommend that in children with a previous history of drugs causing pulmonary toxicity such as bleomycin, I-131 treatment must be given with extra caution given the risk for pulmonary fibrosis (4S).
[D7]		Radioiodine refractory disease
	27A	We suggest that, when radioiodine refractory disease is suspected, its presence should be thoroughly investigated and confirmed before considering systemic targeted therapy. An observation or wait-and-see strategy may be appropriate (4W)
	27B	We suggest that targeted therapy should be reserved only for patients with large-volume disease which is significantly progressing on TSH-suppressive therapy and not amenable to surgical approach and should preferably be given in a research setting (4W).

Location	#	Recommendation or suggestion
[D8]		Late effects of treatment of DTC
	28A	We suggest counseling pediatric DTC patients about the risk of developing recurrent laryngeal nerve injury or hypoparathyroidism after thyroid surgery and salivary gland dysfunction after exposure to I-131. In addition, the potential risk of subsequent primary neoplasms after I-131 treatment related to I-131 activity and possible risk for cardiac dysfunction after prolonged
	28B	TSH suppression should be mentioned (3W)
	28C	We recommend that the recurrent laryngeal nerve and parathyroid gland function is monitored post-operatively (3S).
	28D	We suggest that all post-pubertal males who receive I-131 may be counseled upon the possibility of (transient) decreased fertility and semen preservation could be offered (3W).
	28E	We suggest that all pediatric DTC patients receive additional calcium and vitamin D
	28F	supplementation therapy for optimal bone mineralization during follow-up (4W).
		We suggest that all patients with pediatric DTC should be offered psychosocial support (4W).
		We suggest that future studies should further evaluate the prevalence and clinical significance of diastolic dysfunction in survivors of pediatric DTC after prolonged TSH suppressive therapy (4W).
[D9]		Follow-up scheme and transition to adult care
	29	We suggest to continue follow-up of children with DTC for at least 10 years; thereafter, the follow-up strategy should be the result of shared decision-making between the physician and the patient (4W).

(S) Strong recommendations are clinically important best practice and should be applied to most patients in most circumstances. (W) Weak statements should be considered by the clinician and will be an applicable best practice only to certain patients or under certain circumstances. CCS, childhood cancer survivor; DTC, differentiated thyroid carcinoma; FDG PET/CT, [18F] fluorodeoxyglucose positron emissive tomography computed tomography; FNB, fine needle biopsy; I-123, iodine-123; I-124, iodine-124; I-131, iodine-131/radioactive iodine; PHTS, PTEN hamartoma syndrome; Tg, thyroglobulin; TSH, thyroid stimulating hormone; US, ultrasound

[A] Organization of care and goals for treatment of pediatric thyroid nodules and differentiated thyroid carcinoma

A1. Target population: pediatric patients

The expert panel has formulated this guideline specifically for children <18 years of age presenting with a thyroid nodule or DTC. Special recommendations for the management of DTC in this age group are necessary because of differences in presentation and genetics of DTC and the relevance of treatment-related late effects of DTC in young individuals. Moreover, monitoring changes in thyroid nodules in children is not straightforward due to the dynamic changes during development in childhood with a progressive increase in thyroid volume. There is a paucity of data to guide the interpretation of such changes and adult data have limited relevance.

The cut-off age of 18 years may be considered arbitrary, as the behavior, natural history, and characteristics of DTC do not suddenly change at this age. It must be taken into account that behavior and characteristics of DTC change with increasing age. In particular, patients in the age group of 16–25 years may either have DTC that behaves as ‘typical’ childhood DTC or may have a more ‘adult’-like behavior. Such patients, presenting with ‘typical’ childhood DTC may benefit from treatment along the pediatric guidelines, and it is clear

that future clinical trials to provide more data to guide, age-appropriate management of thyroid cancer in children and adolescents, are needed. Due to these differences and the fact that adult recommendations have been developed for individuals aged ≥18 years, this recommendation is intended for individuals <18 years of age.

A2. Thyroid expert team

Due to its rarity, centralization of care to expert centers is an important step for improving the management and outcome of children with DTC (11). For this reason, it is recommended that children with DTC are treated in a center with an experienced team of thyroid cancer experts, including a pediatric and adult endocrinologist, pediatric radiologist, ('high volume') pediatric thyroid cancer surgeon, ('high volume') pediatric surgeon experienced in thyroid surgery, pathologist, nuclear medicine physician, clinical geneticist, pediatric psychologist, and a pediatric oncologist. Centers with a higher volume of pediatric thyroid cancer cases can provide experience at each stage of the management pathway, with, for example, specific expertise in diagnostics and age-appropriate specialist nursing support. For thyroid surgery specifically, previous studies have shown that the higher number of thyroidectomies per surgeon correlates with improved quality of oncologic surgery as well minimizing rates of surgical morbidity such as hypoparathyroidism and recurrent laryngeal nerve injury (12, 13, 14).

We strongly recommend that patients are discussed within the setting of a multidisciplinary expert team in order to benefit from combined expertise and to optimize outcomes while minimizing treatment-related morbidity.

Recommendation 1:
We recommend that a child with suspicion of thyroid cancer, proven DTC or MTC should be referred to an experienced multidisciplinary thyroid team, specifically with experience in pediatric thyroid cancer (4S).

A3. Goals of therapy for DTC in children

The management of pediatric DTC is challenging given that children present more often with extensive and aggressive disease which has, however, little impact on life expectancy. This emphasizes the importance of considering and minimizing the long-term side effects of treatment. The optimal treatment approach to pediatric DTC may be complex and cannot be generalized due to variation in the individual presentation, risk factors, and prognosis. In the management of pediatric DTC, defining several goals of therapy may contribute to the improvement of outcomes.

The survival rates of children with DTC are generally excellent (10-year survival >98%) (2, 15). The first important goal of management is to maintain this excellent prognosis of pediatric DTC.

Unfortunately, life-long treatment-related complications are frequently seen, of which the most common are hypoparathyroidism, recurrent laryngeal nerve injury, and salivary gland dysfunction (sections 'I-131 therapy' and 'Late effects of treatment'). Therefore, the second important goal of DTC management is to minimize short- and long-term adverse effects (14, 16).

Recommendation 2:
We recommend that children with DTC are stratified according to those who may benefit from higher-intensity treatment vs. those in whom lower-intensity treatment will suffice.

By stratification, the goals of therapy for pediatric DTC (to maintain the high survival rate with low recurrence rate and to minimize adverse effects of treatment) will be reached (4S).

In order to achieve these two goals, children with DTC should be stratified according to risk, to determine individualized treatment plans. Successful risk stratification may prospectively identify children who will benefit from higher-intensity treatment vs those in whom lower-intensity treatment will suffice.

[B] Recommendations for pediatric thyroid nodules

The management of thyroid nodules in children is challenging with the obvious goal to identify children with a malignant nodule, because a benign nodule does not always require treatment. Thyroid cancer is very rare in childhood with a reported prevalence of 1:1,000,000 in children <10 years, and up to 1:75,000 in children of 15–19 years of age when diagnosed based on clinical signs and symptoms (17). When populations are screened, ultrasound (US) may detect small, clinically unapparent DTCs at higher incidences, without evidence that treatment of such nodules will decrease mortality rates or improve patient health outcomes (18).

The prevalence of benign thyroid nodules in childhood has been described to be around 0.5–2% dependent on the screening method, either by palpation (19) or US (20), and on the definition of size that is documented (>5 mm or >10 mm). When offering thyroidectomy for benign disease, the possible lifelong adverse events of surgery must be borne in mind, starting with the lifelong need for levothyroxine (LT4) replacement therapy after thyroidectomy and, in a small but significant percentage of cases, permanent hypoparathyroidism that will also require a lifelong need for calcium and vitamin D replacement therapy (21).

B1. Prevalence of incidental (non-clinically relevant) thyroid nodules during childhood

In adults, asymptomatic small thyroid nodules are very common (increasing with age) and are often found incidentally (22). The majority of these remain asymptomatic for the rest of their lives.

The expert panel questioned the prevalence of non-clinically relevant thyroid nodules during childhood (Appendix A, [Q9]). A literature search was performed (Appendix B). The largest data resource was found in the surveillance programs in Fukushima and other parts of Japan that were not contaminated (Aomori, Yamanashi, and Nagasaki). These data revealed that the prevalence of US-detected thyroid nodules of >5 mm or cysts of >20 mm in Japanese children is around 1.0% (20). The prevalence of non-clinically relevant thyroid nodules in childhood was found here to vary between 0.6 and 2% (Appendix C) (23, 24). Based on these results, the expert panel suggests that prospective studies should be performed to increase the level of evidence to provide more certainty in determining the prevalence of non-clinically relevant thyroid nodules in childhood in different populations. However, when conducting such a study, the potential harm caused by association of over-diagnosis should be outweighed for the benefit of detection (21).

B2. Risk of malignancy in a thyroid nodule during childhood

Thyroid nodules in children are reported to be at two- to three-fold increased risk of being malignant when compared to thyroid nodules in adults. Dependent on the background iodine status of the country (due to the fact that in iodine-deficient countries, thyroid nodules are more prevalent), the risk for children of a clinically relevant thyroid nodule (>1 cm) being malignant is 20–25% compared to in 5–10% for a thyroid nodule in adults, respectively (25, 26, 27).

The expert panel questioned the state of evidence of using neck US to distinguish a benign thyroid nodule from thyroid cancer in a child (Appendix A [Q1]). A literature search was performed (Appendix B). For this question, studies were only included when the respective investigators were blinded for the outcome of the assessment modality. The specificity and sensitivity of thyroid US to distinguish a benign thyroid nodule from thyroid cancer in children were found to vary depending on which US characteristic was assessed and on the use of combinations of such characteristics (Appendix C). The sensitivity for the following US characteristics was: hypoechogenicity: 52.2–63.0% (28, 29), calcifications: 5.3–63.6% (28, 29, 30), taller-than-wide shape: 21.2–26.4% (28, 30), irregular margin: 51.9–73.3% (29, 30, 31), and increased vascularization: 69.6–90.9% (29, 30). When characteristics were combined, the sensitivity of combined radiographic features increased to 28.1–93.2% (30, 32, 33). The specificity of the US characteristics was reported as follows: hypoechogenicity: 50.2–84.0% (28, 29), calcifications: 89.2–98.5% (28, 29, 30), taller-than-wide shape: 89.7–92.3% (28, 30), irregular margin: 80.2–94.4% (29, 30, 31), and increased

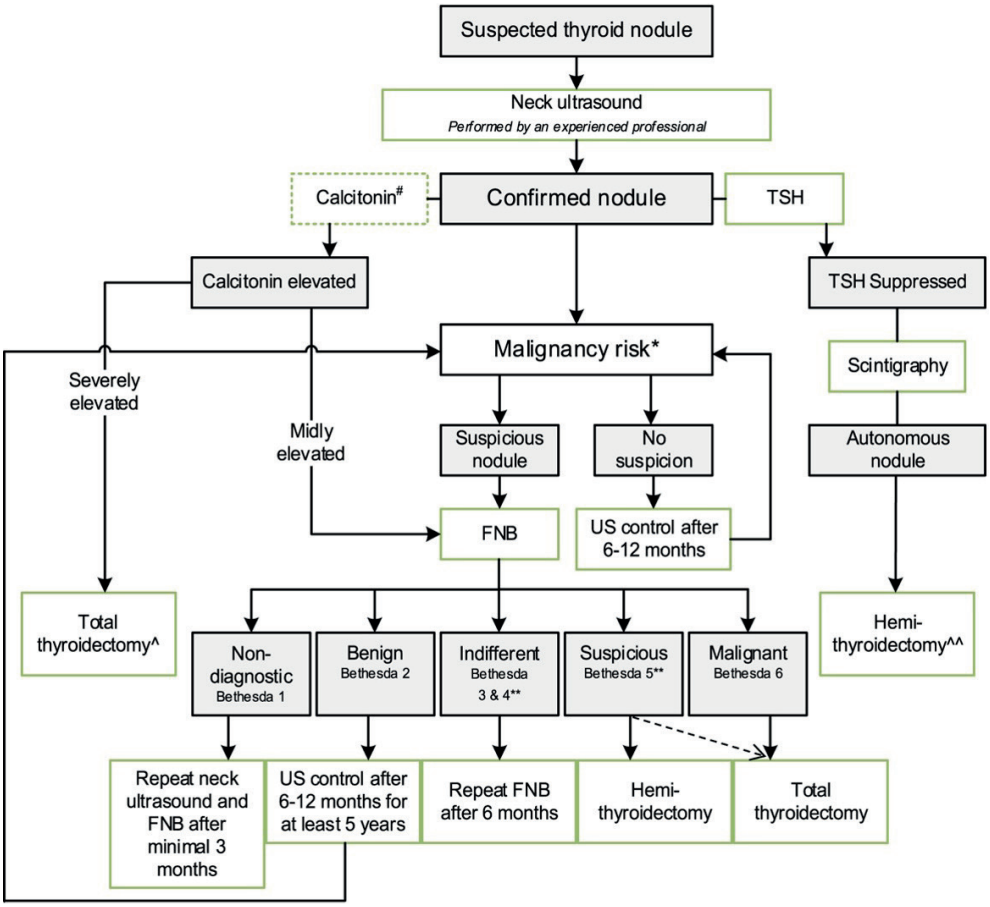
vascularization: 25.9–97.8% (29, 30)**.** When features were combined (depending on study), specificity increased and varied between 41.4 and 100% (30, 32, 33).

There are several US scoring systems to help stratify for which nodules fine-needle biopsy (FNB) (including fine-needle cytology) is indicated (34, 35, 36). The performance of the US scoring systems is comparable; however, their limitations should be recognized, as these scoring systems are based on adult populations and have not been validated in children. For example, the adult dimensional criteria should not be applied to children who often have smaller thyroid dimensions (37, 38). As mentioned, several specific individual US features may increase the likelihood of a nodule being malignant. It is important that investigators recognize and identify these features so they can guide appropriate management. A US scoring system should be used to systematically report these (suspicious) features of the nodule.

Recommendation 3A:
We recommend to undergo thyroid US to assess the risk of cancer in a thyroid nodule, based on multiple US characteristics. However, US alone cannot definitively distinguish a benign thyroid nodule from thyroid cancer. For this reason, in suspect nodules, FNB is recommended (2S) (figure 1).

Recommendation 3B:
The expert panel recommends, in children with thyroid nodule(s), a complete neck US to evaluate all cervical levels for the presence of lymph node enlargement (4S).

Figure 1. Flowchart of initial evaluation, treatment, and follow-up of the pediatric thyroid nodule.



#The expert panel suggests considering the measurement of serum calcitonin in children suspect of MTC based on individual conditions and the preference of the physician (Recommendation 5A). The expert panel suggests that, in selected cases (conditions which suggest MEN2, a positive family history of MEN2, or in case of bulky thyroid disease), measurement of calcitonin may be of additional value for early diagnosis of MTC (Recommendation 5B). *Malignancy risk (suspicious vs no suspicion) is based on neck US characteristics (37), section 'B2. Risk of malignancy in a thyroid nodule during childhood'), history of radiation, and (signs of a) pre-disposition syndrome. If there is a significant increase in nodule size or the US characteristics change over time, (repeated) FNB should be performed. **Analysis of the presence of other oncogenic drivers and gene fusions (e.g. RET/PTC and NTRK-fusions) may be considered in Bethesda 3, 4, or 5 due to the fact of increasing awareness that these are also associated with the presence of PTC (39). In case a *BRAF* V600E mutation is found, the risk of the thyroid nodule being malignant is high but needs to be confirmed, for example, by frozen section during thyroid surgery. ^Total thyroidectomy after proven presence of MTC. ^^Alternatively, FNB can be performed; in case of DTC, a total thyroidectomy should be performed.

B3. Presence of lymph node metastases

The expert panel questioned (1) the sensitivity and specificity of suspicious US findings in a lymph node for predicting the presence of DTC metastasis and (2) whether imaging modalities other than neck US could contribute to evaluating the presence of lymph node

and/or distant metastases pre-operatively (Appendix A [Q2, Q5]). Literature searches were performed (Appendix B); however, for both questions, no studies were found with evidence regarding the sensitivity and specificity of different suspicious US characteristics in a lymph node predicting DTC presence in childhood. Therefore, the expert panel referred to adult literature, in which the sensitivity of the US characteristics predictive of malignant lymph node involvement was reported as follows: microcalcifications: 5–69%, cystic aspect: 10–34%, peripheral vascularity: 40–86%, hypoechogenicity: 30–87%, and round shape: 37% (40, 41). The specificity was reported as follows: microcalcifications: 93–100%, cystic aspect: 91–100%, peripheral vascularity: 57–93%, hypoechogenicity: 43–95%, and round shape: 70% (40, 41).

At the time of review of these guidelines, a first study including children had been published. In this study including 52 children and adolescents with proven DTC, a significant association was seen between abnormal lymph node histology and round shape (P=0.0002) and abnormal echotexture (P≤0.0001) or vascularity (P≤0.0001) (42). Sonographic findings correctly predicted whether the nodes were histologically involved with metastatic disease in 42/52 (81%). Sensitivity of sonography was 79%, specificity was 84%, positive predictive value was 90%, negative predictive value was 70%, and accuracy was 81%. These new results may be used to guide the investigator and emphasize the importance of performing neck US by an experienced thyroid ultrasonographer.

B4. Histopathologic characteristics of DTC

PTC is the dominant variant of DTC. Several low- and high-risk (of extent of disease) subtypes of PTC are described, such as the follicular variant (low risk) and tall cell and diffuse sclerosing variants (high risk) (Table 4) (43).

Table 4. High- and low-risk histological subtypes of DTC and high-risk pathologic characteristics for extent of disease

High risk	Low risk
A. Histological subtypes	
Tall cell variant of PTC	Follicular variant of PTC
Diffuse sclerosing variant of PTC	Classic variant of PTC
Solid/trabecular variant of PTC	Encapsulated PTC
Poorly differentiated thyroid carcinoma	
B. High-risk characteristics found at pathological examination	
Multifocal disease	
Bilateral disease	
Extracapsular invasion	
Extra thyroidal extension	

Table based on Balachander *et al.* (45), Baumgarten *et al.* (52), Jain *et al.* (51).

Although the expert panel was aware of the fact that, during development of these guidelines, the 5th World Health Organization (WHO) classification system of thyroid carcinoma would be developed, and for this current ETA Guideline, the committee agreed to refer to the most recent published thyroid classification system, the 4th WHO classification system (44).

Low-risk subtypes, such as classic and follicular variants of PTC, account for the majority of DTC and are found in 63–85% (43 ,45). High-risk histologic subtypes of PTC are reported to occur in 15–37% of PTC in children, including the tall-cell variant (7–13%), diffuse sclerosing variant (7–16%), and the solid/trabecular variant (1–4%) (43). The coexistence of foci of poorly differentiated thyroid carcinoma (PDTC) occurs in 2–6% cases of high-risk PTC in children (43).

The diffuse sclerosing variant of PTC occurs in relatively young patients and has been associated with lymphocytic thyroiditis and circulating antibodies. These patients tend to have lymph node and lung metastases at the time of initial diagnosis (46). The survival rate is not significantly different from classic PTC. Cribriform-morular thyroid carcinoma is an entity independent from PTC and is classically associated with familial adenomatous polyposis and also occurs due to somatic mutations (47). The prognosis of cribriform-morular thyroid carcinoma is good, mainly because these tumors tend to be encapsulated/well-circumscribed (48). Follicular thyroid carcinoma (is very rare during childhood and is usually minimally invasive (49). Anaplastic carcinomas are extremely rare in children (50). Histopathology is the cornerstone in post-operative staging of DTC. Particularly, extrathyroidal extension is reported to be predictive for regional lymph node metastasis in pediatric DTC (51, 52). In the new 5th WHO classification, micro-PTC is no longer considered as variant of PTC, which may be even more applicable in children than in adults (53). Also, the term 'poorly differentiated carcinoma' is combined for prognostic purpose with 'follicular-cell derived carcinomas with high-grade features' encompassing both the old PDC ('insular carcinoma') and PTC and FTC with many mitoses and/or foci of necrosis are introduced.

B5. Children at high risk for developing DTC

Children with a history of exposure to neck irradiation, I-131-MIBG or due to radioactive fallout (defined as exposure to a thyroid dose of 100–500 mGy or more (54)), with a positive family history for thyroid cancer or known to have a thyroid cancer predisposition syndrome (Table 5) may be considered as high risk of developing thyroid nodules and DTC. When such children present with a thyroid nodule, the risk of the nodule being malignant is increased (55). Surveillance programs for these patients aim to identify thyroid nodules suspicious of DTC at an earlier stage so that overall morbidity and mortality can be decreased. As with surveillance of general populations, the potential benefits of surveillance should outweigh any potential harm.

Table 5. Genetic syndromes associated with thyroid neoplasia

Inherited tumor syndrome	Germline pathogenic variant and mode of inheritance	Type of thyroid neoplasia	Syndromic features noted on clinical examination (listed in approximate order of appearance; some features only appear in adulthood)	Additional clinical features
Familial adenomatous polyposis (FAP) (includes Gardner syndrome and Turcot syndrome)	*APC* Autosomal dominant 20% cases arise *de novo*	Cribriform–morular cancer	Congenital hypertrophy of the retinal pigment epithelium (CHRPE), congenital absence of teeth, delayed eruption of teeth, dentigerous cysts, supernumerary teeth, odontomas, epidermoid cysts, fibrous dysplasia of the skull, mandibular osteomas, fibromas, desmoid tumors, and pilomatricomas.	Hepatoblastoma, medulloblastoma, multiple adenomatous polyps throughout the gastrointestinal tract, principally affecting the colon with high likelihood of malignant transformation, as well as upper GI tract adenomas and adrenal adenomas.
Carney complex	*PRKAR1A* Autosomal dominant 30% cases arise *de novo*	Papillary thyroid cancer, follicular adenoma, and follicular thyroid cancer	Pale brown to black lentigines of skin, lips, and oral mucosa, soft tissue myxomas, Schwannomas, and epithelioid-type blue nevi.	Benign adrenal tumors (primary pigmented nodular adrenocortical disease), pituitary tumors (often somatotropinomas), large cell calcifying Sertoli cell tumors, breast ductal adenoma, osteochondromyxoma, and psammomatous melanotic Schwannoma of the nerve sheath.
DICER1 syndrome	*DICER1* Autosomal dominant	Multinodular goiter, papillary thyroid cancer, and poorly differentiated carcinoma	Macrocephaly (occipitofrontal circumference > 97th centile).	Pleuropulmonary blastoma, ovarian Sertoli–Leydig cell tumors, cystic nephroma, ciliary body medulloepithelioma, botryoid-type embryonal rhabdomyosarcoma, nasal chondromesenchymal hamartoma, pituitary blastoma, pineoblastoma, Wilms tumor, and juvenile intestinal hamartomas.
PTEN Hamartoma tumor syndrome (PHTS) (includes Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, and *PTEN*-related Proteus syndrome)	*PTEN* Autosomal dominant Over 10% of cases arise *de novo*	Multinodular goiter, follicular adenoma, papillary thyroid cancer (classical and follicular variant) Follicular thyroid cancer (FTC cases are more common than PTC)	Macrocephaly (occipitofrontal circumference > 97th centile) and dolichocephaly, learning difficulties, autism and developmental delay, lipomas, vascular features including hemangiomas and arteriovenous malformations, gingival hypertrophy, oral papillomas, facial papules, acral keratoses, palmoplantar keratosis, trichilemmomas, pigmented macules of the glans penis, and overgrowth of tissues.	Benign and malignant tumors of the breast, colon, endometrium, and kidney, adult Lhermitte–Duclos disease due to cerebellar dysplastic gangliocytoma.

Inherited tumor syndrome	Germline pathogenic variant and mode of inheritance	Type of thyroid neoplasia	Syndromic features noted on clinical examination (listed in approximate order of appearance; some features only appear in adulthood)	Additional clinical features
Werner syndrome	*WRN* Autosomal recessive	Papillary thyroid cancer, follicular thyroid cancer, and anaplastic thyroid cancer	Short stature (lack of pubertal growth spurt), cataracts, premature aging, tight atrophic skin, ulceration, hyperkeratosis, pigmentary alterations, regional subcutaneous atrophy, and characteristic 'bird-like facies', hypogonadism, secondary sexual underdevelopment, premature greying and thinning of scalp hair, pes planus, and abnormal voice.	Malignant melanoma, meningioma, soft tissue sarcomas, leukemia and pre-leukemic conditions of the bone marrow, primary bone neoplasms, osteoporosis, soft tissue calcification, evidence of premature atherosclerosis, and diabetes mellitus.

Table 4 in the 2015 ATA Pediatric Guidelines (8) formed the basis for this table.

Several surveillance recommendations are available, such as the 2018 International Guideline Harmonization Group (IGHG) recommendations on thyroid cancer surveillance in survivors of childhood, adolescent, and young adult cancer (56), for children with thyroid cancer predisposition syndrome such as DICER-1 and *PTEN* hamartoma syndrome (PHTS) (57, 58, 59) and for children after nuclear accidents (54).

The advantage of surveillance of patients at risk is the detection of DTC at an earlier stage, which possibly reduces the extent of surgery or additional radioiodine therapy and, with that, morbidity. Furthermore, if no cancer is found with surveillance, its intensity or frequency may be reduced in these patients, which may decrease fear of cancer.

Disadvantages of surveillance include the uncertainty of the benefit of early treatment for DTC (since most DTC can be cured) and false-positive results leading to unnecessary interventions such as neck US and even FNB. This may not only cause unnecessary anxiety, stress, or inconvenience for the patient but also higher healthcare costs and may represent a risk for complications following unnecessary surgery. In addition, surveillance could lead to detection of small nonaggressive DTC, which would never have caused clinical problems and thus may lead to overtreatment. Lastly, false-negative results of surveillance will lead to inappropriate reassurance of the high-risk patient (56).

For this reason, the IGHG has recommended to aim for shared decision-making, to discuss the optimal surveillance strategy together with the patient and family taking into account individual patient circumstances (56). There are both advantages and disadvantages for screening with neck US or clinical neck palpation (Table 6). Initiation of surveillance and the decision regarding which surveillance modality to use should be the result of shared decision-making between the physician and the high-risk patient.

Table 6. Arguments for and against DTC surveillance modalities

Arguments for and against DTC surveillance with neck palpation
Advantages:
Quick, inexpensive, and non-invasive.
High specificity (96–100%) for detecting a thyroid nodule that might represent DTC (many true negatives and few false positives for nodules).
Disadvantages:
Low sensitivity (17–43%) for detecting a thyroid nodule that might represent DTC (few true positives and many false negatives for nodules).
Increase in unnecessary invasive procedures due to false-positive screening results.
Detection of DTC at a more advanced stage (compared to thyroid ultrasonography), possibly leading to increased morbidity, recurrence, and mortality rate.
Diagnostic value depending on experience of the physician (high-interobserver variation).
Arguments for and against DTC surveillance with neck US
Advantages:
Non-invasive.
High sensitivity (~95–100%) for detecting a thyroid nodule that might represent DTC (many true-positives and few false-negatives for nodules).
High specificity (~95–100%) for detecting a thyroid nodule that might represent DTC (many true-negatives and few false-positives for nodules).
Detection of DTC at an earlier stage (compared to neck palpation).
Disadvantages:
Although the sensitivity and specificity to detect a thyroid nodule are high, the diagnostic value of US for predicting whether a detected nodule is DTC is poor: detection of a high number of benign thyroid nodules and small nonaggressive DTC.
Increase in unnecessary invasive procedures due to false-positive screening results.
Diagnostic value depends on the experience of the ultrasonographer (high-interobserver variation).

DTC, differentiated thyroid carcinoma. Adapted from *Cancer Treatment Reviews*, Vol **63**, Clement SC, Kremer LCM, Verburg FA, Simmons JH, Goldfarb M, Peeters RP, Alexander EK, Bardi E, Brignardello E, Constine LS, *et al.*, Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium, pages 28–39, Copyright (2018), with permission from Elsevier (56).

Recommendation 4A:

We recommend that patients with a high risk of developing DTC (history of radiation exposure to the thyroid or a thyroid cancer predisposition syndromes) should be counseled for surveillance (4S).

Suggestion 4B:

We suggest that the initiation of surveillance and the decision regarding which surveillance modality (neck palpation and optionally neck US) to use should be the results of shared decision-making between the physician and the high-risk patient (4W).

B6. Diagnostic value of serum calcitonin in a child with a thyroid nodule

Medullary thyroid carcinoma (MTC) arises from calcitonin-secreting parafollicular C cells. MTC occurs as sporadic and/or hereditary disease (70–75% and 25–30%, respectively). Adults have mostly sporadic disease, caused by somatic *RET* or *RAS* pathogenic variants,

while the vast majority of children have the hereditary form, due to dominantly transmitted or *de novo* germline *RET* proto-oncogene pathogenic variants associated with multiple endocrine neoplasia (MEN) 2A or 2B. MTC accounts for approximately 5% of all pediatric thyroid cancers, with an annual incidence of 0.03/100,000. In children affected with MEN2 syndrome, the age of presentation of MTC depends on the nature of the *RET* pathogenic variant that is present, and prophylactic thyroid surgery is recommended to prevent MTC accordingly (60).

MTC secretes calcitonin; its serum level begins to rise with the development of C-cell hyperplasia and further increases with progression to carcinoma. The expert panel questioned what the state of evidence is to measure calcitonin in the diagnostic work-up of a thyroid nodule (Appendix A [Q8]). A literature search was performed; however, no studies were found (Appendix B).

Although serum calcitonin is a sensitive test for MTC when calcitonin is highly elevated, mildly elevated levels are not specific and can be caused by various drugs, non-thyroid non-malignant conditions, and assay interference (61). Specificity can be improved by measuring calcitonin after calcium stimulation (62). For children presenting with a thyroid nodule who have a family history of MTC or other MEN 2A or 2B-associated conditions, serum calcitonin measurement is advised. However, no clear evidence exists on the potential benefit of measuring calcitonin on a routine basis in children presenting with a thyroid nodule. However, since MTC >1 cm will cause severe elevation of calcitonin, a low calcitonin level in a thyroid nodule of >1 cm excludes MTC. Therefore, the decision for measuring calcitonin in a child resenting with a thyroid nodule is based on individual conditions and the preference of the physician. If a thyroid nodule in a child is confirmed to be MTC, *RET* genetic screening should be performed, since in the majority of cases of MTC in children, a '*de novo'* hereditary form or a 'hidden' hereditary form with an unknown family history has been found (63).

The focus of these current guidelines is the management and treatment of children with DTC; therefore, the expert panel refers to previous studies regarding the management and treatment of MTC in children (64).

Suggestion 5:
We suggest that, in selected cases (conditions which suggest MEN2, a positive family history of MEN2 or in case of bulky thyroid disease), measurement of calcitonin may be of additional value for early diagnosis of MTC (4W).

B7. Evaluation of the child with a thyroid nodule

See figure 1.

B8. Molecular testing in FNB specimen

The evidence for the benefit of molecular testing in thyroid nodules, in terms of clear clinical implications, is limited. However, this is a rapidly changing field. The expert panel questioned whether currently available evidence supports performing molecular testing in the FNB specimen of a thyroid nodule in a child to determine the likelihood of it being malignant (Appendix A [Q3]). No evidence was found for children (Appendix B, C).

Molecular alterations are found in 77–92% of pediatric DTC (39, 65, 66, 67). In pediatric PTC, BRAF mutations are less common compared to adults. *BRAF* V600E mutations have not been found in benign thyroid neoplasms (65). For this reason, molecular analysis of a *BRAF* V600E mutation in FNB specimens classified as Bethesda 5 could be helpful for the diagnosis of PTC. In case where a *BRAF* V600E mutation is found, the risk of the thyroid nodule being malignant is high but needs to be confirmed, for example, by frozen section during thyroid surgery.

Analysis of the presence of other oncogenic drivers and gene fusions (e.g. RET/PTC and NTRK fusions) may be considered in Bethesda 3, 4, or 5 due to the fact of increasing awareness that these are also associated with the presence of PTC (39, 68). A shift toward the evaluation and management of pediatric DTC by identifying oncogenic drivers and gene fusions in the diagnostic work-up may be expected because knowledge of these molecular alterations may increase the accuracy of cytology results currently classified as indeterminate (39). However, the expert panel agreed that the current evidence is not sufficient to incorporate this as a standard of care for all children with thyroid nodules suspicious of DTC. Analysis of other oncogenic drivers and gene fusions could be performed in a research setting.

Suggestion 6:
We suggest that molecular gene analysis for the presence of *BRAF* V600E mutation in an FNB specimen may be helpful for the diagnosis of PTC and therefore may be considered in the diagnostic work-up. The presence of PTC however must be confirmed cytologically or histologically (preoperative FNB or intraoperative frozen section) before total thyroidectomy is performed (4W).

B9. Role of surgery for benign thyroid lesions

For benign thyroid lesions (thyroid cysts or nodules with Bethesda II on FNB), follow-up is recommended with US after 6–12 months. For a stable lesion, subsequent US follow-up is recommended every 12–24 months, for at least 5 years (8).

When there is a significant change in palpable or US characteristics, repeated FNB should be considered (69, 70). When benign nodules cause clinical symptoms (e.g. compression symptoms and cosmetic concerns), surgery may be the preferred choice of treatment (8, 71).

When a thyroid nodule is found in a child with a background of Graves' disease, there is a slightly increased risk for malignancy (72). Indications for FNB however do not change. When surgery is indicated in such children, total thyroidectomy is recommended above hemithyroidectomy.

In children, tumors of uncertain potential of malignancy (oncocytic lesion and follicular neoplasia) are diagnosed through FNB up to 35% (8). Studies found that 28% of AUS/FLUS lesions and 58% of those suggestive of follicular or Hurthle cell neoplasm are malignant (73, 74), which prompts surgical treatment. If FNB of the thyroid nodule shows indifferent results (Bethesda 3 or 4), repeated FNB is suggested after 6 months (Table 3). If FNB again is indifferent, it is suggested to discuss about the patient in the multidisciplinary board regarding the subsequent appropriate diagnostic approach (e.g. molecular imaging or diagnostic surgery). Diagnostic hemithyroidectomy is the recommended surgical approach for unifocal lateralized benign lesions. Total or near-total thyroidectomy is recommended in case of lesions in both lobes (e.g. symptomatic nodular goiter).

Recommendation 7A:
We recommend that benign nodules are followed by serial US and should undergo repeat FNB if suspicious features develop (4S).

Suggestion 7B:
We suggest hemithyroidectomy or total thyroidectomy for benign nodules, performed by an experienced high-volume pediatric thyroid cancer surgeon, in patients with compressive symptoms, cosmetic concerns, or according to patient/parent preference after counseling of the possible benefits and risks of thyroid surgery (4W).

B10. Autonomous thyroid nodules in children

Autonomous thyroid nodules are diagnosed as autonomous nodule when thyroid stimulating homone (TSH) is suppressed, and scintigraphy confirms the functional hyperactivity of the nodule. Autonomous nodules are usually found in post-pubertal girls; however, they are very rare in children, and (large) cohort studies are lacking (75). As in adults, autonomous thyroid nodules in children are mostly benign (76), but malignancy may be present. Unlike Graves' disease, the autonomous thyroid nodule is usually progressive and does not regress spontaneously. In children, such nodules are most often caused by somatic mutations that increase the constitutive activity of the TSH receptor (TSHR). There are two treatment options for a permanent cure of a hyperactive nodule: surgery or administration of I-131 therapy. Due to the risk of malignancy present in an autonomous nodule during childhood (77), the expert panel agreed to recommend surgery as preferred treatment for the autonomous nodule in a child to obtain definitive histological diagnosis. The administration of I-131 may be considered for small nodules. An argument in favor of I-131 treatment is the avoidance of adverse events due to thyroid surgery such as hypoparathyroidism or recurrent laryngeal nerve injury (known complications of thyroidectomy).

Suggestion 8A:
We suggest hemithyroidectomy for autonomous nodules during childhood, which must always be performed by an experienced high-volume pediatric thyroid cancer surgeon (4W).

Recommendation 8B:
We recommend discussion of the advantages and disadvantages of surgery vs radioiodine treatment using shared decision-making in each individual case (4S).

[C] Thyroid carcinoma management guideline

C1. Pre-operative evaluation

Pre-operative evaluation of the child with DTC must comprise a clinical and comprehensive neck US investigation, laboratory testing, and FNB, flanked by genetic testing when family history is suggestive of familial disease (78, 79, 80). Palpation of the neck may identify pathological thyroid nodules or lymph nodes; however, US examination including all six cervical lymph node levels is more sensitive and well tolerated. US can be useful to guide FNB allowing cytology and/or molecular work-up to guide broader examination. Where there is suspicion of extrathyroidal, extensive neck nodal, or infiltrative disease, anatomic imaging modalities, for example MRI or CT, may be valuable to direct surgery (78, 79, 80).

Vocal cord exam can be of additional value in children with bulky disease to be optimally informed pre-operatively. The expert panel questioned the sensitivity of different imaging modalities for the presence of pre-operative metastasis (Appendix A [Q5]). A literature search was performed; however, no literature was found (Appendix B).

The expert panel agreed that in children with large or fixed thyroid masses, vocal cord paralysis, bulky metastatic lymphadenopathy, or (suspected) tumor invasion in the esophagus or trachea determined by physical examination or extensive neck US, a pre-operative MRI of the neck is recommended.

Local advanced disease, with the exception of metastatic lymphadenopathy, is rare in children. In case of extensive cervical lymphadenopathy, the expert panel suggests considering a low-dose CT of the thorax without contrast medium to assess the presence of pulmonary metastases; however, these metastases will also become visible at the moment of I-131 scanning. A contrast-enhanced CT is best avoided unless explicitly desired for surgical planning. If contrast-enhanced CT is performed, there should be an interval of at least 6 weeks to several months before I-131 treatment is given to optimize the uptake of I-131 in the benign or malignant thyroid cells.

In case of suspicious lateral neck lymph nodes (size, aspect, or US characteristics), FNB is recommended to confirm metastases. In addition, thyroglobulin (Tg) measurement on needle-washing fluid could be considered to confirm metastases.

Recommendation 9A:
We recommend neck palpation, comprehensive neck ultrasonography, and laboratory work-up as minimal pre-operative evaluation measures in the pediatric population. The expert panel suggests further genetic or imaging diagnostics in case of suspicion of familial or extensive disease (4S).

Suggestion 9B:
We suggest additional pre-operative investigations using MRI of the neck and/or low-dose non-contrast CT of the thorax in case of bulky disease or suspicion of lung metastases (4W).

Recommendation 9C:
We recommend confirmation of suspicious lateral lymph nodes (size, aspect, or US characteristics) with FNB (4S).

Suggestion 9D:
We suggest the assessment of vocal cord function in children with bulky disease pre-operatively (4W).

C2. Surgical approach for DTC

Surgical approach for DTC (in general)

In the majority of cases, pediatric thyroid cancer presents with locally advanced tumor growth and early cervical lymph node metastases, which impact surgical approach and distinguish the management of pediatric DTC from adult DTC.

In the discussion of whether subtotal thyroid resection or lobectomy should be considered instead of total thyroidectomy in the treatment of pediatric DTC; the associated complication risks (i.e. hypoparathyroidism and recurrent laryngeal nerve palsy) need to be weighed against the likelihood of persistent and recurrent DTC (81, 82). Total thyroidectomy is required to enable radioiodine therapy (78, 81, 82). Adequate primary surgery is the premise to avoid neck recurrence and defines the ongoing course of the disease (78, 81, 82).

The expert panel questioned the difference in the outcome of pediatric DTC after total thyroidectomy vs hemithyroidectomy or subtotal thyroidectomy (Appendix A [Q10]). A literature search was performed (Appendix B, C). One study reported a possible superiority of total thyroidectomy to subtotal thyroidectomy in pediatric DTC from a perspective of disease/recurrence-free survival (univariate analysis) (83). However, in a multivariate analysis, no difference in outcome was found between total thyroidectomy and subtotal

thyroidectomy (83, 84). Bal *et al.* (2015) found total thyroidectomy to be a significant prognostic factor for remission (univariate analysis and multivariate analysis) (85). Disease-free survival in children with low-risk disease without clinically apparent nodal disease (by pre-operative physical examination, US, FNB, and intraoperative inspection) and without gross extrathyroidal extension (based on imaging/clinical features) treated by lobectomy was shown not to be inferior to that in children treated by total thyroidectomy (86). With these results in mind, the excellent prognosis of childhood DTC and the necessity to minimize the risk of complications and to maintain quality of life, less extensive surgery may be considered more frequently in low-risk pediatric patients (78). However, studies about the impact of limited surgery on recurrence and remission rates in children are lacking. For this reason, prospective studies are needed before such recommendations can be made.

Surgical approach for co-incidentally found, very small DTC (exception)

Due to the fact that the diameter of thyroid cancer is not related to the presence of cervical lymph node metastases (87), total thyroidectomy is recommended in all children with DTC regardless of the size of the nodule. However, as mentioned above, considering the excellent prognosis of DTC, the expert panel questioned whether children with very small lesions (found coincidentally) with no clinical signs could be treated differently (Appendix A [Q11]). A literature search was performed. No studies were found to evaluate differences in outcome between patients with DTC <1 cm (also defined in literature as thyroid microcarcinoma (TMC)) treated with total thyroidectomy vs hemithyroidectomy or subtotal thyroidectomy.

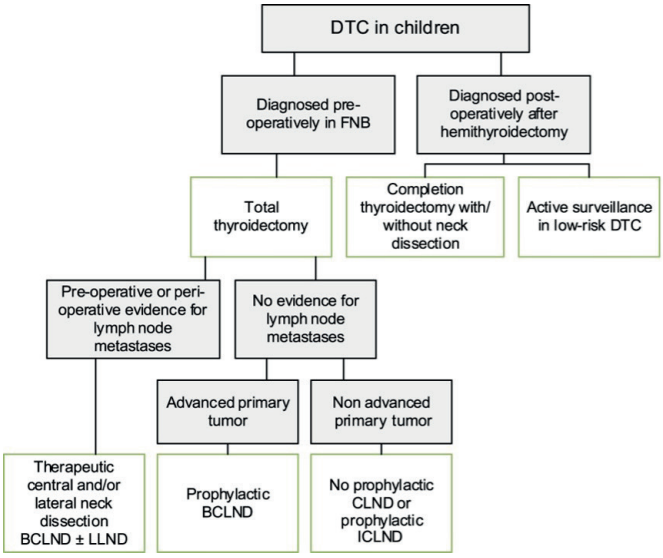
Two studies were found that reported no differences in disease-specific survival and overall survival between patients with TMC and patients with DTC >1 cm, although patients with TMC were more often treated with subtotal thyroidectomy/lobectomy/isthmusectomy, with no additional I-131 treatment (88, 89) (Appendix B, C).

Prospective studies are necessary to evaluate if pediatric patients with small thyroid carcinoma may be treated with less extensive surgery in case of non-aggressive disease. For such studies, it may be considered to offer limited surgery to those with determinants for excellent recurrence-free and overall survival, such as classical PTC or intrathyroidal tumor localization with intact capsule (83, 88, 90).

The expert panel discussed the approach to a child with 'incidental' DTC found on post-surgical pathology for another presumed benign thyroid condition, for example, hemithyroidectomy, for autonomous nodule or multinodular goiter. A small case series (26 patients, all adults) was found that showed no difference in outcome (i.e. disease-free at median follow-up of 4 years) in patients who underwent total thyroidectomy vs active surveillance (91). Similar to the 2015 ATA Pediatric Guideline, the expert panel recommends extensive neck US in these cases to detect contralateral disease/regional lymph node spread (8). Patients with no disease in US may be stratified as low risk and regular surveillance screening can be undertaken. In patients who are found to have contralateral disease/regional lymph node involvement in US, cytological confirmation of the node should be performed.

Suggestion 10A:
We suggest total thyroidectomy as treatment for children with DTC (3W). See Recommendation 10C for exceptions (figure 2)

Figure 2. Flowchart of surgical approach for DTC in children.



BCLND, bilateral central lymph node dissection; CLND, central lymph node dissection; DTC, differentiated thyroid carcinoma; FNB, fine needle biopsy; ICLND, ipsilateral central lymph node dissection. 'Active surveillance' in low-risk DTC implies US of the leftover thyroid tissue, including the evaluation of the cervical lymph nodes every 6–12 months by neck palpation and US.

Recommendation 10B:
We recommend that future studies be conducted that evaluate the impact of limited surgery for pediatric DTC with respect to recurrence and remission rates (4S).

Suggestion 10C:
We suggest that, in pediatric patients with incidentally found, very small thyroid carcinoma and non-aggressive histological features, hemithyroidectomy may be considered as therapeutic option (4W).

C3. Therapeutic central and lateral neck dissection

The expert panel agreed that the indication for central and/or lateral lymph node dissection (CLND and LLND, respectively) is based on pre-operative clinical assessment with neck palpation and extensive US or other imaging modalities suggesting nodal neck disease. The indication for compartment-oriented LLND is lymph node metastasis identified by neck US

and diagnosed in FNB and/or Tg measurement on needle-washing fluid. In children, the risk of lymph node metastasis is higher than in adults.

However, often, the predictors of nodal neck disease of DTC such as tumor size of T3/T4, tumor multifocality, thyroid capsule infiltration, diffuse sclerosing variant, lymphatic and vascular invasion can only be assessed post-operatively (87, 92). Frozen section histopathology may help to identify all or some of these features. The incidence of positive lymph nodes can only be assessed in routine systematic neck dissection, which results in further patient qualification for radioiodine therapy. Therefore, attempts have been made to generate risk factors and prediction models for lateral lymph node metastasis, as reported by Liang *et al.* (93). The authors assessed 102 children and adolescents with PTC and found that independent risk factors for lateral lymph node metastasis were multifocality, tumor size, and the number of central lymph node metastases.

Prophylactic CLND aims at elimination of micrometastases of DTC to optimize outcome, improving cure rates and minimizing lymph node relapses. However, especially the CLND exposes the parathyroid glands and their vascularization, and to a lesser extent risks, the recurrent laryngeal nerves. The main complication of CLND is post-operative transient and permanent hypoparathyroidism, even more so in the pediatric population, followed by transient and permanent recurrent laryngeal nerve palsy. Therefore, indications for prophylactic CLND in children should be limited and reserved for identified risk factors (14, 78).

A literature search was performed for the differences in the outcome of DTC in children treated with a (prophylactic) CLND vs no (prophylactic) CLND (Appendix A [Q12], B, C). Conflicting results were found. Rubinstein *et al.* suggested that an aggressive surgical approach may simultaneously decrease the risk of recurrence and improve prognosis in patients with more advanced or aggressive disease (94). Olmsted *et al.* showed no difference in recurrence-free survival among patients treated with LND compared to limited node excision of no LND (95). However, location of LND was not specified. It remains unclear if these patients underwent prophylactic CLND.

Prophylactic CLND is debatable in children as well as in adults. It should be borne in mind, however, that the risk for lymph node metastases is significantly higher in children. The benefits of prophylactic CLND must be balanced with the low risk of missing clinically significant disease during pre-operative (US) or intraoperative assessment and the risk of post-operative complications. The expert panel agreed that prophylactic CLND should only be performed in advanced thyroid cancer (extracapsular extension, vascular invasion, and distant metastases). However, bearing the above in mind, ipsilateral prophylactic CLND may be considered in patients without suspicious features for advanced thyroid cancer on neck US to possibly reduce the risk of reoperation and the necessity of I-131 therapy. Of note, surgical experience is crucial for preventing life-long complications. Prophylactic neck dissection is still the best therapeutic option for patients with advanced thyroid primary

disease when performed by high-volume surgeons (78).Prospective studies are needed to compare the difference in outcome of DTC in children treated with prophylactic CLND vs no prophylactic CLND.

Suggestion 11A:
We suggest that prophylactic central lymph node dissection should only be performed in advanced thyroid cancer (extracapsular extension, vascular invasion, and distant metastases). It can be avoided or limited to ipsilateral lymphadenectomy in patients without suspicious features for advanced thyroid cancer on neck US (4W).

Suggestion 11B:
We suggest that therapeutic central lymph node dissection should always be recommended in pediatric DTC in case of suspicious central lymph nodes based on neck US or intraoperative assessment, or perioperative visible extracapsular tumor growth (4W).

Recommendation 11C:
We recommend that therapeutic lateral lymph node dissection is performed in all children with pre-operatively proven lymph node metastases or in case of evident (pathological) lateral lymph node(s). The expert panel does not recommend prophylactic lateral lymph node dissection (4S).

C4. Surgical complications of thyroidectomy and neck dissection

As in the case of adults, pediatric DTC surgery carries specific risks, clearly correlated with the extent of surgery and the surgical expertise. The most frequent complications are post-operative transient and permanent hypoparathyroidism, transient and permanent recurrent laryngeal nerve palsy, bleeding, and thoracic duct fistula and nerve damage following LLND (96, 97, 98). Due to the close anatomical relation of the thyroid gland with the recurrent laryngeal nerve, damage can occur leading to a hoarse voice, and in case of bilateral damage, respiratory problems. The parathyroid glands may be difficult to identify leading to transient or permanent hypoparathyroidism post-operatively. The number of surgical adverse events decreases in experienced teams (99).

A clear volume–outcome relationship is observed with favorable outcomes and minimal complication rates in expert centers dedicated to pediatric endocrine surgery (98). Surgical diligence, application of magnification loupes, bipolar forceps, and technical innovations such as intraoperative nerve monitoring, parathyroid fluorescence and parathyroid hormone assessment, and access to frozen section histopathology may improve surgical outcome. In the management of apparent complications, these need to be specifically addressed, for example with early calcium- and/or vitamin D supplementation, immediate evacuation of hematoma, or logopedic training for recurrent nerve palsy (96, 97, 98)).

Recommendation 12:
We recommend that all children with DTC should be operated on by high-volume surgeons with experience in pediatric thyroid cancer and who are embedded in a center with expertise in the management of DTC (4S).

C5. Post-operative staging

The expert panel searched for the most sensitive imaging modality for the presence of DTC, post-operatively (Appendix A [Q7], B), but the literature search did not yield any studies comparing various possible modalities. Therefore, reverting to general medical and empirical principles to select those procedures that are both sensitive and sensible was necessary.

In general, especially in children, radiation exposure due to medical procedures must be minimized. For post-operative staging, measurement of Tg, a specific thyroid cell marker, can be used. There is however lack of pediatric literature on cut-off values for low Tg levels (on levothyroxine) and this may be assay-dependent; for this reason, cut-off levels should be determined by the local expert team.

The expert panel agreed that in pediatric DTC patients with low Tg levels, additional staging is unlikely to be necessary, especially when I-131 therapy is planned as post-therapy, scintigraphy will yield highly sensitive staging information. In those patients not deemed to need I-131 (non-advanced DTC), additional staging will be superfluous.

Furthermore, US and MRI appear to be preferable over CT *per se* if, for example, staging of the neck is warranted. In cases where CT may provide distinct advantages, for example where pulmonary metastases are suspected, it should be considered.

The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control TNM staging system is widely used for predicting the prognosis of DTC in adults (100). However, the TNM staging system comes with limitations regarding the assessment of the prognosis of DTC in pediatric patients: only two disease stages can be identified (stage I: no distant metastasis; stage II: distant metastasis), since all pediatric patients are <45 years of age and secondly, the disease-specific mortality is extremely low. Despite this, the TNM staging system seems to be the most preferred system to be used for staging pediatric DTC.

Recommendation 13A:
We recommend that post-operative staging is done using the surgical report, histological report, measurement of Tg, and I-131 post-therapy scintigraphy (4S).

Suggestion 13B:
We suggest that the AJCC TNM classification system should be used to describe the extent of disease in pediatric DTC (4W).

C6. I-131 therapy

I-131 therapy for benign and malignant thyroid disease has been successfully used for 80 years. Over this time, it has been applied extensively in adult and in pediatric patients alike and has contributed to a normalization of life expectancy in DTC. In pediatric patients, in particular, I-131 therapy can be extremely helpful; even in case of widely disseminated pulmonary metastases, patients may be cured by one or more courses of I-131.

Yet, the indications for adjuvant post-operative I-131 therapy are a subject of debate, both in terms of which patients should receive it and which therapeutic goal (remnant ablation, adjuvant treatment, or treatment of known disease) should be strived for (101). Especially for patients without lymph node or distant metastases, it has not been cleared beyond a doubt whether I-131 can improve survival, reduces recurrence rates, or both in these patients. The expert panel searched for specific histopathological criteria related to distant/any metastases (Appendix A [Q6], B). No evidence of specific histopathological criteria predicting lymph node metastases and/or distant metastases was found. Liu *et al.* reported T3 and T4 tumors and lymph node metastases as factors associated with distant metastases in children (102). The expert panel also questioned whether the outcomes of microcarcinoma treated with I-131 differ from that of microcarcinoma not treated with I-131 (Appendix A [Q13], B), but no literature was found to answer this question.

Considering the possibility of a generally increased genetic susceptibility of patients who develop cancer at such a young age, it remains questionable whether the indiscriminate administration of ionizing radiation during childhood might not do more harm than good. Thus, a risk-benefit evaluation and shared decision-making are key components of pediatric DTC management.

Response to I-131 may be observed up to 15–18 months after therapy (103); therefore, long intervals of at least 12 months are suggested before retreatment. For I-131 therapy, in pediatric patients, special considerations apply because of differences in biological behavior and differences in dosing (see section 'Targeted therapy in the management of pediatric DTC') related to patients' lower bodyweight and distinct metabolism in children (see section 'Targeted therapy in the management of pediatric DTC'). Taking into account the inherently good prognosis in most children with DTC, potential adverse effects in patients with a long life expectancy (see section 'Late effects of treatment') need to be carefully considered (see section 'Late effects of treatment'). Studies specifically examining the potential benefits of I-131 in children are difficult to perform because the number of patients is small. As especially the distinction between remnant ablation and adjuvant treatment in I-131 therapy has only been introduced in past few years, this small number of patients also precludes us from making any evidence-based recommendation on the precise goal of I-131 therapy. However, in adults, the advent of novel Tg assays has made remnant ablation as a goal *per se* more and more superfluous. If administered correctly, I-131 therapy in the hands of specialists is a highly effective oncologic therapy, which has greatly contributed to the generally favorable

outcome of patients with pediatric DTC. After so many years of experience, harmonization, and standardization, (international) registries could be a crucial step forward to personalized treatment strategies.

Suggestion 14A:
We suggest that I-131 therapy is indicated for all children following total thyroidectomy, for the treatment of persistent locoregional disease, remnant thyroid cells, or nodal disease that cannot be resected for as well as iodine avid distant metastases (M1) (4W).

Suggestion 14B:
We suggest that, for patients with persistent disease following post-operative I-131 therapy, the decision to pursue an additional course of I-131 therapy should be individualized according to previous response (4W).

Suggestion 14C:
We suggest that the minimal interval between I-131 treatments for DTC in childhood should be recommended to be around 1 year (4W).

C7. I-131 activity

The question of I-131 activity selection, that is the 'optimal' dosage, is of ongoing relevance since very limited evidence is available in the literature. The expert panel questioned what the most optimal dose effect curve is of radioiodine with least side effects calculated by body weight/fixed activity or dosimetry; however, no literature was found (Appendix A [Q14], B).

As a theoretical construct, the activity which delivers an absorbed dose of radiation is sufficient to destroy a lesion/metastasis while low side effects should be chosen. As a standard of care empirically derived, fixed activities are used, and therapy is repeated as deemed necessary. Several parameters are considered equally or even more important than the administered activity, such as I-131 avidity of tumor tissue, residence time of I-131, the effective I-131 half-life, and tumor size and shape. A practical approach was successfully established in one institution in the management of young patients following radiation-induced thyroid cancer (104). This protocol included the administration of 50 MBq/kg bodyweight for remnant ablation/adjuvant therapy and 100 MBq/kg for the treatment of known metastases (104). However, using a fixed activity approach does not take into account the individuality of the patient. Alternatively, dosimetric strategies have been introduced over the last decades. Here, the patients' iodine biokinetics are determined to calculate the activity as high as safely administrable, thus targeting the safety of the procedure (i.e. 2 Gy to the blood and limit of 3 gigabecquerel (GBq) I-131 retained whole body activity 48 h after I-131 in the presence of (pulmonary) metastases) in an attempt to avoid damage to the hematopoietic system as well as pneumonitis or pulmonary fibrosis, respectively (105). These limits likely must be adapted to account for the lower total mass of the lungs of pediatric patients.

The objective of lesion dosimetry is to determine the radioiodine activity that delivers the intended absorbed dose to ablate thyroid remnant or to treat metastatic disease. More recent studies based on measurements with improved equipment (positron emission tomography (PET)/CT) and more suitable tracers for lesion dosimetry (I-124) support the hypothesis that therapeutic outcome correlates with the absorbed dose administered to the target tissue (106, 107, 108, 109).

Suggestion 15:
We suggest that an individual patient-based approach should be used to calculate the optimal activity of I-131 taking into account the potential side effects of I-131 with increasing activity. The preferred administered activity for an individual should be discussed in the multidisciplinary tumor board taking the individual characteristics of the patient into account (4W).

C8. Preparation of the patient for treatment with I-131

It is generally accepted that adequate TSH stimulation (usually indicated by achieving a level of TSH > 30 mU/L (110)) is necessary for optimal I-131 therapy of DTC. This can be achieved by two methods: either by thyroid hormone withdrawal (THW) or by administration of recombinant TSH (rhTSH). Although rhTSH administration has been studied extensively in adults, experience with rhTSH in children is limited at best, and consequently, this drug is not registered or licensed for use in the pediatric population. The expert panel searched for studies on rhTSH effectiveness and safety in children (Appendix A, [Q15]) and retrieved three (Appendix B, C) (111, 112, 113).

All three studies reported TSH levels after rhTSH (2 × 0.9 mg) stimulation of >50 mU/L, and no significant side effects were reported. No studies were found reporting on iodine uptake after rhTSH injection in children. Although rhTSH from this limited data appears to be safe and able to achieve adequate TSH levels, it cannot be conclusively stated that rhTSH is equivalent to the conventional method of THW regarding therapeutic efficacy of I-131 treatment based on this small body of evidence. Furthermore, the considerable costs and potential reimbursements by local health insurance of rhTSH may also affect the decision regarding the use of this preparation method.

A second cornerstone of preparation for I-131 treatment generally consists of a low-iodine diet for a period of 1–2 weeks before administration; however, a recent study showed that a 4-day low-iodine diet seems to be sufficient in areas with iodine-sufficient intake (40, 114, 115). Although in use for many years, its effect on therapy outcome is not uniformly accepted; here, local iodine sufficiency status might also play a role. Although its merit is still subject to some scientific debate, a low-iodine diet before I-131 therapy may favorably influence the uptake of I-131 in DTC during therapy and will do no harm. Therefore, the expert panel agreed to recommend a low-iodine diet for at least 4 days before the administration of I-131 treatment (115).

Recommendation 16A:
We recommend that TSH stimulation (>30 mI/L) is induced before I-131 therapy in order to facilitate I-131 uptake (4S).

Suggestion 16B:
We suggest that stimulated TSH can be achieved either using thyroid hormone withdrawal or rhTSH. The expert panel did not reach consensus on the optimal way of preparation. The decision for one against the other is up to the clinical experience of the treating team (3W).

Suggestion 16C:
We suggest that a low iodine diet for at least 4 days before I-131 therapy may be favorable for iodine uptake (4W).

C9. Targeted therapy in the management of pediatric DTC

Pediatric DTC commonly presents with advanced disease at diagnosis with a high prevalence of cervical lymph node metastases and lung metastases, usually identified on the whole-body scan performed after I-131 treatment. However, the outcome of these cases is good, and death-related events are very rare. The major reason for this good outcome is the responsiveness of the metastatic lesions to I-131 therapy. Very rarely, children with metastatic thyroid cancer require therapies other than I-131. It is however interesting to recall that childhood PTC has a high prevalence of RET/PTC rearrangements as well as NTRK fusions (116). This information is particularly relevant since new tyrosine kinase inhibitors (TKIs) directed against either *RET* or *TRK* alterations (117, 118) are under development and have already reached the approval of FDA and EMA for adult patients. The expert panel searched the outcome of DTC in children treated with surgery and I-131 vs those treated with different treatment modalities (Appendix A [Q18], B). Mahajan *et al.* reported three cases for whom lenvatinib was given (119). Two patients remained clinically stable on lenvatinib 11 and 23 months after initiation of therapy. The third patient transitioned to a tumor-specific targeted therapy after 1 month. Waguespack *et al.* have reported one 14-year-old female treated with sorafenib who showed significant improvement in lung metastases 67 days after start of treatment (120).

Based on these case reports, the expert panel agreed that targeted therapy may play a role in the management of disease in very rare cases of pediatric progressive I-131-refractory PTC, for whom no standard therapy exists (Appendix C). There is currently no consensus on the absolute definition or criterion that defines that a patient has I-131-refractory DTC. Each patient should be managed individually with a thorough understanding of the many factors that enter the appraisal of the likelihood that a tumor will be refractory to I-131, as well as weighing the patient's specific clinical scenario and the risks and benefits of I-131 therapy. Pediatric progressive I-131-refractory PTC may be suspected in cases with presence of more than one metastatic lesion with at least one lesion without I-131 uptake in the post-therapy

scan, structural progression of tumors after I-131 therapy despite the presence of iodine uptake in the post-therapy scan, or significant uptake on FDG PET/CT (121, 122).

Suggestion 17:
We suggest that, in specific cases, treatment with targeted therapy may be considered, but this should preferably only be given in the setting of clinical trials (4W).

C10. Somatic molecular testing (in thyroid carcinoma tissue)

Molecular testing may be useful to understand the tumor etiology, behavior, predict prognosis, and possibly guide the development of novel treatment strategies.

As pediatric PTCs exhibit a distinct genetic background, it is not usually classified into *BRAF* V600E -like and *RAS*-like tumors. In pediatric DTC, *BRAF* V600E mutation has been described to be present in 25–30%, dependent on age (123). In the studies performed after the Fukushima accident, however, about 60–70% of patients with minuscule PTCs detected in screening projects display *BRAF* V600E mutations (124, 125). The frequency of *BRAF* V600E mutation is low in sporadic pediatric DTC cases as well as in radiation-exposed cases (126). *RET* gene fusion together with other fusion types is detected in 60–70% of pediatric DTC patients in comparison to 15% in adults. RAS gene family mutations are much rarer in pediatric PTCs (<5%) than in adult PTCs. NTRK fusions occur approximately in 10% (range: 0–26%) of all pediatric PTCs (43). The expert panel questioned whether molecular testing in thyroid carcinoma tissue in a child alters its management (Appendix A [Q4]). No evidence was found on altering the management after specific genetic findings such as rearrangements in thyroid carcinoma tissue (Appendix C).

The expert panel is aware that this is a rapidly changing field. In line with the recommendations regarding molecular testing in FNB specimen, the expert panel recommends analyzing the presence of oncogenic drivers and gene fusions in thyroid carcinoma tissue in a research setting. Molecular testing may also be performed in rare, advanced cases with I-131 refractory DTC who could benefit from systemic therapy since systemic therapy may re-express the sodium/iodide symporter (NIS) in tumor cells, for example in DTC (119, 127).

Suggestion 18A:
We suggest that molecular testing in pediatric thyroid carcinoma tissue should be recommended in research setting but the result has currently no consequences for pediatric DTC management (4W).

Suggestion 18B:
We suggest that for cases with I-131 refractory DTC, molecular testing in pediatric thyroid carcinoma tissue should be recommended as the result may have consequences for pediatric DTC management (4W).

C11. Treatment for pediatric radiation-induced DTC

Exposure to radiation (external beam and accidental or therapeutic I-131) is a well-known risk factor for developing DTC, especially when exposed during childhood (128, 129). In childhood cancer survivors (CCS) who received radiation to the neck, the risk of DTC was found to increase linearly with increasing estimated radiation dose to the thyroid gland, with a plateau around 10–30 Gy and declining thereafter, consistent with the cell-killing effect (130, 131). The latency time between radiation exposure and the development of DTC is broad, with a minimum latency time of approximately 5–10 years. The risk of developing DTC is elevated up to 50 years after radiation exposure (17). This underscores the importance of long-term follow-up of CCS at risk. The expert panel questioned if presentation, outcome, or disease course of DTC in children with a history of radiation exposure are different than in children without a history of radiation exposure for which treatment or follow-up should be adjusted (Appendix A [Q23]). A literature search was performed (Appendix B, C) (132, 133, 134, 135).

CCS with subsequent DTC tended to have on average smaller tumors and presented more often with bilateral disease (132, 133). Pacini *et al.* reported more frequent extra-thyroidal extension and lymph node metastases in radiation-induced thyroid tumors in children diagnosed in the Chernobyl region (134). No significant differences were found between CCS with subsequent DTC and patients with sporadic DTC in the occurrence of surgical complications, recurrence rate, or disease-related death (132, 133). It may be questioned whether treatment and follow-up of DTC in patients after exposure to I-131 or with a history of radiation should be different compared to patients with sporadic DTC, since no differences were found in outcome. However, CCS were found to have more frequent bilateral disease. For this reason, the expert panel agreed that subsequent DTC should minimally be treated with total thyroidectomy. In addition, several medical and psychosocial considerations may be taken into account for CCS (Table 7) (136). Each patient with a history of radiation will have unique characteristics. Caregivers should individually design the optimal treatment and follow-up plan and include the patient and their parents in the decision-making.

Suggestion 19A:
We suggest that children with radiation-induced DTC should undergo total thyroidectomy because of the increased risk for bilateral disease (3W).

Suggestion 19B:
We suggest that for CCS with DTC, specific medical and psychosocial considerations should be taken into account, requiring an individual treatment and follow-up plan (4W).

Table 7. Issues specific for childhood cancer survivors developing subsequent differentiated thyroid cancer

Issue	Example	Possible consequence
Previous radiation dose from prior diagnostics and treatment	High cumulative radiation dose	Avoidance, when possible, of CT scan or I-131 in the evaluation and treatment of DTC
Previous exposure to toxic agents for the childhood cancer	Bleomycin increases the risk of pulmonary dysfunction Alkylating agents and abdominal irradiation increase the risk of gonadal dysfunction Total body irradiation or ^{131}I-MIBG treatment increases the risk of bone marrow toxicity and tertiary malignancies Chest irradiation increases the risk for breast cancer	May increase the risk for adverse effects of I-131 in the treatment for DTC
Possibility of the presence of a genetic predisposition syndrome	Possible underlying genetic mutation may be present, both causing the childhood malignancy and the thyroid malignancy; the fact that an individual has already had cancer during childhood and subsequently develops thyroid cancer may indicate a germline genetic susceptibility to develop cancer	May influence the decision to use adjuvant treatment with I-131 with regard to the risk of developing a third malignancy
Risk of cardiotoxicity and prescribing levothyroxine therapy	Anthracycline chemotherapy agents or chest irradiation may increase the risk of cardiotoxicity	Consider keeping TSH levels in the lower normal but not in suppressed range
Psychological aspects	Fear of unfavorable prognosis similar to the previous cancer	The psychological impact of DTC diagnosis as a second primary malignancy may be higher than the diagnosis of sporadic DTC

DTC, differentiated thyroid carcinoma; MIBG, meta-iodobenzylguanidine; TSH, thyroid-stimulating hormone. Adapted, with permission, from van Santen *et al.* (136).

C12. Treatment for DTC in children with genetic syndromes

DTC may occur in children with a pathogenic variant in a tumor predisposition syndrome known to result in benign thyroid lesions and DTC (Table 5, section B5) (80, 137, 138). As an increased head circumference may point toward the diagnosis of PHTS or DICER1 (139, 140), this should always be part of the physical examination of the child with a thyroid nodule or DTC. DTC cancer predisposition syndromes include pathogenic variants in the following genes: *APC, DICER1, PRKAR1A, PTEN,* and *WRN*. The appearance of DTC may be the presenting tumor in a hitherto unrecognized syndromic diagnosis in a child or may develop in a child who is at risk of and being monitored for their high-risk thyroid disease, as part of surveillance specific to their syndromic diagnosis. This question is important, because if children with an inherited DTC-prone genetic condition do have a poorer outcome, the 'watch and wait' policy for children at high risk for thyroid neoplasia may need to be reconsidered, with prophylactic thyroidectomy as a possible risk-reducing intervention, to avoid DTC that can be contemplated. Additionally, if a DTC-predisposing pathogenic variant would require more aggressive treatment, then genomic testing at presentation should be recommended for all pediatric cases with possible DTC, to provide best possible oncological management and care.

The expert panel questioned during presentation, outcome and/or disease course of DTC in children with genetic syndromes is different than in children without genetic syndromes for which treatment and/or follow-up should be adjusted (Appendix A [Q22]). A literature search was performed (Appendix B, C) (58, 141). Van der Tuin *et al.* have shown a cohort of ten children with *DICER1*-related DTCs (141). Thyroid specimens of all patients showed diffuse nodular hyperplasia with multiple, discrete, well-circumscribed, and occasionally encapsulated nodules. No infiltrative growth, extrathyroidal extension, vascular invasion, or lymph node metastasis were seen. The authors concluded, based on clinical, histological, and molecular data, that most *DICER1*-related DTCs could be considered as a low-risk subgroup. Another review reported on disease behavior and outcome of DTC in children with PHTS (58). In this review, five cohort studies were reported, and the incidence of DTC in childhood ranged from 4 to 12%. In addition, in total, 27 cases were identified. FTC was diagnosed in 52% of pediatric DTC patients. No evidence was found for a different clinical behavior of DTC in PHTS patients compared to sporadic DTC. DTC in pediatric PHTS patients does not seem to be more aggressive than sporadic DTC. However, detection of *DICER-1* or PHTS in children with DTC will affect the counseling and follow-up of families regarding the surveillance of organs at risk for malignancies.

Suggestion 20:
We do not suggest the adjustment of treatment or follow-up of DTC for children with DICER1 or PHTS or any other thyroid cancer predisposition syndrome (3W).

[D] Surveillance and follow-up

D1. TSH levels during follow-up

The expert panel did not consider it necessary to perform a new literature search on the TSH level issue during follow-up. The expert panel agreed that LT4 therapy is indicated in all children with DTC after total thyroidectomy to suppress TSH at least until clinical remission of the disease (i.e. undetectable levels of serum Tg on LT4, undetectable levels of Tg antibodies, negative neck US, and, if performed, negative whole-body scan 1 year after last treatment).

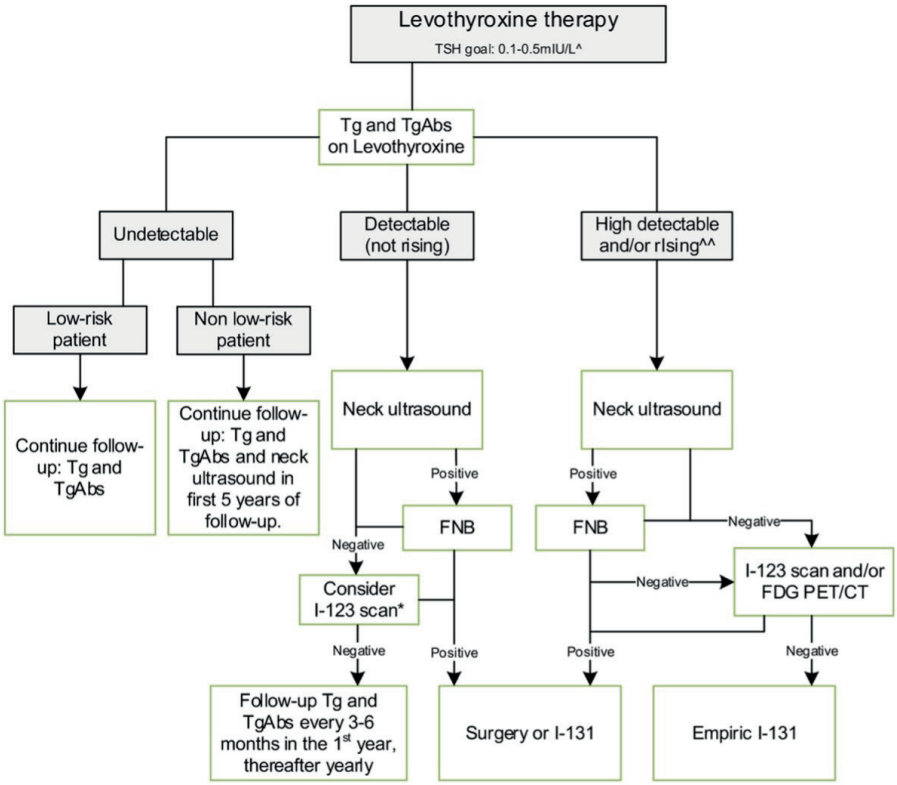
While the TSH level should be suppressed, FT4 should be maintained in the normal range to prevent symptoms and signs of thyrotoxicosis. It is important to know that children, especially young children, commonly require a greater amount of LT4 per kg of body weight with respect to adults, and considering that they are growing, frequent monitoring to confirm that the daily dose is appropriate is warranted. Periodic monitoring of the body weight and height to confirm a correct normal growth is also indicated. When, after 1 year, clinical remission is reached (undetectable levels of serum Tg on LT4, undetectable levels of Tg antibodies, negative neck US, and, if performed, negative whole-body scan), and slightly higher TSH levels may be accepted (low-normal values with substitutive LT4 treatment).

Because of lack of evidence on this topic for children with low-risk DTC not treated with I-131, the expert panel suggests keeping TSH in the low-normal range.

Suggestion 21A:
We suggest that TSH levels should be kept suppressed with concomitant high-normal values of FT4 until full clinical remission, while a low-normal value of TSH (between 0.3 and 1.0 mU/L)) should be advised thereafter (4W) (figure 3).

Suggestion 21B:
We suggest the measurement of TSH and FT4 to monitor the level of suppression or substitution of the LT4 therapy every 3–6 months during growth and puberty and thereafter once a year (4W).

Figure 3. Flowchart of follow-up of children with DTC having received complete remission after initial treatment with total thyroidectomy and I-131.



This flowchart is developed for children with DTC having received complete remission defined as: undetectable levels of serum Tg on LT4, undetectable levels of Tg antibodies, negative neck US, and if performed, negative whole-body scan 1 year after last treatment. ^In the first year until clinical remission, TSH levels should be suppressed, while a normal low value of TSH (between 0.5 and 1.0 mU/L) will be advisable thereafter. ^^The definition of consistent rising Tg on LT4 is debatable; the levels of Tg as well as the doubling time should be taken into account and weighted in the individual patient. *The expert panel suggests that, in children with detectable (but not rising) Tg and no focus on neck US, in individual cases, I-123 scanning may be considered. When both US and radioiodine imaging did not yield a focus, FDG PET/CT may be considered.

D2. Tg measurement during follow-up

Tg is a tumor marker for DTC, but interpretation of Tg needs to be in the context of previous therapy and TSH levels and can also be raised due to thyroid trauma (e.g. FNB/surgery/I-131). Historically, treatment of DTC in children has followed adult guidelines where the goal of treatment was elimination of evidence of disease (e.g. undetectable Tg levels). Given the excellent prognosis, the slow growth of DTC, and highly sensitive Tg measurement, one may question whether it is necessary to aim for undetectable Tg levels during follow-up at cost of potential adverse effects of additional I-131 after surgery. The goal of treatment is to tailor therapy in order to limit overtreatment. For patients with less-differentiated tumors, post-operative Tg may be a less-sensitive marker; however, this is very rare in childhood. Current guidelines suggest the measurement of Tg dependent on risk stratification (3–6 monthly for either 2 (low risk) or 3 years (intermediate/high risk) and then annually (8, 142).

Highly sensitive Tg (hs-Tg) assays have improved sensitivity and precision for Tg and allow the detection of very-low Tg levels, reflecting minimal amounts of thyroid tissue, even without TSH stimulation (143, 144). For this reason, Tg measurement using hs-Tg assays is preferred in follow-up of pediatric DTC.

Circulating Tg antibodies (TgAbs) can affect Tg measurement, and guidelines suggest measuring Tg and TgAbs during follow-up. The expert panel suggests that, in case of circulating TgAbs, these may be measured as 'alternative' tumor marker especially when newly occurring or rising. It must be taken into account, however, that TgAbs appear to be more common in pediatric DTC and in those with lymph node metastasis. In almost 50%, TgAbs resolve in 2 years and there is no associated long-term prognostic significance to date (145).

Recommendation 22A:
We recommend that serum Tg is a reliable marker in the follow-up after treatment for DTC in childhood. The expert panel suggests that serum Tg should be assessed every 6 months during the first 3 years, and annually thereafter (4S).

Suggestion 22B:
We suggest that, in case of circulating TgAbs, these may be measured as 'alternative' tumor marker (4W).

Suggestion 22C:
We suggest that a highly sensitive Tg assay should preferably be used in the follow-up of pediatric DTC patients (4W).

D3. US during follow-up

Neck ultrasonography is a pivotal imaging procedure for detecting DTC locoregional relapse/metastases in adult patients (146). Although in children with DTC, the high prevalence of large inflammatory lymph nodes may reduce specificity (147), its ubiquitous availability together with absence of radiation exposure makes this procedure of particular value in pediatric DTC patients (147).

The expert panel searched the value in terms of sensitivity and specificity of neck US for recurrent DTC in the follow-up of children with DTC (Appendix A [Q19], Appendix B, C) (148). Vali *et al.* have reported the sensitivity and specificity of neck US for recurrent/persistent disease in the follow-up of DTC in 40 patients (median age, 14.3 years) (148). Suspicious characteristics were defined as: hypoechoic appearance, hyperechoic foci, peripheral vascularization, and round-shape node without hyperechoic hilum. Histopathology was considered as the gold standard to assess the results of neck US, in cases where histopathology was not available, a combination of stimulated Tg levels >10 ng/ml and post-therapy whole-body radioiodine scan was used as the gold standard. The sensitivity and specificity were 85.7 and 89.4%, respectively.

In the case of detectable Tg levels after initial treatment (i.e. total thyroidectomy followed by I-131 therapy), neck US can disclose even small locoregional disease persistence/relapse amenable for further surgical treatment. Furthermore, this procedure can guide FNB of lymph nodes to obtain cytological or biochemical (i.e. Tg measurement in needle wash-out) confirmation before surgery (147). Conventionally, routine neck US at regular intervals has been the standard of care for many years. However, recently in adult patients, it was shown by several groups that its use during the follow-up could be reserved for patients with biochemically incomplete response after initial treatment (i.e. Tg levels ≥1 ng/mL) (149), as in patients with lower Tg levels, the number of false-positive lesions, and consequently unnecessary diagnostics, far outweighs the number of true-positive ones. Considering the low burden of neck US and the possibility of this modality to detect lymph node metastases that are unable to secrete Tg, the expert panel agreed that a neck US once a year in the first 5 years after diagnosis of DTC may be helpful. However, this decision should be made by the clinician who is taking care of the child, depending on the stage of disease at presentation and the individual preferences of the patient and their parents. Considering the abovementioned possible risk for false-positive findings on neck US, especially in children, an option could be to perform neck US during the first year of follow-up but thereafter, only in cases with rising Tg or TgAbs or suspicion of recurrence of disease. In all cases, neck US should always be performed by a professional with expertise in neck US in childhood.

Recommendation 23A:
We recommend follow-up with neck US in combination with serum Tg measurement for the detection of recurrent DTC (2S).

Recommendation 23B:
We recommend that neck US is performed by a professional with experience in neck US in childhood (4S).

Suggestion 23C:
We suggest that annual neck US be performed in the first 5 years of follow-up. In low-risk patients, the expert panel suggests, after the first year of follow-up, to only perform neck US in cases with rising Tg or TgAbs or suspicion of recurrence of disease to avoid false-positive findings (4W).

D4. Other imaging modalities (I-131, I-124, I-123, or FDG PET/CT scans) during follow-up

Although in adults, diagnostic radioiodine scintigraphy with I-123, I-124, or I-131 as well as PET/CT with FDG is commonly used in patients with suspected persistent or recurrent disease, there is little evidence and no prospective studies as to their precise efficacy and indication (40). In the pediatric DTC population, a specific search to this extent search yielded no evidence of the sensitivity of these techniques in this population (Appendix A [Q20], B, C). Therefore, the expert panel concluded that prospective studies are needed to determine the sensitivity of radioiodine imaging and FDG PET/CT for the detection of persistent or recurrent disease in children who have been treated for DTC.

Until sufficient prospective evidence for evidence-based recommendations is available, the expert panel agreed that only experience-based recommendations can be formulated. Certainly, in pediatric patients, neck US is preferable to radioiodine imaging and FDG PET/CT. If neck US however did not detect thyroid tissue, the next step may be radioiodine imaging (under TSH stimulation, Recommendation 16B), as radioiodine avid disease in children is common, whereas radioiodine negative disease is rare (104). When both US and radioiodine imaging are negative, FDG PET/CT may be considered.

Suggestion 24A:
We suggest that children with undetectable Tg on LT4 during follow-up after treatment for DTC should not undergo other imaging modalities (I-131, I-124, I-123, or FDG PET/CT scans) (4W).

Suggestion 24B:
We suggest that, in children with detectable (but not rising) Tg on LT4 and no focus on neck US, in individual cases, I-123 scanning may be considered. If no source of Tg is found, serum Tg and serum TgAbs must be followed every 3–6 months. In case of further rising Tg or TgAbs, further imaging is indicated (4W).

D5. Persistent/recurrent cervical disease

The expert panel searched for differences in outcomes between children with measurable but not rising Tg on LT4 after initial treatment for DTC (incomplete biochemical response) with I-131 compared to a wait-and-see approach (incomplete biochemical response) (Appendix A [Q16]) but no literature was found (Appendix B). In addition, the expert panel performed a literature search on the difference in outcome between patients with recurrent disease/progressive thyroid cancer treated with additional I-131/surgery/other vs a wait-and-see approach (Appendix A [Q17], B). However, again, no studies were found.

Based on these searches and expert opinion, the expert panel agreed to recommend that in children with persistent but not rising Tg on LT4, primarily neck US is recommended, and if negative, I-123 scanning may be considered (under TSH stimulation, Recommendation 16B). If no residual or recurrent disease is found, serum Tg on LT4 and serum TgAbs must be followed every 3–6 months (wait-and-see). In case of consistent rising Tg on LT4 or TgAbs, neck US is recommended, and a I-123 scan and/or FDG PET/CT may be considered to locate the origin of persistent/recurrent disease. The expert panel agreed to not define an exact value for high or rising Tg, as this is dependent on the assay and the course over time. The definition of consistent rising Tg on LT4 is debatable; the levels of Tg as well as the doubling time should be taken into account and weighted in the individual patient. Considering the excellent outcome of childhood DTC and the risk for adverse late effects of I-131, empiric treatment may only be considered after the abovementioned diagnostic modalities have failed to identify a source of rising Tg on LT4 or rising TgAbs.

When a source for the consistent rising Tg on LT4 or TgAbs is found, surgical or I-131 therapy is indicated, dependent on the risk–benefit ratio of both treatment options, bearing in mind the patient's medical history and previous I-131 exposure. Also, in case of small lymph nodes metastases and a history of repeated I-131 treatments, a wait-and-see strategy can also be advocated. No evidence is available to support that earlier treatment of small lymph node metastases will result in better outcome.

The expert panel suggests that prospective studies are needed to evaluate the outcome of a wait-and-see approach of children with measurable but not rising Tg during follow-up. Also, studies are needed to assess the best approach for children with recurrent disease or progressive thyroid cancer with regard to treatment possibilities (additional I-131 vs surgery vs wait-and-see approach).

Suggestion 25A:
We suggest to perform neck US in children with consistently rising Tg on LT4 or TgAbs. In these cases, additional I-123 and/or FDG PET scanning may be considered. Surgery or I-131 therapy is indicated depending on the size, tumor load, and degree of progression (4W).

Suggestion 25B:
We suggest that empiric I-131 iodine treatment be only recommended if the abovementioned diagnostic modalities have failed to identify a source of rising Tg on LT4 or rising TgAbs (4W).

D6. Pulmonary metastases

Distant metastases in pediatric DTC patients are mainly found in the lung. Overall, these can be detected in up to 20% of DTC patients and are observed particularly in those with extensive regional lymph node metastases (150). In the vast majority of cases, these lesions are micrometastases, and being well-differentiated and iodine avid, respond to I-131 therapy (i.e. 85% of patients) (151).

However, most patients are not cured of their disease, but even in these patients, after treatment, metastatic stability is observed over time and the disease-specific mortality rate is low (<2%) (151, 152, 153). In patients with previous positive post-therapeutic I-131 whole-body scan (WBS), an I-123 diagnostic (DxWBS) may be of value in the case of detectable Tg levels suggestive of persistent or recurrent disease to identify iodine avid disease amenable to further I-131 therapy. However, pulmonary metastases may not be visualized on I-123 DxWBS (154). In this setting, considering that structural and biochemical response to first I-131 may be observed up to 15–18 months after therapy (103), long intervals of at least 12 months are suggested before retreatment, even in the rare case of disease progression. Although complete remission may be achieved after therapy, repeated I-131 administrations should always be evaluated with caution and proposed after adequate interval.

In any case, a pulmonary function test is recommended before retreating patients with diffuse lung metastases. In children with a previous history of drugs causing pulmonary toxicity such as bleomycin, I-131 treatment must be given with extra caution given the risk for lung fibrosis (155).

Recommendations 26A:
We recommend that I-131 is the first-line therapy for patients with pulmonary metastases (4S).

Suggestion 26B:
We suggest that a pulmonary function test should be performed, before repeated I-131 treatment of patients with diffuse lung metastases (4W).

Recommendations 26C:
We recommend that in children with a previous history of drugs causing pulmonary toxicity such as bleomycin, I-131 treatment must be given with extra caution given the risk for pulmonary fibrosis (4S).

D7. Radioiodine refractory disease

In pediatric DTC patients, metastatic disease is well differentiated and often characterized by intense iodine uptake on post-therapeutic I-131 WBS. Responses to I-131 in this setting are good and patients often achieve complete remission after repeated I-131 therapeutic courses (103, 105). In the pediatric population, I-131 refractory disease is rare (109). In the setting of radioiodine refractory thyroid cancer not amenable to surgical resection, systemic therapy with TKIs may be considered. However, although TKIs have been largely and successfully used in adult patients, molecularly targeted therapy has not been applied in a large cohort of DTC pediatric patients and only few case report or series are available in literature (119, 120). Although encouraging results have been reported, a long duration of treatment with TKIs could significantly influence the quality of life and should be reserved only for specific patients as I-131 refractory pediatric DTC patients usually do well on TSH-suppressive levothyroxine therapy alone (156). In this clinical setting, the definition of I-131 refractory disease is of primary importance considering that very few pediatric patients will not respond to I-131 and even in this setting, may remain stable or without symptoms over the years (122).

Suggestion 27A:
We suggest that, when radioiodine refractory disease is suspected, its presence should be thoroughly investigated and confirmed before considering systemic targeted therapy. An observation or wait-and-see strategy may be appropriate (4W).

Suggestion 27B:
We suggest that targeted therapy should be reserved only for patients with large-volume disease which is significantly progressing on TSH-suppressive therapy and not amenable to surgical approach and should preferably be given in a research setting (4W).

D8. Late effects of treatment

Due to the excellent prognosis of pediatric DTC, it is of great importance to be aware of and to minimize the adverse effects of treatment. Of the adverse effects of treatment, hypoparathyroidism and salivary gland dysfunction are most prevalent. The prevalence of hypoparathyroidism has been shown to be related to the experience of the endocrine surgeon (99).

TSH-suppressive therapy in adult DTC survivors has been shown to be related to the risk of cardiovascular and all-cause mortality (157). Also, in children, diastolic dysfunction has been shown to be present after treatment for pediatric DTC (158). Another possible late effect of TSH suppression in combination with hypoparathyroidism is loss of bone mineral density (16, 158, 159). I-131 treatment has been associated with salivary and lacrimal gland dysfunction and secondary primary malignancies (SPM) and may possibly affect male fertility (160, 161).

Several studies have shown an increased risk to develop SPM after treatment for DTC and it has been shown to be related to the cumulative I-131 activity (162, 163, 164, 165). However, a cohort described by Verkooijen *et al.* showed an overall increased standardized incidence rate for second primary tumors but not for second primary tumors following I-131 therapy (162). The findings of this latter study suggest a genetic mechanism instead of a causal relation. Several different reports on the risk of SPM in relation to RAI have been made on this subject; however, most studies have limitations and more long follow-up studies are necessary. In one study, the risk to develop SPM in young patients (<25 years) receiving I-131 was found to be comparable to that in adults (163). However, in another study, the overall relative risk (RR) for developing SPM in adults with DTC, dependent on age at DTC treatment and latency time, varies between 0.98 (0.58–1.65) and 1.37 (1.13–1.66) for neurologic and hematologic SPMs, respectively (164). Also, Marti *et al.* reported an increased risk of SPM in young adult patients (standard incidence ratio (SIR) 1.42) after treatment with I-131 for DTC (163). In this study, mainly salivary carcinoma was reported (SIR, 34.12; *P*=0.0007). Mei *et al.* reported that 4.4% of adult patients treated for DTC developed a SPM after 2 years (169). A recent review on the risk of SPMs, especially secondary hematologic malignancies (SHMs), attributable to RAI therapy was published, concluding (based on low-quality evidence) that an excess risk for the development of SPM cannot be excluded but is expected to be small (166). An even more recent study by Pasqual *et al.* however pooled nine US Surveillance, Epidemiology, and End Results (SEER) cancer registries including 27,050 ≥ 5-year survivors and found that 6% of solid and 14% of hematologic malignancies in pediatric and young adult DTC survivors may be attributable to RAI (165).

Damage to testicular cells induced by the beta and gamma radiation could cause transient subfertility in male adults which could cause decreased semen quality, elevated levels of luteinizing hormone (LH), and follicle-stimulating hormone and decreased levels of testosterone (167, 168, 169). On the other hand, long-term data have shown that men treated with I-131 had normal semen quality and were able to conceive healthy children (161, 168, 170). However, data on male fertility in boys treated with I-131 is scarce;

therefore, the expert panel suggests that post-pubertal males who receive I-131 may be counseled about the possibility of (transient) decreased fertility and semen preservation could be offered.Next to physical late events, psychosocial effects of having had thyroid cancer in childhood may be present during adulthood.

The expert panel questioned which late effects should be screened for after treatment for pediatric DTC. Consensus was achieved to counsel and screen for hypoparathyroidism and recurrent nerve injury and to counsel on the risk of male fertility and SPM after I-131. A literature search was performed on the frequency and risk for other adverse effects of treatment for DTC (Appendix A [Q21], B, C) (16, 158, 171, 172, 173, 174, 175, 176).

Studies were identified that the investigated presence and risk factors of cardiac dysfunction, salivary gland dysfunction, influence on long-term quality of life, bone mineral density, and female fertility in survivors of DTC (16, 158, 171, 172, 173, 174, 175, 176). Diastolic dysfunction was found in 21.2% of asymptomatic pediatric DTC survivors (158). In these survivors, the systolic function was unaffected. Also, neither atrial fibrillation nor an association with biomarkers such as NT-proBNP, hs-troponin-T, or galectin was described. The clinical significance of these findings will have to be studied in future cohorts.

Two studies described the prevalence of salivary gland dysfunction after radioiodine treatment in survivors of DTC. Salivary dysfunction and xerostomia were found in 1.9–47.6% and 35.5% of the DTC survivors, respectively (16, 171). Selvakumar *et al.* found a relationship between salivary gland dysfunction with increasing I-131 activity; a lower salivary secretion and more xerostomia complaints were found in patients treated with a higher cumulative I-131 activity (171).

Quality of life and course of life studies have been reassuring, and scores of survivors did not seem to differ significantly from controls (173). However, more physical problems, more role limitations due to physical problems, and more mental fatigue were described by DTC survivors (173, 176).

Few studies have investigated bone mineral density in survivors of DTC. No differences were found with respect to bone mineral density (BMD) and Z scores at any site evaluated by DXA and in bone microstructure parameters between survivors of DTC and controls (174, 175). However, calcium–vitamin D3 medication had a beneficial effect on BMD. TSH-suppressive therapy does not seem to affect BMD in women treated for DTC at young age, at least after 10 years of follow-up.

Only one study was found that reported on female fertility in survivors of pediatric DTC (172). In this study, neither major abnormalities in reproductive characteristics nor in predictors of ovarian failure in female survivors of DTC, who received I-131 treatment during childhood, were found.

In conclusion, hypoparathyroidism, cardiac dysfunction, and salivary gland dysfunction occur in 23.8, 21.2, and 1.9-47.6% respectively. No significant effect of treatment for pediatric DTC was found on overall quality of life, bone mineral density, or female fertility.

Suggestion 28A:
We suggest counseling pediatric DTC patients about the risk of developing recurrent laryngeal nerve injury or hypoparathyroidism after thyroid surgery and salivary gland dysfunction after exposure to I-131. In addition, the potential risk of subsequent primary neoplasms after I-131 treatment related to I-131 activity and possible risk for cardiac dysfunction after prolonged TSH suppression should be mentioned (3W).

Recommendation 28B:
We recommend that the recurrent laryngeal nerve and parathyroid gland function is monitored post-operatively (3S).

Suggestion 28C:
We suggest that all post-pubertal males who receive I-131 may be counseled on the possibility of (transient) decreased fertility and semen preservation could be offered (3W).

Suggestion 28D:
We suggest that all pediatric DTC patients receive additional calcium and vitamin D supplementation therapy for optimal bone mineralization during follow-up (4W).

Suggestion 28E:
We suggest that all patients with pediatric DTC are offered psychosocial support (4W).

Suggestion 28F:
We suggest that future studies should further evaluate the prevalence and clinical significance of diastolic dysfunction in survivors of pediatric DTC after prolonged TSH suppressive therapy (4W).

D9. Follow-up scheme and transition to adult care

Most recurrences of DTC occur within the first 5 years after diagnosis (177), and also late recurrences occurring >20 years after initial diagnosis have been described, especially in older studies (177). These patients were, however, treated before hsTg assays were available, and these late recurrences may therefore become unusual in the future (109). In addition, also the psychological impact of prolonged follow-up of DTC and continuous fear of recurrence while in fact, this risk decreases with prolonged follow-up time, must be taken into account, especially in children, despite the fact that this risk decreases with prolonged follow-up time. With this in mind, the expert panel suggests to continue follow-up for least 10 years; thereafter, the follow-up strategy should be the result of shared decision-making between the physician and the patient.

The medical specialties involved in the treatment and follow-up of pediatric DTC vary between European countries (11). The expert panel agreed that the follow-up of children with DTC should be performed by a pediatric thyroid carcinoma expert, within a thyroid expert team, whereby the type of expert is based on the organization of care in each country. Furthermore, as most children are diagnosed between ages of 15 and 18 years, a close cooperation between pediatric and adult clinical teams is needed to enable good transitional clinical care.

Suggestion 29:
We suggest to continue follow-up of children with DTC for at least 10 years; thereafter, the follow-up strategy should be the result of shared decision-making between the physician and the patient (4W).

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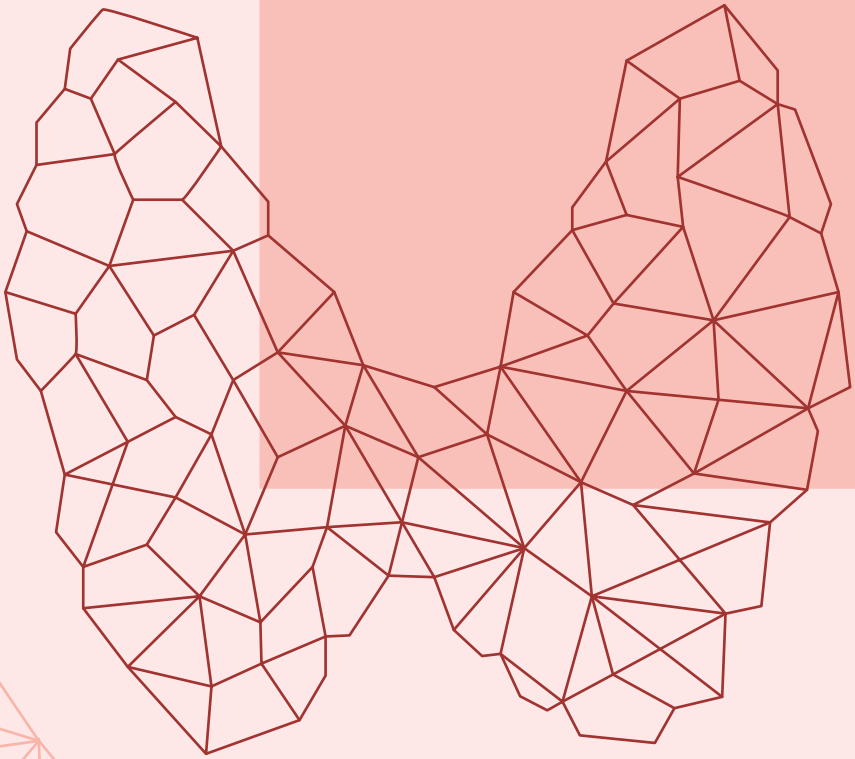
Supplementary materials

Appendix A. Clinical questions
Appendix B. Pubmed searches
Appendix C. Summary tables

Available online at: https://etj.bioscientifica.com/view/journals/etj/11/6/ETJ-22-0146.xml?alreadyAuthRedirecting&body=supplementarymaterials-49140



6

Does ultrasound really contribute to detection of residual/recurrent disease after pediatric thyroidectomy? Considerations for a "thyroglobulin-first" approach

Chantal A. Lebbink, Hanneke M. van Santen, Alan Daneman, Jonathan D. Wasserman

Submitted

Dear Editor,

Between 39 and 67% of children with differentiated thyroid carcinoma (DTC) are at low-risk of residual or recurrent disease (RRD) per the recent American Thyroid Association (ATA) Pediatric Risk Stratification criteria (1–3). Surveillance comprises biochemical, sonographic and radionuclide imaging. The relative strength of each modality to identify structural RRD (sRRD), particularly in the context of low-risk pediatric disease, has not been established.

The combination of serum thyroglobulin (Tg) and cervical ultrasound (US) is used to detect sRRD following total thyroidectomy (4,5). US, however, is highly operator-dependent (6). Previous studies have demonstrated that US in adult ATA low-risk patients is more likely to yield false-positive findings than true structural recurrence (7,8). Inflammatory cervical lymph nodes are common in children, further contributing to potential false-positive US. Indeterminate or suspicious US, in the absence of biochemical evidence of disease, may contribute to patient and provider worry, as well as unnecessary investigations and/or interventions. It is unclear whether, in the context of undetectable or low-detectable Tg, such findings are actionable, and if they are associated with independent risk for RRD.

We conducted a retrospective study of all patients <18 years who underwent total thyroidectomy for DTC at The Hospital for Sick Children from 2010-2020, to explore the value of routine US surveillance in follow-up of pediatric DTC (supplementary table 1).

Data were abstracted from US reports, without re-review of the primary images, as we sought to assess the "real-world" impact of the radiologists' impression on decision-making. Reports were categorized as: (1) "reassuring" (there were no findings concerning for sRRD), (2) "indeterminate" or (3) "suspicious" for sRRD. "Indeterminate" reports included those describing i) lesions without comment regarding significance, ii) lesions "of uncertain significance", or iii) lesions that "may" reflect sRRD per the reporting radiologist. Criteria used at our institution for suspicion of LN metastases have been previously described (5,9). US was performed 6 months after thyroidectomy and then every 6-12 months with contemporaneous Tg and Tg-antibody (TgAb). This study was approved by the research ethics board (#1000035326) with waiver of informed consent. Additional imaging or interventions performed within 6-months were considered to reflect direct sequelae of the US study and/or disease present at the time of the US. Risk stratification was based on ATA Guidelines (1) with modification as outlined in supplementary data. Disease status was classified as previously defined (10). Detailed methods are included in the supplementary data.

In total, 260 US studies were assessed. The mean number of US per patient per year was 2.1 over a median follow-up of 2.3 years (range 0.6-9.5). Overall, 112/260 (43.1%) US reports were classified as "reassuring" (figure 1, table 1). "Indeterminate" findings were documented in 42.3% (110/260) and "suspicious" findings in 14.6% (38/260). sRRD was confirmed in 11/56 (19.6%) patients (supplementary table 2).

1) Reassuring US findings

sRRD was never diagnosed in the context of a "reassuring" US study. Twenty-five patients had "reassuring" *initial* post-operative US. None developed structural recurrence during follow-up, regardless of initial ATA risk stratum. Disease status at last follow-up for these patients was: 16/25 no evidence of disease; 6/25 indeterminate response (4 with TgAb and 2 with low-detectable thyroxine-suppressed thyroglobulin Tg (LT4-Tg<1 ug/L); 3/25 biochemically-incomplete response.

Eighteen individuals progressed from "reassuring" to "indeterminate" or "suspicious" US findings during follow-up. In 1/18 (supplementary table 2, patient #39), presumed sRRD was diagnosed based on elevated Tg, indeterminate US and no radioiodine uptake. A schematic of subsequent ultrasounds, relative to prior ultrasound is shown in supplementary figure 2.

2) Indeterminate US findings

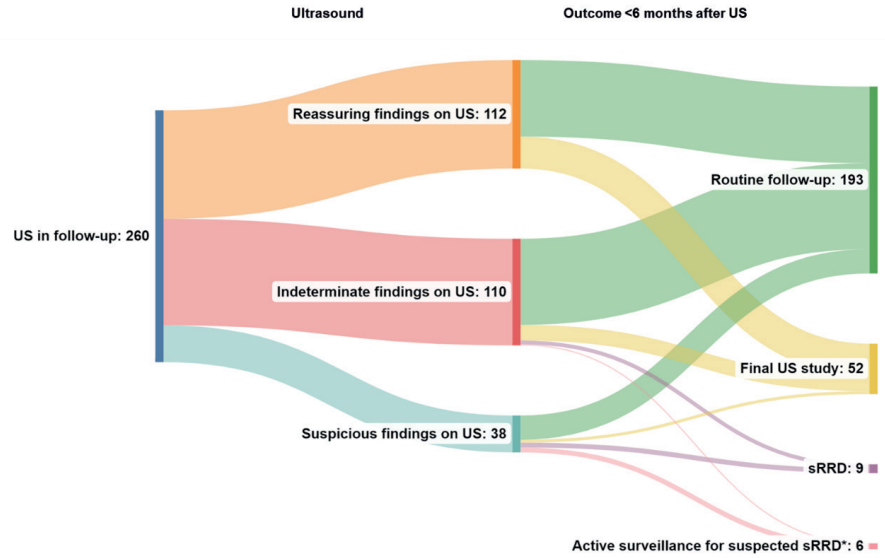
sRRD was diagnosed within 6 months of 5/107 (4.7%) indeterminate studies, all coincident with elevated Tg or TgAb. These were considered to reflect accurate detection of structural disease by US.

3) Suspicious US findings

Of 38 "suspicious" studies, structural disease was confirmed within 6 months on 10 occasions (26.3%). Among patients with suspicious US findings at *any* point during their follow-up course, 35% (7/20) developed sRRD. Conversely, 13/56 (23%) patients had ≥1 suspicious US during their course, and never developed sRRD. Overall, 31/56 patients had at least one indeterminate/suspicious US and did not develop sRRD.

Figure 1. Short-term outcomes within 6 months of surveillance investigations

A.



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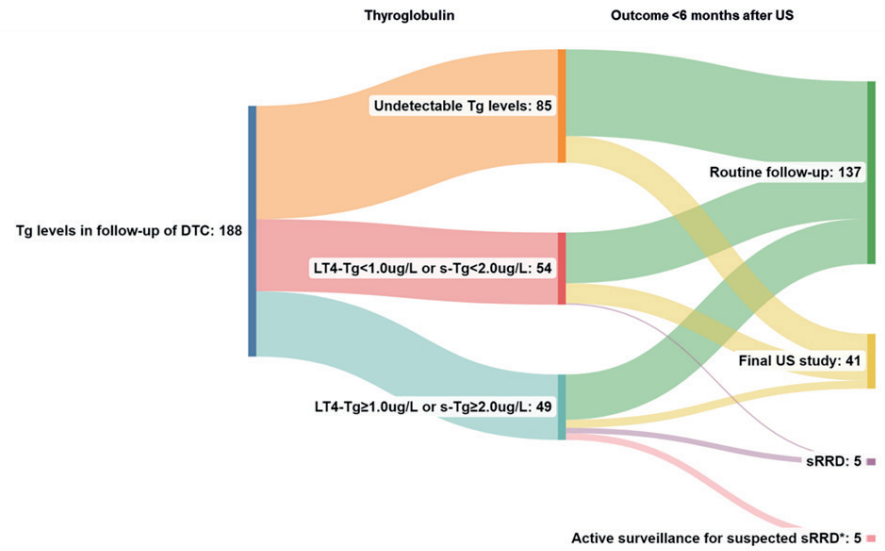

A. *Outcomes based on US results*: US reports were classified as "reassuring" in 112/260, "indeterminate" in 110/260 and "suspicious" in 38/260. 193 US were followed by routine follow-up without additional interventions, whereas sRRD was confirmed after 9 US studies and "active surveillance for suspected malignancy" was documented after 6 US studies. For 52 ultrasounds, this was the final study prior transition to adult care. None of these studies was followed by additional investigations or interventions within 6 months of the US. In 4/56 patients RRD was confirmed after the final US and was classified as sRRD (n=2) or active surveillance for suspected sRRD, without cytological, histological or radionuclide confirmation (n=2).

B. *Outcomes based on thyroglobulin measurement*. Undetectable Tg was never associated with sRRD within 6 months of US, while a single patient with a low detectable Tg (LT4-Tg<1.0 or sTg <2.0 ug/L) was found to have sRRD within 6 months.
Abbreviations—DTC: differentiated thyroid carcinoma; LT4-Tg: Thyroxine-suppressed Thyroglobulin; sRRD: structural residual or recurrent disease; Tg: thyroglobulin; US-ultrasound

Table 1. Tg/TgAb titres in FU of DTC in children per US study

	Total (n=260)	**US Reassuring (n=112)**	**US Indeter-minate (n=107)**	**US Suspicious (n=41)**	**P**
Lab results					
% of studies where LT4-Tg<1 or sTg<2	73.2 (139/188)	82.0 (73/89)	73.3 (55/75)	45.8 (11/24)	0.002
% of studies where TgAb >ULRR, n (%)	20.2 (48/238)	12.5 (13/104)	23.5 (23/98)	33.3 (12/36)	0.016
Interventions					
Intervention within 6 months after US, n (%)[a]	N=278	N=112[b]	N=114	N=52	N/A
Routine follow-up	208 (74.8)	109 (97.3)	88 (77.2)	11 (21.2)	
Additional US <120 days	10 (3.6)	1[c] (0.9)	3 (2.6)	6 (11.5)	
Active surveillance for suspected malignancy	19 (6.8)	0 (0.0)	8 (7.0)	11 (21.2)	
Cytological/histological confirmation	8 (2.8)	0 (0.0)	3 (2.6)	5 (9.6)	
RAI treatment	2 (0.7)	0 (0.0)	2 (1.8)	0 (0.0)	
Ancillary imaging modalities (MRI/CT/FDG PET/CT/RAI scan (non-routine[d]))	31 (11.2)	2[e] (1.8)	10 (8.8)	19 (36.5)	

Data were excluded if there was no Tg and TgAb titre measured within 60 days of US.
[a]All interventions within 6 months were included. Some patients underwent >1 intervention during this interval.
[b]No clinical report was found after n=1 US examination
[c]Elevated Tg was indication for additional US <120 days
[d]For the initial period of this study, (2010-2015), RAI imaging was performed per routine surveillance paradigm. For the purposes of this analysis "non-routine" designates any RAI scan that was performed in evaluation of a clinically suspicious finding (based on biochemistry, examination, or US) outside of routine surveillance.
[e]Indication based on elevated Tg levels
Abbreviations: US, cervical ultrasound; FU, follow-up; LT4-Tg, Tg measurement on LT4 replacement therapy; sTg, stimulated thyroglobulin (TSH>30 mIU/L); ULRR, upper limit reference range; RAI, radioactive iodine; N/A, not applicable

Outcomes relative to Tg

1) Undetectable Tg

In patients with undetectable Tg, reassuring, indeterminate and suspicious US findings were documented in 49.4% (42/85), 42.4% (36/85) and 8.2% (7/85) of contemporaneous studies. Undetectable Tg was never associated with sRRD within 6 months of US.

Seven patients had undetectable Tg at one point, which subsequently became (low) detectable. One developed structural recurrence (supplementary table 2, patient #39). In retrospect, the undetectable Tg was obtained using a prior-generation assay with a functional sensitivity (FS) of 0.9 ug/L (versus the current assay with FS=0.1 ug/L).

2) Low-detectable Tg levels (LT4-Tg<1.0 or sTg <2.0 ug/L)

Among patients with low-detectable Tg, reassuring, indeterminate and suspicious findings were present in 57.4% (31/54), 35.2% (19/54) and 7.4% (4/54) of US. Reassuring or indeterminate US findings in the context of low-detectable Tg were never associated with sRRD within 6 months of US.

Four patients had low-detectable Tg and suspicious US. Recurrence was confirmed histologically in one. Another transitioned to adult care immediately thereafter, and final disease status could not be ascertained and was censored. The remaining two did not develop sRRD after 3.5 and 7.2 years of follow-up. The false-positive rate of indeterminate or suspicious US findings with low-detectable Tg was 21/22 (95.5%)).

sRRD was confirmed during follow-up in three patients with low-detectable Tg at any point (supplementary table 2, patients #3,35,53). All three had suspicious or indeterminate findings on their *initial* post-operative US. Test characteristics of US based on Tg are summarized in supplementary tables 3&4.

Outcome among patients with elevated TgAb

Presence of TgAb was not associated with sRRD (p=0.263). Among all five patients with elevated TgAb who developed sRRD, the *initial* US after primary therapy demonstrated indeterminate or suspicious findings.

Outcome by risk strata

Supplementary table 5 summarizes US findings by stratum. Per-patient, sRRD was found during follow-up in 17.9% (5/28) low-risk, 37.5% (3/8) intermediate-risk and 15.0% (3/20) high-risk patients (p=0.424).

Discussion

Sonographically indeterminate findings are common during surveillance of DTC and are infrequently diagnostic of sRRD. This highlights the challenges inherent to interpretation of post-operative US for surveillance.

Our data illustrate that US in patients with undetectable Tg is associated with a high false-positive rate. Even among patients with low-detectable Tg, only 4.3% of indeterminate or suspicious USs were associated with sRRD. Moreover, a reassuring *initial* post-operative US was a strong favorable prognosticator. No patient with a reassuring *initial* US developed RRD during follow-up. Notably, 35% of patients progressed to undetectable Tg without any therapeutic intervention, following ≥1 indeterminate or suspicious US. Thus, decisions to pursue intervention should not be based on imaging alone.

We were intrigued to find rates of RRD not significantly different among those with initial low, intermediate, and high risk. There are several possible explanations. First, we excluded low-risk patients who underwent lobectomy. This would *a priori* constitute the lowest risk category. Moreover, among the high-risk patients, those with distally metastatic disease and R2 resection were excluded. Thus, by design, patients at lowest and highest risk for RRD were excluded, leading to potential overestimation and underestimation of recurrence risk, respectively. Finally, the rate of RRD in this cohort was low, and it was likely underpowered to detect meaningful distinctions.

There are several limitations to this study. Due to transition to adult care after age 18, this cohort has a relatively brief median follow-up duration of 2.3 years. Thus, we were unable to assess for late recurrence following transition. US images were interpreted, over the course of this study, by 12 different pediatric radiologists, leading to potential heterogeneity of interpretation and reporting. No standardized report was used for sonographic findings. US reports frequently described "stable findings" without elaboration regarding the degree of sonographic concern. Nonetheless, these studies are reflective of experience in typical clinical practice.

The high rate of indeterminate US reports supports the need for a "common language" in reporting surveillance US and we would endorse development and validation of a standardized reporting tool applied to post-thyroidectomy investigations, akin to the pre-operative TI-RADS instrument used for thyroid nodules (11).

Although the limited size of this cohort and short follow-up duration preclude over-arching recommendations, several modifications may be considered: First, we endorse an *initial* post-operative US for all patients. For those where the initial post-operative US is clearly reassuring, without elevated TgAb, it may be reasonable to limit surveillance to a "Tg-first" approach, with subsequent US limited to the context of rising Tg. This may also apply to those with undetectable or low-detectable Tg during follow-up, given the low rate of sRRD. Applying this approach to the current cohort would have reduced the number of US performed by 101 (39%) without missing sRRD.

We advocate US surveillance for individuals with elevated TgAb, at least until TgAb titres are within the reference range, whereupon circulating Tg can be accurately assessed.

Validation of these observations in a larger (and/or multi-center) cohort as well as collaboration with adult institutions to facilitate extended follow-up following transition of care would be important to establish generalizability of these findings.

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11. Grant EG, Tessler FN, Hoang JK, et al. Thyroid ultrasound reporting lexicon: White paper of the ACR thyroid imaging, reporting and data system (TIRADS) committee. *Journal of the American College of Radiology*. 2015;12(12):1272-1279.

Supplementary materials

Supplementary data

Methods

Clinical management

Over the study period, the approach to managing DTC evolved (1). Prior to the 2015 ATA guidelines, routine surveillance for all patients included semi-annual thyroxine-suppressed thyroglobulin (LT4-Tg), TgAb, cervical US, and annual surveillance diagnostic RAI whole body scanning (RAI WBS). In the analysis of clinical management following US, data from routine surveillance RAI WBS (absent clinical suspicion) pre-2015 were excluded from the analyses.

Tg levels were classified as: 1) undetectable, 2) low-detectable (LT4-Tg<1.0 or sTg <2.0 ug/L) (1) or 3) elevated (LT4-Tg ≥1.0 or sTg≥2.0 ug/L). Stimulated Tg (sTg) was typically measured after LT4-withdrawal with TSH>30 mIU/L. Patients with TSH above treatment targets, but without undergoing deliberate LT4-withdrawal were included in the LT4-Tg analysis. TgAb was considered positive if the reported value was above the laboratory's upper limit of the reference range at the time of analysis.

Definitions

Risk stratification

Risk stratification was based on 2015 ATA Guidelines with the following deviations: patients with ≤5 metastatic LN in level VI (N1a) were considered to have 'low risk' disease; patients with >5 LNs in level VI or minimal N1b (level I-V) disease (≤5LNs) were considered to have 'intermediate risk' disease and patients with extensive N1b (>5 lateral cervical LNs) or locally invasive disease (T4 tumors) were considered to have 'high risk' disease.

Definitions for residual or recurrent structural disease

<u>True-positive US findings:</u>

Suspicious US findings were deemed to be true-positive for structural disease if 1) DTC was confirmed by cytology or histology, 2) positive RAI WBS after additional ^{131}I treatment or 3) suspicious findings were noted on US/ancillary imaging modalities, with elevated Tg levels and a comment in the chart documenting 'active surveillance for suspected malignancy'.

<u>False-positive US findings:</u>

Suspicious US findings were considered false-positive for structural disease when 1) histology obtained by surgical intervention did not confirm DTC or 2) RAI WBS after additional ^{131}I treatment was negative for iodine-avid disease, and no further interventions confirming DTC were performed during the follow-up period.

<u>"True-negative" US findings:</u>

US was considered "true-negative" if, after a negative US, no other structural evidence of disease was identified during subsequent follow-up.

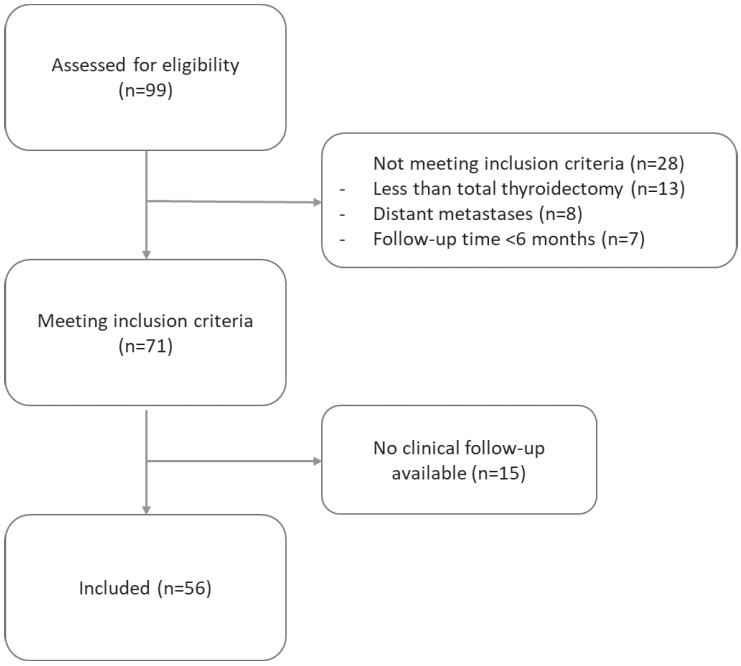
"False-negative" US findings:

US was considered "false-negative" following a reported reassuring study, when DTC was subsequently confirmed by cytology or histology, cervical ^{131}I uptake, or other imaging modalities with findings corresponding to the US, and a clinician note documenting 'active surveillance for suspected malignancy'.

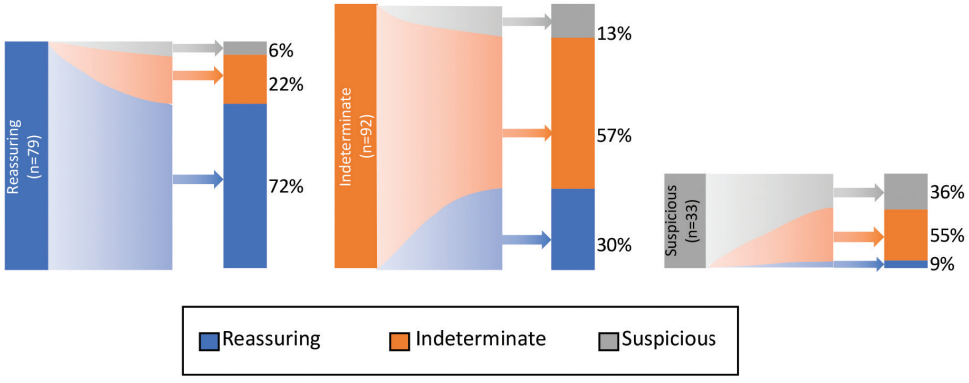
Reference

1. Francis GL, Waguespack SG, Bauer AJ, et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2015;25(7):716-759.

Supplementary Figure 1. Patients included in the study.



Supplementary Figure 2. Distribution of ultrasound findings and result of subsequent ultrasound 6 months later. The final US study prior to adult transition was not included.



Supplementary Table 1. Patient characteristics per patient and per US exam

Characteristics		
# of patients	56	
# of US	260	
# of US/patient/year	2.1	
Age at diagnosis, median (range) (years)	14.6 (6.4-17.4)	
Follow-up time per patient, median (range) (years)	2.3 (0.6-9.5)	
% female at birth	68% (38/56)	
Histology, n (%)		
Papillary thyroid carcinoma	55 (98.2)	
• Classic variant	25 (45.5)	
• Follicular variant	9 (16.1)	
• Diffuse sclerosing variant	12 (21.4)	
• Tall cell variant	1 (1.8)	
• Mixed histology	5 (8.9)	
• Other variant/not specified	3 (5.4)	
• Follicular thyroid carcinoma	1 (1.8)	
% patients treated with ^{131}I ablation therapy	55% (31/56)	
Total # ^{131}I treatments (range)	0-2	
T stage, n (%)		
T1a	6 (10.7)	
T1b	15 (26.8)	
T2	24 (42.9)	
T3a	10 (17.9)	
T3b	0 (0.0)	
T4a	1 (1.8)	
Lymph node metastases at diagnosis, n (%)		
N0a	12 (21.4)	
N0b	7 (12.5)	
N1a	15 (26.8)	
N1b	22 (39.3)	
Initial Risk Stratification, n (%)	**By patient**	**By US exam**
Low risk	28 (50.0)	135 (51.9%)
Intermediate risk	8 (14.3)	30 (11.5%)
High risk	20 (35.7)	95 (36.5%)

Supplementary Table 2. Overview of US results, interventions, and outcome per patient

# Patients	Year of diagnosis	Initial treatment	ATA risk	1	2	3	4	5	6	7	8	9	10	11	sRRD	Last Tg	Disease status last clinical evaluation
1	2015	TT no RAI	Low	I	I	R	R	R	I	R						0.07	No evidence of disease
2	2020	TT no RAI	Low	I	I	I										0.1	No evidence of disease
3	2019	TT no RAI	High	I	I	I	I								+	0.12	No evidence of disease
4	2020	TT no RAI	Low	R	R											0.2	No evidence of disease
5	2019	TT no RAI	Intermediate	R												0.44	Indeterminate disease status
6	2014	TT no RAI	Low	I	I	R	R	R	R							0.6	Indeterminate disease status
7	2018	TT no RAI	Low	R	I	R	R									0.8	Indeterminate disease status
8	2019	TT no RAI	High	R	I	R										1.11	Biochemical disease
9	2016	TT no RAI	Low	I	R	R	R	R	S	I						2.8	Indeterminate disease status
10	2020	TT no RAI	Low	R	I	R										6.18	Biochemical disease
11	2017	TT no RAI	High	I	I	S	I	I	I	I						TgAb	Indeterminate disease status
12	2017	TT no RAI	Low	R	R											TgAb	Indeterminate disease status
13	2020	TT no RAI[a]	Intermediate	I**											+	TgAb	Structural disease
14	2015	TT no RAI	Low	R	R	I	R	R	R	R	I	I	I	R		undetectable	No evidence of disease
15	2015	TT no RAI	Low	R												undetectable	No evidence of disease
16	2015	TT no RAI	Low	R	R	I	R	S	I	I						undetectable	No evidence of disease
17	2016	TT no RAI	Low	S	I	I										undetectable	No evidence of disease
18	2016	TT no RAI	Low	I	S	I										undetectable	No evidence of disease
19	2018	TT no RAI	Low	R^	I	I	R	I	R	R						undetectable	No evidence of disease
20	2019	TT no RAI	High	R												undetectable	No evidence of disease
21	2019	TT no RAI	High	I	I	I	I	I								undetectable	No evidence of disease
22	2019	TT no RAI	High	R												undetectable	No evidence of disease
23	2020	TT no RAI	Low	R	R	R	R									undetectable	No evidence of disease

# Patients	Year of diagnosis	Initial treatment	ATA risk	1	2	3	4	5	6	7	8	9	10	11	sRRD	Last Tg	Disease status last clinical evaluation
24	2020	TT no RAI	Low	I	R	R										undetectable	No evidence of disease
25	2018	TT no RAI	Low	R	R											undetectable	No evidence of disease
26	2013	TT with RAI	Low	R	R	R	R	R								0.05	No evidence of disease
27	2014	TT with RAI	High	R	S	R	I									0.06	No evidence of disease
28	2020	TT with RAI	Intermediate	I												0.07	No evidence of disease
29	2016	TT with RAI	Intermediate	I	I	S									+	0.11	Structural disease
30	2015	TT with RAI	Low	S	S*	R									+	0.11	No evidence of disease
31	2019	TT with RAI	Intermediate	R												0.12	No evidence of disease
32	2015	TT with RAI	High	S	I	S	I	I	I	R	R	R	I	R		0.17	No evidence of disease
33	2020	TT with RAI	Intermediate	I	R	R										0.3	Indeterminate disease status
34	2019	TT with RAI	High	I	R	R	R									0.4	Indeterminate disease status
35	2014	TT with RAI	Low	I	I										+	0.45	Structural disease
36	2016	TT with RAI	Low	I	S	I	S	S	S	I					+	0.67	Indeterminate disease status
37	2019	TT with RAI	High	R	R	S	I									1.08	Biochemical disease
38	2011	TT with RAI	Low	I	I	R	R	R	R	R	R	R	R	R		1.14	Biochemical disease
39	2010	TT with RAI	Low	S	I	R	R	I	I	I	I	S	I		+	13.3	Biochemical disease
40	2020	TT with RAI	High	S	I	I									+	2.1	Structural disease
41	2019	TT with RAI	High	S	S	S									+	27.17	Structural disease
42	2014	TT with RAI	Low	I	S											TgAb	Indeterminate disease status
43	2015	TT with RAI	High	R	R	R	R	R								TgAb	Indeterminate disease status
44	2017	TT with RAI	High	R	R	I	S	R								TgAb	Indeterminate disease status
45	2021	TT with RAI	High	R												TgAb	Indeterminate disease status
46	2016	TT with RAI	Intermediate	I	I	S	I	I	S	I	S	S	S		+	TgAb	Structural disease
47	2016	TT with RAI	High	S	I											undetectable	No evidence of disease

# Patients	Year of diagnosis	Initial treatment	ATA risk	1	2	3	4	5	6	7	8	9	10	11	sRRD	Last Tg	Disease status last clinical evaluation
48	2010	TT with RAI	Low	R	R	R	R	R	R							undetectable	No evidence of disease
49	2011	TT with RAI	High	R	R	R	S	I	I	R						undetectable	No evidence of disease
50	2011	TT with RAI	Low	R												undetectable	No evidence of disease
51	2012	TT with RAI	Low	I	R											undetectable	No evidence of disease
52	2013	TT with RAI	High	S^	S^	S	I	R	I	R						undetectable	No evidence of disease
53	2015	TT with RAI	Low	S	S	S^	S^	I	I	I	I	I	I	I	+	undetectable	No evidence of disease
54	2015	TT with RAI	Intermediate	R	R	I	I	I	I	R	I	I	I			undetectable	No evidence of disease
55	2015	TT with RAI	High	I	I	R	R	I	I	I	I	R				undetectable	No evidence of disease
56	2016	TT with RAI	High	I	I	I	R	R	I	I	I	R				undetectable	No evidence of disease

Legend

R Reassuring US findings

I Indeterminate/uncertain US findings

S Suspicious US findings

sRRD: structural residual or recurrent disease

Histology/cytology

Routine follow-up

Additional US <120 days

Active surveillance for suspected malignancy

Ancillary imaging modalities (CT/MRI/non-routine RAI scan)

RAI treatment

Unknown

Peak Tg = after curative intent

N/A= not applicable

^additional US <120 days, ancillary imaging

*additional RAI treatment

**ancillary imaging, FNAC, surgery

[a]RAI therapy planned but deferred due to COVID-19 imposed restrictions

Supplementary Table 3. Test Characteristics of US in FU of sRRD

	sRRD present (<6mo)	sRRD absent (<6 mo)	
US suspicious or indeterminate	N= 15 (10 suspicious, 5 indeterminate)	N = 114 (89 suspicious, 25 indeterminate)	PPV: 11.6% [10.5% to 12.9%]
US reassuring	N=0 Sensitivity: 100.0% [78.2% to 100.0%]	N = 79 Specificity: 40.9% [33.9% to 48.2%]	NPV: 100%

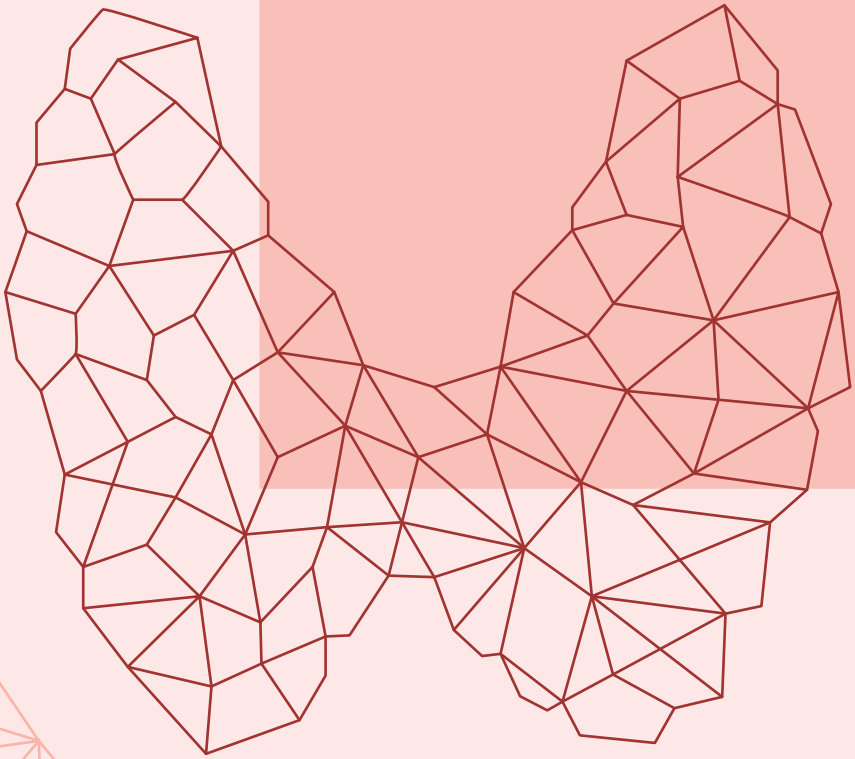
Supplementary Table 4. Test Characteristics of US in FU of sRRD of based on Tg levels

	sRRD present (<6 mo)	sRRD absent (<6 mo)	
Undetectable Tg or LT4-Tg <1.0ug/L or s-Tg<2.0ug/L US suspicious or indeterminate	1	53	PPV: 1.9% [1.5% to 2.2%]
US reassuring	0	50	NPV: 100.0%
	Sensitivity: 100.0% [2.5% to 100.0%]	Specificity: 48.5% [38.6% to 58.6%]	
Elevated Tg levels ≥ 1ug/L or s-Tg ≥ 2ug/L US suspicious or indeterminate	9	21	PPV: 30.0% [24.8% to 35.8%]
US reassuring	0	13	NPV: 100.0%
	Sensitivity: 100.0% [66.4% to 100.0%]	Specificity: 38.2% [22.2% to 56.4%]	

No patients had detectable Tg antibodies.

Supplementary Table 5. ATA risk stratification versus US findings

	US reassuring (n=112)	US Indeterminate (n=107)	US Suspicious (n=41)	Structural residual/recurrent disease (n) DTC <6 mo
Low risk	51.1% (69/135)	36.3% (49/135)	12.6% (17/135)	7.4% (8/108)
Intermediate risk	23.0% (7/30)	56.7% (17/30)	20.0% (6/30)	12.5% (3/24)
High risk	37.9% (36/95)	46.3% (44/95)	15.8% (15/95)	5.3% (4/76)



7

FDG PET/CT in differentiated thyroid cancer patients with low thyroglobulin levels

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Abstract

Objective

To evaluate the usefulness of [18F]fluorodeoxyglucose (FDG) positron emissive tomography (PET)/CT in patients with low detectable thyroglobulin levels suspicious for persistent or recurrent differentiated thyroid cancer (DTC).

Methods

A retrospective case series study evaluating FDG PET/CT in patients with detectable thyroglobulin (Tg) levels (≥0.20 and <10.00 ng/mL) after initial treatment with total thyroidectomy and I-131 thyroid remnant ablation for pT1-3aN0-1bM0 DTC. Sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of FDG PET/CT were calculated.

Results

Twenty-seven patients underwent FDG PET/CT. Median Tg level at FDG PET/CT was 2.00 ng/mL (range 0.30-9.00). FDG PET/CT was positive in 14 patients (51.9%): lesions suspicious for lymph node metastases were depicted in 12 patients, and lung metastases in 2. DTC was confirmed in 13/14 FDG PET/CT-positive patients. In 9/13 patients with a negative FDG PET/CT, DTC was confirmed ≤3 months after FDG PET/CT. The sensitivity, PPV, specificity and NPV were 59.1, 92.9, 80.0 and 30.8%, respectively.

Conclusions

This case series shows that FDG PET/CT might be useful to detect persistent or recurrent DTC in patients with low detectable Tg. However, when FDG PET/CT is negative, this does not rule out DTC and further investigations are necessary.

Introduction

Despite excellent survival, up to 20% of patients with differentiated thyroid cancer (DTC) will develop recurrent disease after initial treatment (1). Serum thyroglobulin (Tg) measurements play a pivotal role in the detection of recurrent disease. The high diagnostic value of serum Tg measurements as a marker for metastases and/or recurrent disease is universally accepted (2). In all patients, in addition to serum Tg measurement, neck ultrasound (US) is recommended at least once 6–12 months post-treatment and periodically in the follow-up depending on the patient's risk for recurrent disease and Tg status (1).

It is no longer recommended to perform routine radioactive iodine (RAI) scanning in low-risk patients without biochemical evidence of recurrent disease. However, for intermediate or high-risk DTC, the American Thyroid Association (ATA) management guidelines on the management of patients with thyroid nodules and DTC suggest that a diagnostic whole-body scan (WBS) using RAI can be useful for the detection of recurrent or persistent disease (1). Unfortunately, the diagnostic yield of RAI scanning is low and often results in negative investigations (3, 4). Even in patients treated empirically with high activities of I-131, post-therapeutic RAI WBS is shown to be negative in up to 50% of patients (5, 6, 7).

Currently, [18F]fluorodeoxyglucose positron emissive tomography CT (FDG PET/CT) is only recommended in case of negative RAI WBS in combination with serum Tg levels >10 ng/mL (1). There is increasing evidence that FDG PET/CT has a high diagnostic accuracy in this setting (8). Because of the low diagnostic yield of diagnostic RAI WBS, we started using FDG PET/CT instead of RAI WBS in patients with new detectable Tg on levothyroxine (LT4) levels to locate possible persistent or recurrent disease.

In this case series, we retrospectively evaluated the results of FDG PET/CT as a first-line nuclear imaging modality in patients suspected of persistent or recurrent DTC without first performing RAI WBS.

Methods

A retrospective analysis was performed of all patients with DTC (pT1-3aN0-1bM0) with detectable Tg levels (≥0.20 ng/mL and <10.00 ng/mL) after total thyroidectomy and I-131 thyroid remnant ablation who underwent FDG PET/CT (at least 6 months after I-131 ablation) in our hospital in the period from 2012 to 2020. Scan results, management and follow-up of patients were retrospectively evaluated.

Tg was measured using an IRMA (Brahms, Henningsdorf, Germany) between 2012 and October 2017, and a chemiluminescence immunoassay (Liaison, DiaSorin, Saluggia, Italy) in the period October 2017 until 2020, according to the manufacturer's instructions.

General patient characteristics, information about thyroid cancer treatment and available US results were gathered from the patient files. FDG PET/CT scans were re-evaluated by a nuclear medicine physician on study-specific parameters if these parameters were not previously described.

Image acquisition and analysis

PET of the head and neck and body area was acquired using a TruePoint Biograph mCT40 scanner (Siemens). After a fasting period of at least 6 h, patients received an intravenous injection of 2 MBq/kg FDG. Approximately, 60 min after FDG injection, separate head and neck and body PET/CT images were acquired. A low-dose CT scan was performed using care dose 4D and care kV, reference parameters: 40 mAs, 120 kV; subsequently, two 4-min bed positions PET with time-of-flight and point spread function (TrueX) reconstruction, four iterations, 21 subsets, with a filter of 5 mm full width at half maximum, slice thickness 3 mm. Standardized uptake value (SUV) calculations were performed using the lean body mass corrected formula on a separate PET reconstruction according to the European Association of Nuclear Medicine recommendations (9, 10). Patients were on thyroid hormone replacement therapy during FDG PET/CT, no recombinant thyroid-stimulating hormone (TSH) was prescribed.

Definitions

Tumor staging was recorded according to the eighth edition Tumor, Node, Metastasis classification system for DTC of the Union for International Cancer Control (11).

The most recent TSH and Tg on LT4 measurements before administration of FDG were recorded. If Tg on LT4 levels were unknown, TSH-stimulated Tg values were recorded. Elevated thyroglobulin antibodies (TgAb) were defined as TgAb >50 kU/L.

Results of the FDG PET/CT were categorized as negative or positive for the presence of possible DTC. If positive, the location of lesions was described as neck levels (lateral compartment (II, III, IV and V), central compartment (VI), mediastinal (VII), submandibular/submental (I)), lungs and/or other.

Clinical management after FDG PET/CT was defined as a wait-and-see strategy, surgery and/or RAI <3 months after FDG PET/CT. Three months after a wait-and-see strategy, Tg on LT4 levels was classified as undetectable (<0.20 ng/mL), low detectable (0.20–1.00 ng/mL), stable (Tg: >1.00 ng/mL with <1.00 ng/mL increase/decrease of Tg level in 3 months), rising (Tg: >1.00 ng/mL with >1.00 ng/mL increase of Tg level in 3 months) or decreasing (Tg: >1.00 ng/mL with >1.00 ng/mL decrease of Tg level in 3 months).

Positive FDG PET/CT findings were deemed true positive when DTC was confirmed by histology, post-RAI therapy scan after additional I-131 treatment or DTC was biochemically

suspected; in case of Tg on LT4 levels ≥0.20 ng/mL 3 months after a wait-and-see strategy. Positive FDG PET/CT findings were deemed false positive when histology obtained by surgical intervention did not confirm DTC or Tg levels decreased spontaneously and became undetectable 3 months after FDG PET/CT without intervention.

In FDG-negative patients with undetectable Tg on LT4 levels (<0.20 ng/mL) 3 months after FDG PET/CT without intervention, the FDG PET/CT was deemed true negative. Negative FDG PET/CT findings were deemed false negative when DTC was confirmed by histology, post-RAI therapy scan after additional I-131 treatment or DTC was biochemically suspected if Tg on LT4 levels remained detectable ≥0.20 ng/mL after 3 months without intervention.

Based on this classification, values were calculated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Disease status at the last moment of follow-up was defined as the presence or absence of structural disease (clinical and/or radiological evidence of disease) and/or biochemical disease (Tg on LT4 ≥0.20 ng/mL), or deceased due to DTC or due to other causes.

Statistical analysis

In this case series, descriptive analyses were done. Baseline factors, tumor-related characteristics, treatment modalities and results of the FDG PET/CT were described as percentage of the cases. The PPV and NPV of FDG PET/CT were calculated for persistent or recurrent DTC. The SPSS (26.0) statistical package was used for analyses.

Results

Patient characteristics

Twenty-seven patients (median age at diagnosis 40.7 years, 81.5% female) underwent FDG PET/CT for suspected persistent or recurrent DTC in the period 2012–2020 (table 1). Pertinent clinical and pathological characteristics are included in tables 1 and 2.

Table 1. General patient characteristics (*n*=27). Data are presented as *n* (%), *n* or as indicated

Characteristics	Values
Female gender	22 (81.5)
Age (years) at diagnosis of DTC, mean (range)	40.7 (16.6–73.9)
Year of diagnosis (range)	2006–2018
Follow-up in years, median (range)	6.0 (1.6–14.3)
Type of thyroid carcinoma	
Papillary thyroid carcinoma	24 (88.9)
Follicular thyroid carcinoma	3 (11.1)
TNM stage[a]	
T1	9 (33.3)
T1a	4
T1b	5
Unknown	0
T2	5 (18.5)
T3	13 (48.1)
T3a	5
T3b	1
Unknown	7
Lymph node metastases (N), *n* (%)	
N0	10 (37.0)
N1	17 (63.0)
N1a	3
N1b	13
Unknown	1
Post-ablation scintigraphy	
Thyroid remnant	21/27 (77.8)
Lymph node metastases	5/27 (18.5)

[a]Stage determined according AJCC eighth edition (11).
DTC, differentiated thyroid carcinoma; RAI, radioactive iodine.

Median Tg on LT4 level at time of FDG PET/CT was 2.00 ng/mL (range 0.30–9.00). FDG PET/CT was performed after a median time of 1.4 years (range 0.6–6.3) after RAI ablation.

Results of FDG PET/CT

In 14 patients (51.9%), FDG-positive lesions were found, of whom 12 patients had FDG-positive lymph nodes in the neck (figure 1 and table 3). Median SUV_{max} of detected lymph nodes was 3.0 (range 1.5–7.4). FDG-positive lymph nodes were mostly located in the lateral compartment (66.7%). In two patients, PET/CT detected FDG-positive lesions compatible with lung metastases. In 92.9% (13/14) of patients with positive FDG PET/CT, DTC was confirmed by histology, a positive post-RAI therapy scan after additional I-131 treatment or by remaining detectable/rising Tg levels.

In 13 patients, FDG PET/CT was negative. However, in nine of these patients, DTC was confirmed by histology (n=2) or post-RAI therapy scan after additional I-131 treatment (n=1) or these patients were biochemically suspect of DTC by remaining detectable (n=5)/rising (n=1) Tg levels 3 months after wait-and-see strategy.

The calculated sensitivity, PPV, specificity and NPV were 59.1, 92.9, 80.0 and 30.8%, respectively.

Correlation with US

Twenty-two out of 27 patients (81.5%) underwent neck US within 3 months prior to FDG PET/CT.

In eight patients, neck US showed suspicious findings for DTC. In five out of eight neck US-positive patients, FDG PET/CT was concordant and the presence of DTC was confirmed. Three out of eight patients had a positive neck US and a negative FDG PET/CT. After a wait-and-see strategy, Tg levels became undetectable in one patient and remained low detectable (≤1.00 ng/mL) after 3 months in two patients.

In 14/22 patients, neck US was negative. In 8/14 patients with negative US, FDG PET/CT depicted lesions suspicious for DTC, of which seven were considered true positive. In two out of seven of these patients, lymph node metastases were found on a targeted neck US afterward, whereby these patients could be treated surgically. FDG PET/CT also provided an indication for additional I-131 treatment because of inoperable disease (n=2) or lung metastases (n=1). In two patients, DTC was biochemically suspected because of rising Tg levels 3 months after the wait-and-see strategy.

In 6/14 patients, neither neck US or FDG PET/CT detected lesions suspect of DTC. However, in three of these patients, DTC was found within 3 months after FDG PET/CT: two patients had histologically proven DTC (fine needle biopsy) and in another patient, Tg level doubled.

Table 2. Patient characteristics FDG PET/CT in follow-up of DTC (n=27)

Case	Sex	Age	Histo-logy	TNM	RAI (MBq)	US results				Serum Tg (ON/OF*)	Time between RAI and FDG PET/CT (years)	FDG uptake	
						+/−	LN/TR	Level	Side				
1	F	19.0	PTC	T3N1bM0	5550	+	LN	IV	L	0.70	3.9#	+	LN Unilateral; Aspecific lung nodules
2	F	62.8	PTC	T1bN1bM0	1100	−				1.00	4.7	+	LN Bilateral
3	M	33.0	PTC	T1bN1bM0	1100	+	LN	II	L	2.00*	2.0	−	Aspecific lung nodule
4	F	45.6	FTC	T3aN0M0	1100	−				2.00	3.4	+	Lung
5	M	29.4	PTC	T1aN1bM0	5550					1.00	2.4	−	Aspecific lung nodule
6	F	17.0	PTC	T3aN1bM0	5550	−				5.00	5.4#	−	
7	F	16.6	PTC	T1bN1bM0	7400	−				0.40	0.6	−	
8	F	35.5	PTC	T3aN1bM0	4400	+	LN	III, IV, VI	L	4.80	0.6	+	LN Central, Unilateral
9	F	39.8	PTC	T3N0M0	1100					2.00	1.5	+	Lung
10	M	69.5	PTC	T1aN1bM0	1100	−				4.00	3.7	−	
11	F	73.9	FTC	T3N0M0	5550					4.00	5.3	−	
12	F	22.2	PTC	T2N0M0	1100					7.40	4.9	−	
13	F	57.2	PTC	T3N1aM0	7400	−				1.00	0.6	+	LN Thyroid bed, Central Mediastinal
14	F	39.8	PTC	T3N0M0	7400	−				.30	0.9	+	LN Central; Additional detected Coloncarci-noma
15	M	70.9	PTC	T1aN1bM0	1100	+	LN	NS	R	4.00	1.0	−	
16	F	50.6	FTC	T2N0M0	3735	−				9.00	4.2#	−	Rectumcarci-noma

SUV_{max} (LBM) (LN/lung)	Treatment after FDG PET/CT	Result of treatment (after 3 months)	Tg on LT4 after intervention (ng/mL)	Follow-up time (year)	Final outcome at last moment of follow-up	Tg on LT4 at last moment of follow-up
2.69 (IV L)	Surgery	Positive histology	0.50	6.1	Structural and biochemical disease	0.96
2.81 (IIb R)	Surgery	Negative histology	0.51	6.9	No evidence of structural/ biochemical disease	<0.20
	Wait-and-see	NA	<0.20	6.6	Biochemical disease	0.83
	RAI	Tg decline	0.90	6.4	Structural and biochemical disease	2.60
	Wait-and-see	NA	1.00	6.3	Biochemical disease	1.40
	Surgery	Positive histology	0.50	8.6	Biochemical disease	0.63
	Wait-and-see	NA	<0.20	3.4	No evidence of structural/ biochemical disease	<0.20
5.00 (III L), 2.00 (IV L), 2.19 (IV L), 2.83 (VI)	Surgery and RAI	Positive histology	0.55	1.6	Biochemical disease	0.46
	Wait-and-see	NA	2.00	6.9	Structural and biochemical disease (RAI refractory disease)	45.00
	Surgery	Positive histology	1.90	6.3	Biochemical disease	3.30
	Wait-and-see	NA	5.00	12.4	Structural and biochemical disease	9.30
	RAI	Tg rising *(No uptake on post-ablation scan)*	19.00	7.1	Structural and biochemical disease (RAI refractory disease)	12.0
3.24 (thyroid bed)	RAI	Tg rising *(Minimal uptake on post-ablation scan)*	2.00	4.9	Structural and biochemical disease (RAI refractory disease)	3.30
4.61 (VII)						
1.83 (VI)	Wait-and-see	NA	0.70	3.8	Deceased (colon carcinoma)^	<0.20
2.52	Wait-and-see	NA	3.0	5.1	Biochemical disease	0.58
	Wait-and-see	NA	18.00	4.9	Structural and biochemical disease	29.0

Case	Sex	Age	Histo-logy	TNM	RAI (MBq)	US results				Serum Tg (ON/OF*)	Time between RAI and FDG PET/CT (years)	FDG uptake	
						+/−	LN/TR	Level	Side				
17	F	24.1	PTC	T1bN1bM0	NS	−				1.00*	1.7#	−	
18	F	26.7	PTC	T3N1bM0	3700					4.00	11.4#	+	LN Central
19	F	28.3	PTC	T3N1bM0	5550	+	TR			3.00	1.4	+	Unilateral LN Bilateral
20	F	27.5	PTC	T1aN1aM0	3700	+		IV	NS	2.80	3.7	−	
21	F	45.0	PTC	T2N1aM0	5550	−				3.10	0.6	+	LN Mediastinal
22	F	38.7	PTC	T1bN0M0	3700	+	LN, TR	I,II	L	.70	3.6	−	Unilateral
23	F	51.1	PTC	T2N1bM0	5550	−				2.00*	2.5	+	LN Unilateral
24	F	50.3	PTC	T2N0M0	3700	−				2.00	6.3	+	LN Central
25	F	58.7	PTC	T3aN0M0	1100	−				2.00	0.9	−	
26	M	30.3	PTC	T3aN1bM0	7400	+	LN	III	L	2.00*	1.3	+	LN Bilateral
27	F	36.0	PTC	T3aN0M0	1100	−				2.00	0.8	+	LN Central

Tumor staging was recorded according the eighth edition TNM classification system for DTC of the Union for International Cancer Control (UICC).
*If Tg on levothyroxine was unknown, TSH-stimulated Tg values are shown. #If time between RAI and FDG was unknown, time between diagnosis and FDG PET/CT was shown. ^Indication for FDG PET/CT was detectable Tg during follow-up. FDG PET/CT showed colon carcinoma, patient deceased of colon carcinoma.
Abbreviations: F, female; FU, follow-up; FTC, follicular thyroid carcinoma; FDG PET/CT, fluorine-18-deoxyglucose positron emissive tomography CT; L, left; LN, lymph node; LBM, lean body mass; M, male; NA, not applicable; NS, not specified; PTC, papillary thyroid carcinoma; R, right; RAI, radioactive iodine; SUV, standard uptake value; Tg, thyroglobulin; TNM, tumor, node, metastasis; TgON, thyroglobulin during levothyroxine treatment; US, ultrasound.

SUV_{max} (LBM) (LN/lung)	Treatment after FDG PET/CT	Result of treatment (after 3 months)	Tg on LT4 after intervention (ng/mL)	Follow-up time (year)	Final outcome at last moment of follow-up	Tg on LT4 at last moment of follow-up
	Wait-and-see	NA	<0.40	3.7	Biochemical disease	0.21
4.83 (VI), 4.49 (IV R), 3.62 (IV R)	Surgery	Positive histology	0.60	14.3	No evidence of structural/ biochemical disease	<0.20
1.89 (larynx)	Surgery	Positive histology	2.00	4.8	Biochemical disease	3.00
1.93 (II L)						
2.07 (II R)						
	Wait-and-see	NA	0.63	5.4	No evidence of structural/ biochemical disease	<0.20
3.11 (VII)	Wait-and-see (lesions too small for surgical intervention)	NA	6.00	1.9	Structural and biochemical disease	8.80
1.58 (IV R)						
	Wait-and-see	NA	0.61	6.0	Biochemical disease	0.71
3.17 (II L)	RAI	Tg decline	0.50	10.1	Biochemical disease	0.26
2.23 (III L)						
7.40 (VI)	Surgery	Positive histology	<0.20	10.0	No evidence of structural/ biochemical disease	<0.20
	Wait-and-see	NA	<0.20	3.8	Biochemical disease	0.26
2.39 (III L)	Surgery	Positive histology	1.30	3.5	Structural and biochemical disease	2.00
3.60 (II R)						
1.52 (VI)	Surgery	Positive histology	<0.20	4.5	No evidence of structural/ biochemical disease	<0.20

Figure 1. Flowchart of FDG PET/CT results of patients with measurable thyroglobulin (n = 27)

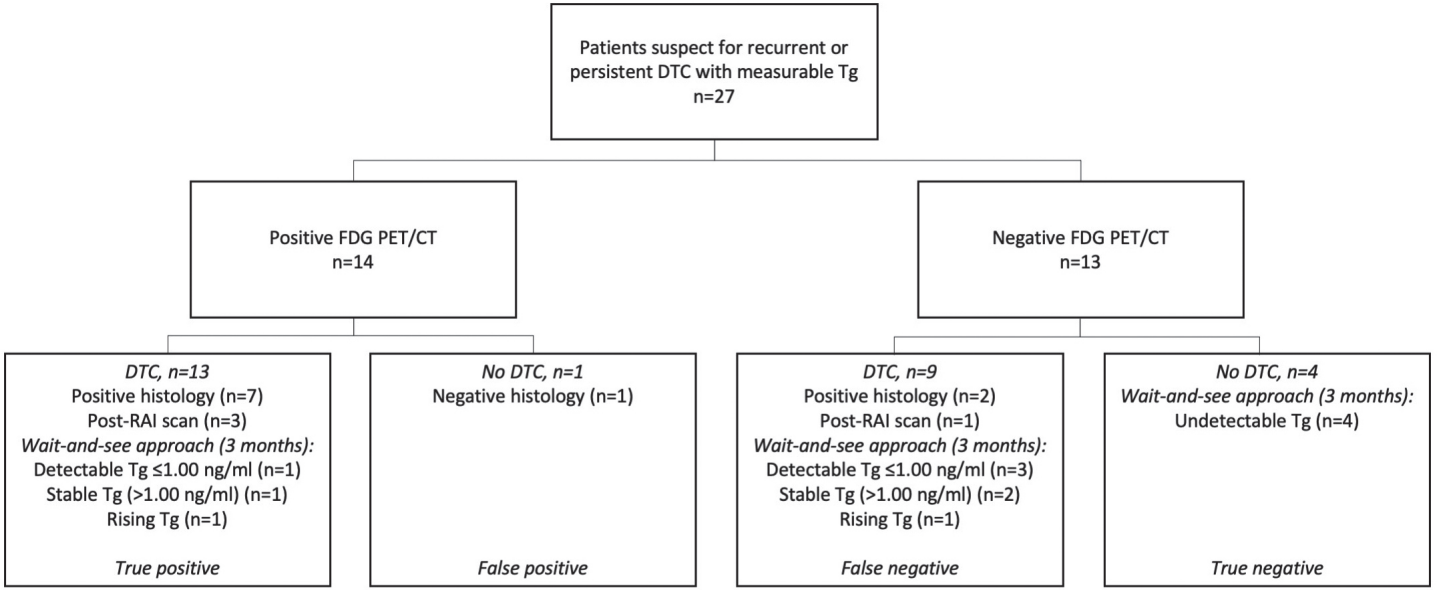


Table 3. Results neck ultrasound and FDG PET/CT during follow-up of DTC (n=27).

Parameters	Values
Time (years) between RAI and FDG PET/CT	1.4 (0.6–6.3)
Tg on LT4 before FDG PET/CT (ng/mL)[a]	2.00 (0.30–9.00)
Elevated TgAb before FDG PET/CT (kU/L)[b]	3 (11.1)
US before FDG PET/CT	22 (81.5)
Negative	14 (63.6)
Positive	8 (36.4)
Unknown	5
FDG PET-positive lesions	14 (51.9)
Neck	12 (85.7)
Lateral	8 (66.7)
Central	6 (50.0)
Mediastinal	2 (16.7)
Lungs	2 (14.0)

Data are presented as median (range) or as *n* (%)
[a]The detection limit of the Tg assay was 0.20 ng/mL.
[b]Cut-off elevated Tg antibodies >50.0 kU/L.
Abbreviations: DTC, differentiated thyroid carcinoma; FDG, [^{18}F]fluorodeoxyglucose; RAI, radioactive iodine; TgAb, thyroglobulin antibodies; Tg on LT4, thyroglobulin during levothyroxine supplementation; US, ultrasound.

Correlation to post-RAI ablation scintigraphy

In five patients, RAI was seen in lymph node metastases. The time between RAI ablation therapy and FDG PET/CT for these patients ranged between 0.6 and 3.9 years. Two out of five patients showed no suspicious findings on US, therefore FDG PET/CT was performed. In both patients, the location of the lesions was similar to those on post-ablation WBS, indicating that RAI was insufficient for the initial treatment of these lesions. In three out of five patients, US showed suspicious findings. However, FNAC was negative for DTC in all of these patients and thus FDG PET/CT was indicated. In retrospect, in only one out of three patients, the location of the lesion was similar to that on post-ablation WBS.

Management and follow-up

Of the 14 patients with a positive FDG PET/CT, eight underwent surgery with curative intent (Table 4). In three of the surgically treated patients, Tg became undetectable, in two patients Tg declined and in two patients Tg stabilized. In one of the surgically treated patients, the FDG PET/CT turned out to be false positive and Tg declined spontaneously within 3 months after FDG PET/CT. Four patients with FDG-positive lesions were treated with RAI, where DTC was confirmed on a post-RAI therapy scan. One of these patients was treated with surgery as well as RAI 3 months after FDG PET/CT; histology confirmed DTC, data on the post-RAI therapy scan could not be retrieved. In three patients, a wait-and-see strategy was chosen resulting in undetectable Tg levels (n=1), low detectable Tg levels (n=1) and rising Tg levels (n=1) 3 months after FDG PET/CT.

Two patients with a negative FDG PET/CT were surgically treated, where DTC was histologically confirmed. In one patient, RAI was given, and DTC was confirmed on the post-RAI therapy scan. Ten patients followed a wait-and-see strategy after negative FDG PET/CT resulting in undetectable Tg levels (n=4), low detectable Tg levels (n=3), stable Tg levels (>1.0 ng/ml) (n=2) and rising Tg levels (n=1) 3 months after FDG PET/CT.

In this case series, FDG PET/CT was discordant with neck US in 45.8% (11/22) of the cases and therefore may have impacted the clinical management.

The median time between FDG PET/CT and the last moment of follow-up was 2.6 years (range: 0.7–7.1 years). At the last moment of follow-up, 4 (28.6%) and 2 (15.4%) of the FDG PET/CT-positive and -negative patients, respectively, showed biochemical (Tg on LT4 <0.20) and structural absence of disease. In 21.4 and 53.8% of the patients with, respectively, a positive and negative FDG PET/CT, biochemical disease (Tg on LT4 ≥0.20 ng/mL) was found without structural evidence of disease on other imaging. Biochemical evidence of disease in combination with a structural disease on imaging was found in 42.9% of the patients with a positive FDG PET/CT and in 30.8% of the patients with a negative FDG PET/CT. In total, one patient with FDG-positive lesions died after the last visit (due to another malignancy).

Table 4. Intervention and disease status at last moment of follow-up (n=27).

	FDG PET/CT patients	
	Positive (n=14)	**Negative (n=13)**
Time between FDG PET/CT and last moment FU in years	2.9 (0.8–7.1)	2.6 (0.7–7.1)
Intervention after FDG PET/CT (<3 months)		
Wait-and-see	3 (21.4)	10 (76.9)
Surgery	7 (50.0)	2 (15.4)
Histology-confirmed DTC	6 (85.7)	2 (100)
RAI	3 (21.4)	1 (7.6)
Surgery + RAI	1 (7.1)	–
Histology-confirmed DTC	1 (100)	–
Disease status at last moment of follow-up all patients		
No structural and biochemical disease	4 (28.6)	2 (15.4)
Biochemical disease*	3 (21.4)	7 (53.8)
Structural and biochemical disease	6 (42.9)	4 (30.8)
Deceased[a]	1 (7.1)	–
Tg on LT4 at last moment of follow-up	0.71 (<0.20–45.00)	0.71 (<0.20–29.00)

Data are presented as median (range) or as n (%)
[a]Cause of death due to other malignancy; *Tg on LT4 ≥0.20 ng/mL.
Abbreviations: DTC, differentiated thyroid carcinoma; FDG, [^{18}F]fluorodeoxyglucose; RAI, radioactive iodine; Tg on LT4, thyroglobulin during levothyroxine supplementation.

Discussion

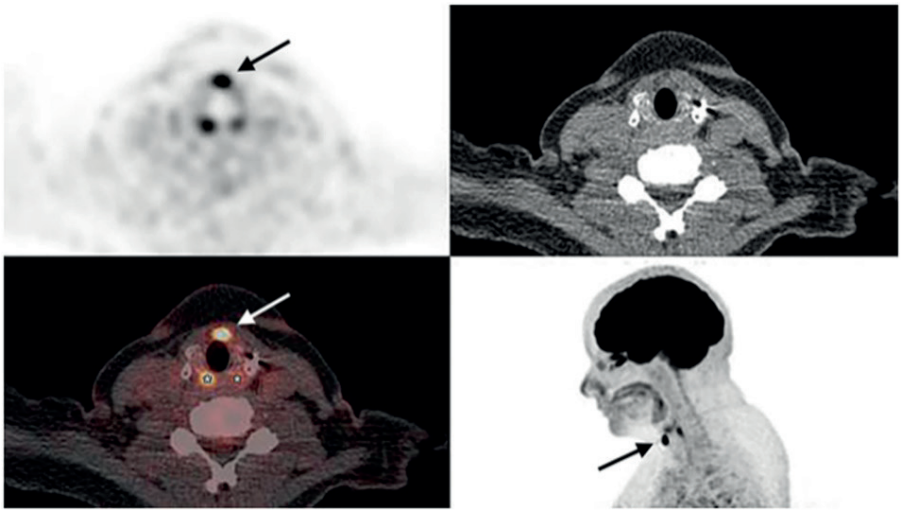
In this case series, we evaluated the usefulness of FDG PET/CT in DTC in patients with low detectable Tg levels (<10.00 ng/mL) suspicious for persistent or recurrent disease.

In this case series, the sensitivity of FDG PET/CT to localize persistent or recurrent DTC was 59%. In 93% of the patients with a positive FDG PET/CT, DTC was confirmed. Only in one patient, a suspicious lesion on FDG PET/CT turned out to be a false positive finding by histology. This high PPV supports the role of FDG PET/CT to detect persistent or recurrent DTC. This is in line with the high PPV of FDG PET/CT for detection of DTC during follow-up described in previous papers (12, 13, 14). However, it should be noticed that FDG PET/CT might show false positive results because of lymph node inflammation (15, 16). Therefore, fine-needle aspiration cytology including Tg measurement in the washing fluid should be considered before surgical intervention.

The low NPV must be acknowledged and illustrates that a negative FDG PET/CT scan may not preclude DTC. In 9/13 patients with a negative FDG PET/CT, DTC was confirmed later during follow-up histologically, on post-RAI therapy scan, or biochemically with persistent detectable Tg levels. This low NPV is comparable with the findings of a recent study by Filippi et al., in which an NPV of 40.1% was reported in patients undergoing FDG PET/CT in the follow-up of DTC (14).

FDG PET/CT confirmed metastases in most patients with a positive neck US. But more importantly, the potential additional value of FDG PET/CT was shown in patients with a negative neck US since FDG PET/CT was able to detect DTC in 50% of patients with a negative neck US. In one-third of these patients, lymph node metastases were found on a targeted neck US afterward, whereby these patients could be treated surgically and be restrained from additional RAI treatment as was the case in patient 26 for example (figure 2). This illustrates well-known drawbacks of neck US; it is highly operator dependent and lymph node metastases with morphological normal appearance s can also contain metastases making them hard to detect on neck US.

Figure 2. Patient with intense focal uptake in a small lymph node (arrow) pre laryngeal/cricoidal



This 50-year-old female (case 24) was diagnosed with PTC (T2N0M0). Six years after RAI ablation therapy, Tg levels were detectable (2.00 ng/mL). However, on neck US no suspicious findings were seen. FDG PET/CT showed a central lymph node (SUVmax 7.40). This lymph node was surgically removed, where after Tg levels became and remained undetectable. In this case, FDG PET/CT was extremely helpful to detect surgically curative disease. These results illustrate the additional value that FDG PET/CT may have for patients with and without suspicious findings on neck US. *Physiological FDG uptake in posterior cricoarytenoid muscles.

In cases where additional surgery is possible, the use of FDG PET/CT before post-therapeutic RAI scanning might prevent unnecessary treatments with high-radiation burden and side effects, such as salivary and lacrimal gland damage or nausea that are often observed in patients receiving high activities of RAI (17, 18).

The ATA guidelines state that FDG PET/CT should be considered in patients with serum Tg levels of >10 ng/mL and in most studies, FDG PET/CT has only been performed if Tg levels were increased to at least >10 ng/mL, because of the fear of loss of sensitivity at lower Tg levels (1, 12, 19, 20). Also, ATA recommends a WBS using RAI for intermediate or high-risk patients for detection of persistent or recurrent disease or persistent disease (1). However, the diagnostic yield of RAI WBS is low, which often results in negative investigations (3, 4, 5, 6, 7).

Our case series suggests that FDG PET/CT might also be of additional value in patients with Tg levels of ≤10.00 ng/mL. The sensitivity of >50% of FDG PET/CT found in this case series with patients with an overall median Tg of 2.00 ng/mL supports the fact that FDG PET/CT may also be useful in patients with low, but detectable Tg levels, to locate possible persistent or recurrent DTC. Our results are in accordance with the results of Choi et al. who investigated the role of FDG PET/CT in patients with low detectable Tg levels; however, in contrast to our cohort, all of those patients had a negative RAI WBS before FDG PET/CT. In this study, the sensitivity of FDG PET/CT in 39 patients with stimulated Tg levels of 2–10 ng/mL was comparable (50.0%) (21).

In another recent study, Filippi et al. evaluated the clinical usefulness of FDG PET/CT in 26 patients with morphological evidence of disease (predominantly detected with US) with stimulated Tg levels ≤10 ng/mL. In this setting, the results of FDG PET/CT investigation led to a change of management in 50% of patients, where patients received surgery, radiotherapy or systemic therapy instead of additional cycles of RAI. The authors concluded that FDG PET/CT may be utilized for the detection of DTC recurrence, not only in patients selected according to ATA criteria but also in different clinical settings, with a meaningful impact on clinical management (14).

In contrast, Agate et al. investigated 49 DTC patients with a biochemical disease (41/49 patients had basal Tg ≤10 ng/mL) and a negative I-131 post-therapy WBS. They concluded that FDG PET/CT was inferior to US for lymph node metastases, since this FDG PET/CT can give both false-positive and -negative results, and inferior to chest CT with iodide contrast for lung metastases due to its lower spatial resolution (22).

Our case series contains limitations. First, our case series were retrospectively evaluated which resulted in potential heterogeneous management approaches. Not in all patients, a neck US was performed before FDG PET/CT and there were probably also many patients in our clinic that had positive US examinations that did not undergo additional FDG PET/CT. Also, none of the patients underwent diagnostic WBS using RAI, therefore we were not able to compare the results of RAI WBS and FDG PET/CT in this setting.

In addition, not in all patients, suspicious lymph nodes were surgically removed; in these cases, DTC could not be histologically confirmed, which is still the gold standard. Next, although the cases series reported here is one of the largest examined with FDG PET/CT as the first-line nuclear imaging modality in case of detectable Tg concentrations <10.00 ng/mL, the patient numbers are still limited.

Lastly, in our case series, FDG PET/CT was performed on LT4 therapy; however, previous studies have suggested that the sensitivity of FDG PET/CT may be slightly improved with TSH stimulation (23, 24).

This case series suggests that FDG PET/CT might be an accurate first-line diagnostic nuclear imaging modality with a high PPV for patients with detectable Tg after treatment during the follow-up of DTC. However, prospective research comparing FDG PET/CT with RAI WBS and neck US is needed to establish the clinical effectiveness of FDG PET/CT in this setting.

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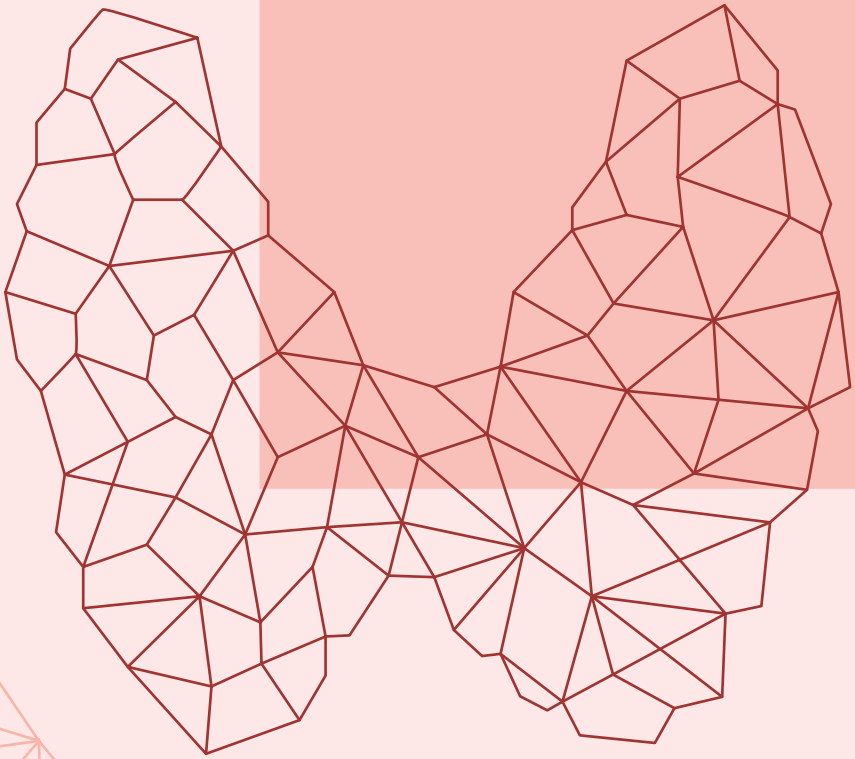

8

Presentation and outcome of subsequent thyroid cancer among childhood cancer survivors compared to sporadic thyroid cancer: a matched national study

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Abstract

Objective

Childhood cancer survivors (CCS) are at increased risk to develop differentiated thyroid cancer predominantly after radiotherapy (subsequent DTC). It is insufficiently known whether subsequent DTC in CCS has a different presentation or outcome than sporadic DTC.

Methods

Patients with subsequent DTC (n=31) were matched to patients with sporadic DTC (n=93) on gender, age and year of diagnosis to compare presentation and DTC outcomes. Clinical data were collected retrospectively.

Results

Among the CCS with subsequent DTC, all but one had received chemotherapy for their childhood cancer, 19 (61.3%) had received radiotherapy including the thyroid region, 3 (9.7%) ^{131}I-MIBG and 8 (25.8%) had received treatment with chemotherapy only. Subsequent DTC was detected by surveillance through neck palpation (46.2%), as a self-identified mass (34.6%), or by chance. Among sporadic DTC patients, self-detection predominated (68.8%). CCS with subsequent DTC tended to have on average smaller tumors (1.9 vs 2.4 cm, respectively, (p=0.051), and more often bilateral (5/25 (60.0%) vs 28/92 (30.4%), p=0.024). There were no significant differences in the occurrence of surgical complications, recurrence rate or disease-related death.

Conclusion

When compared to patients with sporadic DTC, CCS with subsequent DTC seem to present with smaller tumors and more frequent bilateral tumors. Treatment outcome seems to be similar. The finding that one-third of subsequent DTC cases had been treated with chemotherapy only needs further investigation. These results are important for the development of surveillance programs for CCS at risk for DTC and for treatment guidelines of subsequent DTC.

Introduction

Treatment of pediatric malignancies has improved substantially over the past several decades, resulting in a rapidly growing population of long-term childhood cancer survivors (CCS) (1). CCS are at a risk to develop subsequent malignancies, of which approximately 10% involve the thyroid gland (2, 3, 4, 5).

The occurrence of differentiated thyroid carcinoma (DTC) in CCS is predominantly attributable to radiation therapy that directly or incidentally involves the thyroid gland (6). The risk for subsequent DTC increases linearly with increasing estimated dose to the thyroid gland, with a plateau around 10–30 Gy and a decline at higher dose (2, 6). Ionizing radiation exposure at a young age (e.g. <5 years) confers an additional risk factor for DTC after radiotherapy (6). The occurrence of DTC has also been reported among survivors of neuroblastoma treated with ^{131}I-Metaiodobenzylguanidine (MIBG) (7). Moreover, in recent years, a possible role of chemotherapeutic agents in the etiology of DTC is emerging, consistent with evidence for other subsequent malignancies (5, 6, 8).

Children with DTC generally have excellent survival rates, even if the disease presents at a more advanced stage (9). The Dutch Childhood Oncology Group (DCOG-LATER) recommends yearly physical examination (palpation) of the thyroid gland for CCS at increased risk for DTC based on previously given treatments (10). Screening for DTC in CCS can also be done using thyroid ultrasound. In a recent report of the International Guideline Harmonization Group (IGHG) the pros and cons of both surveillance strategies were summarized, and it was recommended to counsel the survivor and, using shared-decision-making, determine the optimal mode of surveillance for each specific individual (11). Treatment for DTC is currently performed in accordance with established treatment algorithms for sporadic thyroid cancer (12, 13).

There are several studies that report generally a similar clinical presentation and outcome of DTC among ionizing radiation-exposed patients in comparison to individuals with sporadic DTC (14-24). These reports, however, concerned predominantly unmatched studies focusing on patients who received radiotherapy for benign lesions or patients who were exposed to radioiodine isotopes released by nuclear reactors. To strengthen the evidence for development of appropriate surveillance and treatment strategies for these individuals, more information is needed in matched cohorts to compare the mode of detection and presentation of disease as well as the outcome.

For these reasons, the aim of the present study was to evaluate the mode of detection, presentation, treatment and outcome of subsequent DTC among CCS in The Netherlands in comparison with a matched sample of patients with sporadic DTC. If such differences were to be found, it could be used to inform current care practices (screening and management) in CCS. To address our objectives, we conducted retrospective chart review studies based on several nationwide patient cohorts.

Subjects and methods

Study populations

We included two source populations to identify CCS with subsequent DTC: (1.) The DCOG-LATER cohort of more than 6000 5-year CCS diagnosed with a primary tumor between 1963 and 2001 in The Netherlands (5). Clinical follow-up and record linkage studies (including cancer and pathology registries), with follow-up coverage until January 1, 2013, revealed 28 patients with subsequent DTC (5). To complete the inclusion of subsequent DTC patients (period 2013–2015), additional record linkage with the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA) revealed two additional cases with subsequent DTC (25); (2.) To obtain subsequent DTC cases among CCS initially diagnosed after 2001, we queried The Netherlands Cancer Registry (IKNL) and identified one additional eligible case. Of these 31 DTC patients, one patient had DTC as third malignancy. The first and subsequent malignancies among CCS were histologically confirmed.

Every subsequent DTC patient was matched to three sporadic DTC patients (total comparison group n=93), based on gender, age at DTC diagnosis (± 2 years), and year of DTC diagnosis (± 5 years). These strict criteria were met for 24/31 subsequent DTC patients. In four cases it was not possible to match for calendar years, and in three cases we were not able to match for gender. These subsequent DTC patients were matched with the best possible matching sporadic DTC patient. Eligible sporadic DTC patients were sampled from two patient series using the following inclusion criteria: (1.) diagnosed with a primary DTC, that is, papillary thyroid carcinoma, papillary microcarcinoma (<1 cm), or follicular carcinoma; (2.) no history of another malignancy; (3.) no exposure to radiotherapy, chemotherapy or hematopoietic stem cell transplantation for non-thyroid neoplasia or benign lesions. For CCS diagnosed with subsequent DTC during childhood (≤18 years) (n=9), matching subjects (n=27) with sporadic DTC were identified from an ongoing National Pediatric DTC study (26). For CCS who developed subsequent DTC after the age of 18 (n=22), matching was done with subjects of the adult study cohort with sporadic DTC from the University Medical Center of Groningen (n=66) (27). No further approval for retrospective data collection and analysis was needed, in accordance with Dutch law.

Data collection and study definitions

Data were collected retrospectively and extracted from existing databases (5, 26, 27) or collected from individual patients' medical records. Pediatric cancer treatment histories for subsequent DTC patients were taken from the DCOG-LATER registry. Radiotherapy exposing the thyroid gland included the following fields: neck (cervical + mantle), head/brain, mediastinum, or total body irradiation (TBI). Cumulative thyroid-directed dose was based on the prescribed radiotherapy dose to the smallest field of the neck; full-field and boost dose were summed.

For all patients, cytology and histopathology findings were scored to determine the characteristics of DTC. Fine needle aspiration cytology (FNAC) results recorded within 6

months of a histological DTC diagnosis were used to define a confirmed DTC. Non-diagnostic findings were, in general, cytological smear samples with too little cells to allow a diagnosis. Diagnostic findings were subdivided into: malignant findings, indeterminate findings, and benign findings. Histopathological DTC data were obtained from the original pathology reports and reviewed by two reviewers (CL/HvS).

Tumor staging was recorded according to the 7th edition TNM (Tumor, Node, Metastasis) classification system for DTC of the Union for International Cancer Control (UICC). TNM stage was classified after the first I-131 treatment. If previous editions were used at time of diagnosis, tumor stage was reclassified into the 7th edition (28).

All patients had been treated for DTC in accordance with local protocols. Initial neck dissection was defined as those performed at most 1 year after initial thyroid surgery. To calculate the cumulative administered I-131 activity, only ablative and therapeutic I-131 administrations were taken into account.

Documented transient hypoparathyroidism was defined as postoperative hypocalcemia (serum calcium value below the reference range) with recovery and no use of medication (Calcitriol, Alfacalcidol or calcium) at 6 months after surgery. Documented permanent hypoparathyroidism was defined as postoperative hypocalcemia with the use of medication (Calcitriol, Alfacalcidol, or calcium) at the last moment of follow-up. Documented transient and documented permanent recurrent laryngeal nerve (RLN) injury after surgery were defined, respectively, as injury mentioned in ear, nose and throat report, or if no report was available, in other medical records, with or without recovery within 6 months after surgery.

Recurrence of DTC was defined as laboratory or radiological evidence of disease activity after remission. Remission of DTC was defined as clinical, radiological and scintigraphic absence of disease activity with an undetectable serum thyroglobulin (Tg) concentration (<1.0 ng/mL) at least 1 year after the last I-131 therapy. Persistent disease was defined as persistent disease or recurrence at last moment of follow-up. If no follow-up data were known, the disease status at last moment of follow-up was noted as unknown. Outcome was only assessed if the last treatment for DTC had been given >1 year ago.

Statistical analysis

Baseline factors, cancer-related characteristics, treatment modalities and outcome in patients with subsequent DTC and sporadic DTC were compared using Student's *t*-test for continuous measurements. Mann–Whitney *U*-tests were performed if the continuous data were non-normally distributed. For categorical data chi-square tests or Fisher's exact tests (if the assumptions for chi-square were violated) were used. Tests were only performed if reasonably complete information on the clinical characteristics of interest was obtained, defined as >50% of each group. All p-values were based on two-sided testing and p-values of <0.05 were considered as statistically significant. The SPSS (25.0) statistical package was used for analysis.

Results

CCS with subsequent DTC

Patient characteristics

Thirty-one eligible CCS with subsequent DTC were included. Median age at diagnosis of the primary childhood cancer was 6.1 (range: 0.3–16.4) years, of which leukemias (35.5%) and lymphomas (19.4%) were most frequent. Almost all patients (93.5%) had received chemotherapy, and alkylating agents had been administered in 75.9% of the CCS and anthracyclines in 55.2%. Radiotherapy to a field l including the thyroid gland was given to 18 patients (58.1%), with a mean cumulative dose of 32.0 (range 7.0–55.8) Gy. Three patients (9.7%) had received ^{131}I-MIBG treatment, with a mean total activity of 12.93 GBq for neuroblastoma, including thyroid prophylaxis (8, 29) Median latency time between primary childhood cancer and subsequent DTC was 17.2 years (range 5.7–33.8) years.

Comparison with sporadic DTC patients

Diagnosis of DTC

Nearly half of the subsequent DTCs (12/26) were detected by neck palpation at the DCOG-LATER outpatient clinic and 9/26 detected a mass in the neck themselves. Five out of 26 subsequent DTC were found as chance finding during diagnostic work-up for hypothyroidism, hyperparathyroidism or PET scanning for non-Hodgkin lymphoma follow-up. When compared to sporadic DTC patients, 33/48 detected a thyroid mass themselves which was significantly different.

At DTC diagnosis, palpability of the nodule at physical examination, median tumor size and presence of palpable pathological cervical lymph nodes were all comparable between subsequent and sporadic DTC (table 1).

Table 1. Comparison of presentation between subsequent DTC patients and sporadic DTC patients in The Netherlands (1968–2015)

Characteristics	Subsequent DTC (n=31)	Sporadic DTC[a] (n=93)	p-value[b]
Age at diagnosis DTC, median (range), years			
All patients	25.6 (6.1–38.0)	26.3 (5.8–38.7)	0.875
Children (<18 years)	13.3 (6.1–17.7)	13.5 (5.8–17.7)	0.797
Adults (≥18 years)	29.8 (18.03–38.0)	29.3(18.2–38.7)	0.982
% DTC child (<18 years)	7 (23%)	20 (22%)	
Gender: number of females (%)	21 (67.7%)	67 (72.0%)	
Calendar year of diagnosis (range)	1986–2015	1973–2015	
1970–1989	1 (3.2%)	12 (13.0%)	
1990–1999	5 (16.1%)	14 (15.1%)	

Characteristics	Subsequent DTC (n=31)	Sporadic DTC[a] (n=93)	p-value[b]
2000–2009	11 (35.5%)	44 (47.3%)	0.236
2010–2015	14 (45.2%)	23 (24.7%)	
Deceased at end of follow-up[c]	4 (13%)	0 (0%)	0.003*
Reason for evaluation			
Palpable mass found by screening (neck palpation)	12 (46.2%)	4 (8.3%)	0.001*
Palpable mass detected by patient	9 (34.6%)	33 (68.8%)	
Symptoms/signs of thyroid dysfunction	2 (7.7%)	2 (4.2%)	
Symptoms/signs due to thyroid nodules	0 (0%)	4 (8.3%)	
Thyroid nodule found on ultrasound	0 (0%)	1 (2.1%)	
Other	3 (11.5%)	4 (8.3%)	
Unknown	5	45	
Palpable nodule			NA
Yes	21 (87.5%)	38 (92.7%)	
No	3 (12.5%)	3 (7.3%)	
Unknown	7	52	
Size (cm) of the nodule, median (range)	3.5 (0.5–5.0)	3.0 (1.0–6.0)	NA
n available data	12/31	24/93	
Palpable cervical lymph-nodes			NA
Yes	6 (33.3%)	12 (37.5%)	
No	12 (66.7%)	20 (62.5%)	
Unknown	13	61	
Ultrasound finding at diagnosis			NA
Maximum size (cm) nodule, mean (±SD)	2.3 (1.2)	2.6 (0.9)	
n available data	18/31	14/93	
Lymphadenopathy			NA
Yes	5 (38.5%)	5 (50.0%)	
No	8 (61.5%)	5 (50.0%)	
Unknown	18	83	
Thyroid dysfunction at time of diagnosis DTC			NA
No	12 (70.6 %)	15 (88.2%)	
Hypothyroidism	1 (5.9%)	2 (11.8%)	
Subclinical hypothyroidism	3 (17.6%)	0 (0%)	
Central hypothyroidism	1 (5.9%)	0 (0%)	
Unknown	14	76	

Percentages of known variables are shown, p-value* significant <0.05; [a]All control patients were matched by age at diagnosis, gender, and calendar year of diagnosis; [b]Missing or unknown values are excluded from statistical testing. For characteristics with >50% missing values per group, p-values were not calculated (denoted as NA, Not Applicable); [c]Causes of death: due to other malignancies (n=3) or non-cancer related death (n=1). Abbreviation: DTC, differentiated thyroid carcinoma.

Ultrasound, cytology and histology findings

Pre-operative ultrasound reports were collected and could be retrieved in 58.1% of CCS and in 15.1% of the matched patients. Maximum nodule size on ultrasound did not differ between subsequent and sporadic DTC patients (mean 2.3 (±SD 1.2) and 2.6 (±SD 0.9) cm, respectively).

Overall distribution of FNAC results (within 6 months of a histological DTC diagnosis) were comparable (table 2). FNAC results of four patients showed benign features; however, after hemithyroidectomy, histology showed a PTC (n=3) and FTC (n=1) (30).

Table 2. Comparison of cytology and histology between subsequent DTC patients and sporadic DTC patients in The Netherlands (1968–2015)

Cytology	**Subsequent (n=31)**	**Sporadic (n=93)**	**p-value[a]**
Mean number of FNACs[b]	1.55	1.44	0.585
n available data	22/31	39/93	
FNAC findings[c]			NA
Non diagnostic	2 (13.3%)	4 (13.8%)	
Malignant	6 (40.0%)	15 (51.7%)	
Indeterminate	5 (33.3%)	8 (27.6%)	
Benign	2 (13.3%)	2 (6.9%)	
Unknown	16	64	
Histology DTC			0.095
Papillary thyroid carcinoma	16 (61.5%)	72 (79.1%)	
Papillary microcarcinoma (<1 cm)	6 (23.1%)	7 (7.5%)	
Follicular thyroid carcinoma	4 (15.4%)	14 (15.4%)	
Unknown	5	0	
Papillary (micro)carcinoma			0.233
Classic variant	10 (45.5%)	28 (50.0%)	
Follicular	10 (45.5%)	20 (35.7%)	
Diffuse sclerosing	1 (4.5%)	2 (3.6%)	
Other	1 (4.5%)	6 (10.7%)	
Unknown	0	23	
Follicular carcinoma			1.000
Minimal invasive	3 (100%)	7 (87.5%)	
Widely invasive	0 (0%)	1 (12.5%)	
Unknown	1	6	
DTC Laterality			0.024*
Unilateral	10 (40.0%)	60 (65.2%)	
Bilateral	15 (60.0%)	28 (30.4%)	

Cytology	Subsequent (n=31)	Sporadic (n=93)	p-value[a]
Isthmus	0 (0%)	4 (4.3%)	
Unknown	6	1	
Multifocality			0.109
Yes	15 (65.2%)	37 (46.3%)	
No	8 (34.8%)	43 (53.8%)	
Unknown	8	13	
Tumor size (cm; largest tumor nodule) median (range)	1.90 (0.10–5.00)	2.40 (0.60–6.50)	0.051
n available data	23/31	71/93	
Tumor size categories[d]			0.239
0.1–0.9 cm	6 (26.1%)	5 (7.0)	
1.0–1.9 cm	6 (26.1%)	17 (23.9%)	
2.0–2.9 cm	5 (21.7%)	23 (32.4%)	
3.0–3.9 cm	4 (17.4%)	11 (15.5%)	
4.0–4.9 cm	1 (4.3%)	8 (11.3%)	
>5.0 cm	1 (4.3%)	7 (9.9%)	
Histology – Spread of DTC			
Encapsulated			0.177
Yes	14 (73.7%)	59 (86.8%)	
No	5 (26.3%)	9 (13.2%)	
Unknown	12	25	
Tumor capsular invasion			0.186
Yes	10 (71.4%)	29 (51.8%)	
No	4 (28.6%)	27 (48.2%)	
Unknown	0	3	
Extracapsular growth			0.743
Yes	7 (58.3%)	19 (34.5%)	
No	5 (41.7%)	36 (65.5%)	
Unknown	2	4	
Extrathyroid extension (tissue invasion)			0.386
Yes	26 (33.3%)	18 (23.7%)	
No	12 (66.7%)	58 (76.3%)	
Unknown	13	17	
Vessel invasion			0.467
Yes	5 (26.3%)	26 (35.1%)	
No	14 (73.7%)	48 (64.9%)	
Unknown	12	19	

Cytology	Subsequent (n=31)	Sporadic (n=93)	p-value[a]
Lymph-node metastases			0.277
Yes	13 (68.4%)	46 (54.8%)	
No	6 (31.6%)	38 (45.2%)	
Unknown	12	9	
TNM classification 7th edition[e]			
T			0.701
T1	10 (40.0%)	24 (28.2%)	
T2	8 (32.0%)	33 (38.8%)	
T3	6 (24.0%)	22 (25.9%)	
T4	1 (4.0%)	6 (7.1%)	
Tx	6	8	
N			0.480
N0	8 (38.1%)	36 (46.8%)	
N1a-N1	13 (61.9%)	41 (53.2%)	
Nx	10	16	
M			1.000
M0	24 (92.3%)	78 (94.9%)	
M1[f]	2 (7.7%)	6 (7.1%)	
Mx	5	9	

Percentages of known variables are shown, p-value* significant <0.05; [a]Missing or unknown values were excluded from statistical testing; [b]Mean number of all performed FNACs before diagnosis DTC; [c]Last FNAC before histological diagnosis <6 months; [d]Tumor categories are based on continuous data. In two sporadic DTC patients, the pathology report showed microcarcinoma; however, no exact tumor size was mentioned; [e]The 7th edition of TNM classification was used for all patients, if previous editions were used in the patient record, all were recoded into the 7th edition of TNM classification; [f]M1 = only lung metastases were found.
Abbreviation: FNAC, fine needle aspiration cytology.

Based on histologic results, subsequent DTCs were two times more likely to be bilateral at diagnosis (15/25, 60%) than sporadic DTCs (28/92, 30%) (p=0.024) and tumors tended to be more often smaller in subsequent DTC patients (size at diagnosis 1.90 (0.10–5.00) cm vs 2.40 (0.60–6.50) cm (p=0.051)). Of all, DTC tumors sized <1 cm were more often seen in subsequent DTC patients (6/23, 26%) compared to sporadic DTC patients (5/71, 7%) (p=0.023). Conversely, in only 8.6% (2/23) of the subsequent DTC patients the tumor size was ≥4.0 cm vs 21.1% (15/71) of the sporadic DTC patients (p=0.226) (table 2). Approximately 15% of DTCs were follicular carcinomas, in both groups.

For evaluation of radiation effects specifically on the presentation of DTC, a subgroup analysis was done for the CCS with a history of neck radiation, TBI or MIBG treatment (n=22). A significant difference was found in tumor size (median 1.25 cm vs 2.40 cm, respectively

(p= 0.010)). No difference was found in tumor size between CCS without radiation exposure and their matched controls (median tumor size 2.80 cm vs 2.40 cm respectively, p=0.847).

In 15/23 (65.2%) and 37/80 (46.3%) of subsequent and sporadic DTC patients, respectively, the tumor had a multifocal character (p=0.109). No significant differences were found in spread of DTC with regards to encapsulation of the tumor (p=0.177), tumor capsular invasion (p=0.186), extracapsular growth (p=0.743), extra thyroid extension (p=0.386), vessel invasion (p=0.467) or lymph-node metastases (p=0.277). Subsequent DTC patients showed more frequent T1a staging compared to sporadic DTC patients (p=0.046). Overall, TNM stage did not differ between subsequent DTC patients and sporadic DTC patients (p=0.701).

Thirteen out of 21 (61.9%) of the subsequent DTC patients had lymph-node metastasis vs 41/77 (53.2%) in the sporadic patients. Of the six subsequent DTC patients with papillary microcarcinoma (<1 cm), two had lymph-node metastases. No association was found between tumor size and occurrence of lymph-node metastases. In total, seven patients had distant (lung) metastases, of which six were ≤18 years at diagnosis. The tumor size of these patients ranged between 1.0 and 6.2 cm. In both groups, the prevalence of lung metastases was similar, 7.7% vs 7.1% in subsequent vs sporadic DTC patients.

DTC treatment

None of the surgical treatment characteristics differed between subsequent vs sporadic patients. All patients (n=124) underwent one or more surgical procedures as part of their DTC treatment. Total thyroidectomy, unilateral hemithyroidectomy, and bilateral hemithyroidectomy were performed in, respectively, 66.7%, 7.4%, and 25.9% of the subsequent DTC patients and in 55.9%, 1.1% and 43.0% of the sporadic DTC patients (p=0.060) (table 3). Fifty-two percent and 52.7% of the subsequent and sporadic DTC patients, respectively, underwent lymph-node dissection(s) of central and/or lateral levels, and I-131 treatment was administered in 85.2% and 98.9% of, respectively, subsequent DTC vs sporadic DTC patients. A significant difference was found between the number of DTC patients that were treated with I-131 (23/27, 85.2% vs 92/93, 98.9%, p=0.009). Three out of four subsequent DTC patients who did not receive I-131 treatment had been diagnosed with a papillary microcarcinoma with no lymph node metastases, one patient had undergone total thyroidectomy at time of data collection and may have been given RAI at later time during follow-up.

Table 3. Comparison of treatment, outcome, and complication rates between subsequent DTC patients and sporadic DTC patients in The Netherlands (1968–2015)

	Subsequent (n=31)	Sporadic (n=93)	p-value[a]
Initial treatment of thyroid cancer			
Surgical treatment			0.060
Total thyroidectomy	18 (66.7%)	52 (55.9%)	
Unilateral hemithyroidectomy	2 (7.4%)	1 (1.1%)	
Bilateral hemithyroidectomy[b]	7 (25.9%)	40 (43.0%)	
Unknown	4	0	
Lymph-node dissection (LND)			0.732
None	12 (48.0%)	43 (47.3%)	
Central LND	2 (8.0%)	11 (12.1%)	
LND incl. lateral levels	9 (36.0%)	34 (37.4%)	
LND, location unknown	2 (8.0%)	3 (3.3%)	
Unknown	6	2	
I-131 treatment[c]			
Number of patients treated with I-131 treatment	23/27 (85.2%)	92/93 (98.9%)	0.009
Number of I-131 treatments, median (range)	1 (1–3)	2 (1–6)	0.268
Cumulative administered dose of I-131 treatment, median (range) GBq	5.399 (1.850–17.910)	7.400 (1.480–35.150)	0.242
Recurrence			
Recurrence			0.288
Yes	4 (20.0%)	10 (11.4%)	
No	16 (80.0%)	78 (88.6%)	
Unknown	11	5	
Treatment recurrence			
Lymph-node dissection	2 (40.0%)	3 (33.3%)	
I-131 treatments	3 (60.0%)	6 (66.7%)	
Cumulative administered dose of I-131 treatment, median (range) GBq	5.550 (5.550–6.008)	5.550 (5.550–5.550)	
Most recent Tg determination elevated			0.166
Yes	3 (14.3%)	5 (5.4%)	
No	18 (85.7%)	87 (94.6%)	
Unknown	10	1	
Disease status at last moment of follow-up			
Time (years) between Dx and last moment of follow-up, median (range)	5.2 (0.1–22.5)	7.5 (0.7–41.5)	0.240
n available data	23/31	92/93	
Disease status at last moment of follow-up[d]			0.024*
Remission	18 (78.3%)	78 (92.9%)	

	Subsequent (n=31)	Sporadic (n=93)	p-value[a]
Active disease: persistent disease	1 (4.3%)	4 (4.8%)	
Active disease: recurrence	2 (8.7%)	2 (2.4%)	
Last treatment <1 year ago	2 (8.7%)	0 (0%)	
Unknown	8	9	
T4 supplementation			0.216
Yes	24 (96.0%)	91 (100%)	
No	1 (4.0%)	0 (0%)	
Unknown	6	2	
Serum Tg antibodies			0.381
Yes	3 (21.4%)	10 (11.4%)	
No	11 (78.6%)	78 (88.6%)	
Unknown	17	5	
Surgical Complications			
Documented hypoparathyroidism			0.456
Transient hypoparathyroidism	4 (12.9%)	21 (22.6%)	
Permanent hypoparathyroidism	11 (35.5%)	33 (35.5%)	
Documented recurrent laryngeal nerve (RLN) injury			0.327
Transient RLN injury	1 (3.2%)	7 (7.5%)	
Permanent RLN injury	3 (9.7%)	17 (18.3%)	

Percentages of known variables are shown, p-value* significant <0.05; [a]Missing or unknown values excluded from statistical testing; [b]Consecutive hemithyroidectomy; [c]Five patients did not receive I-131 treatment (subsequent: $n=4$, sporadic: $n=1$); [d]Loss of follow-up, disease status at last moment of follow-up unknown in 17 patients in total (subsequent $n=8$, sporadic $n=9$).

Disease recurrence and disease status at last moment of follow-up

Median follow-up time after DTC diagnosis was 5.2 years (0.1–22.5) for subsequent DTC vs 7.5 years (0.7–41.5) for sporadic DTC patients (table 3). Recurrence rate between the two groups was comparable; 4/20 (20.0%) of the subsequent DTC and in 10/88 (11.4%) of the sporadic DTC patients (p=0.288) (have) had recurrent disease.

At last moment of follow-up, the disease status was found to be different (p=0.024) in the four categories, with remission of disease in 18/23 (78.3%) and 78/84 (92.9%) of subsequent and sporadic DTC patients, respectively. Persistent disease was similar (4.3% and 4.8%, respectively). In both groups, two patients experienced recurrence of disease at last moment of follow-up. Outcome could not be assessed for two subsequent DTC patients, because diagnosis of DTC was <1 year ago. Results did not change when excluding pediatric DTC patients and microcarcinomas, except for disease status at last moment of follow-up (supplementary table A).

Three out of 14 (21.4%) and 10/88 (11.4%) of subsequent and sporadic DTC patients, respectively, had a history of positive serum Tg antibodies (p=0.381). Vital status at end of follow-up differed between the groups: four subsequent DTC patients were deceased at end of follow-up due to other malignancies (n=3) or non-cancer related death (n=1), whereas sporadic DTC patients were all alive at last moment of follow-up. The distributions of age, gender, and diagnosis period were fairly comparable as expected from the per-protocol matching.

Surgical complications

Documented transient hypoparathyroidism and documented permanent hypoparathyroidism were observed in, respectively, 4/31 (12.9%) and 11/31 (35.5%) of the subsequent DTC patients and in 21/93 (22.6%) and 33/93 (35.5%) of the sporadic DTC patients (p=0.456). Documented postoperative transient and permanent RLN injury was found in, respectively, 1/31 (3.2%) and 3/31 (9.7%) of the subsequent DTC patients and in 7/93 (7.5%) and 17/93 (18.3%) of the sporadic DTC patients (p=0.327).

Discussion

Radiation therapy including the neck region for childhood cancer may result in DTC. It has been suggested that subsequent DTC in CCS may also be related to chemotherapy (2-4, 6). In order to counsel CCS on the most appropriate way to screen for DTC, more knowledge is required upon its behavior in comparison to sporadic thyroid cancer. The prognosis of sporadic thyroid cancer is known to be excellent, even when found in advanced stage. However, the behavior of radiation-induced DTC has been studied insufficiently, for which this matched cohort analysis was performed.

The unique data in this study, integrated from three national initiatives spanning four decades of inclusion, enabled us to address the mode of detection and presentation of subsequent DTC. Our results demonstrate that CCS with subsequent DTC more likely tend to present with smaller tumors and bilateral disease than patients with sporadic DTC. Other characteristics were statistically similar. Of note, one-third of the patients with subsequent DTC did not have a history of radiotherapy directed to the head/neck/upper chest.

A noteworthy finding of this study is that the number of small tumors was significantly increased in the subsequent DTC group, especially in CCS with a history of neck radiation, TBI or MIBG, compared to sporadic patients. These results are in agreement with several previous studies (14, 15, 18, 20, 31) and might be explained by the fact that CCS are carefully followed at follow-up clinics, leading to the detection of DTC in an earlier T stage. Tumor size has shown to be an important factor influencing DTC prognosis and we confirmed from previous findings that tumor size is not associated with the occurrence of lymph-node metastases (32, 33).

The high prevalence of microcarcinoma among subsequent DTC patients did not result in improved outcome results, such as decreased recurrence rates or surgical complications when compared to sporadic DTC. However, it was remarkable that three subsequent DTC patients with microcarcinoma had not been treated with I-131, while all patients with sporadic patients and microcarcinoma (n=7) had been treated with I-131. This may reflect more hesitance in providers to further expose cancer survivors to I-131.

Bilateral tumors were significantly more often diagnosed in subsequent DTC patients. This is consistent with the hypothesis that radiation exposure results in diffuse toxicity and is the major contributing factor in DTC etiology.

Our data confirms previous data that multifocal tumors are more frequent in subsequent DTC patients compared to sporadic DTC patients (19, 23). In the study by Rubino *et al.*, multifocality was more frequent in those who received higher radiation dose at younger age suggesting that multifocality is a direct consequence of radiation exposure (19).

Bilaterality requires total thyroidectomy, and it was observed that, in this cohort, indeed only 1% of patients with subsequent DTC were treated with hemithyroidecomy, in comparison to 7% of sporadic DTC.

Next to bilaterality, multifocality and tumor size, no other significant differences were found in this study between subsequent and sporadic DTC patients regarding histological findings. In this cohort, we found a striking high incidence of documented permanent hypoparathyroidism in all DTC patients, when compared to previous studies in children and adults (34-37). These high percentages should be further explored and may possibly be explained by the strict definition of hypoparathyroidism used in our study. To reduce complications of treatment and considering the rareness of the disease, care for DTC should be centralized and only be done in an experienced DTC center.

Recurrence rates were in line with previous literature, and neither differences in recurrence rates between groups were found, nor was there mortality due to DTC in both groups (38, 39). At last moment of follow-up, patients with subsequent DTC had significantly more frequent persistent disease. A possible explanation may be the fact that, in the subsequent DTC patients, the last treatment was <1 year ago in two patients, in comparison to the sporadic DTC patients of whom last treatment was >1 year ago in all patients. This must be further studied in future cohorts.

One-third of the subsequent DTC patients in this study had not been exposed to radiotherapy. This implies that other causes for subsequent tumor formation must be considered which justifies future research. All had been treated with chemotherapy. Effects of alkylating agents and anthracyclines on the thyroid gland were demonstrated in a large pooling effort by Veiga *et al*. (2, 3). Also, genetic predisposing factors may increase risk of DTC among CCS

(40). The large number of CT scans (>50 for some individuals) is not a negligible factor and should be explored in subsequent work (41, 42). The strength of this study is the fact that data were retrieved from well-characterized study populations including valid methods with retrospective and prospective case-finding for DTC. We estimate that our study captures >90% of all patients with subsequent DTC in The Netherlands in the study period. By matching the CCS to patients with sporadic DTC, comparisons could be made unbiased by factors affecting tumor and outcome characteristics. Lastly, for a fair proportion of the DTC cases, in-depth data were available, making these comparisons possible.

A weakness of this study is the number of missing values owing to the character of the retrospective chart review. The missing data in most cases could be explained by the fact that these patients presented in non-academic hospitals and were then referred to academic hospitals. We were only able to retrieve data from patient charts in the academic hospitals and therefore data are missing. To give insight in the magnitude of missing data, percentages are based on the number of CCSs with available data in the denominator. The fact that subjects included in this study had not been treated with the same treatment protocol in a systematic way, because of pluralism in hospital-dependent treatment protocols, may also be considered a limitation.

Also, even though for patients with subsequent DTC this was a national cohort, the numbers were quite low, making multivariate or survival analysis not possible. Outcomes are therefore not controlled for tumor characteristics and treatment methods. In the future, international collaboration should be aimed to create larger cohorts enabling more solid analyses.

Despite the fact that we had nationwide coverage, our cohort is a modest size sample which precludes strong conclusions. There are several aspects that should be taken into account. Although no difference was found in overall TNM stage, more tumors <1 cm were found (T1a staging) in subsequent DTC patients This may possibly be a consequence of surveillance (10). The results of this study cannot be used, however, to inform screening strategies, such as neck palpation or thyroid ultrasound. For the future, we recommend that all patients with DTC are prospectively recorded and treated in centers of expertise (12). In the medical files of these patients, data on diagnostics, treatment, adverse effects and outcome should be recorded according to standardized definitions to allow for future evaluation of care (12). Development for standardization of care for children with DTC in The Netherlands and in larger European consortia are underway. For patients >18 years of age, standards of care for adults may be used.

In conclusion, patients with subsequent DTC seem to present with smaller tumors and more frequent bilateral tumor localizations than patients with sporadic DTC. In terms of morbidity and mortality, subsequent DTC seems to be similar to that of sporadic DTC. The results of this study do not provide evidence or arguments that different or more aggressive treatment regimens should be used.

The multifocality and bilaterality of DTC after treatment for childhood cancer must be taken into account when deciding on the surgical procedure.

Differences in outcome and prognosis of DTC in CCS without following an active surveillance program could not be excluded.

These results are an important cornerstone for the further development of existing surveillance programs and treatment guidelines for CCS at risk for or presenting with DTC (11). Follow-up studies are needed to explore the potential cause of subsequent DTC in patients without radiation treatment for their primary cancer.

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Supplementary material

Supplemental table A. Comparison of characteristics between subsequent DTC patients and sporadic DTC patients in the Netherlands (1968-2015), excluding pediatric DTC patients and microcarcinoma

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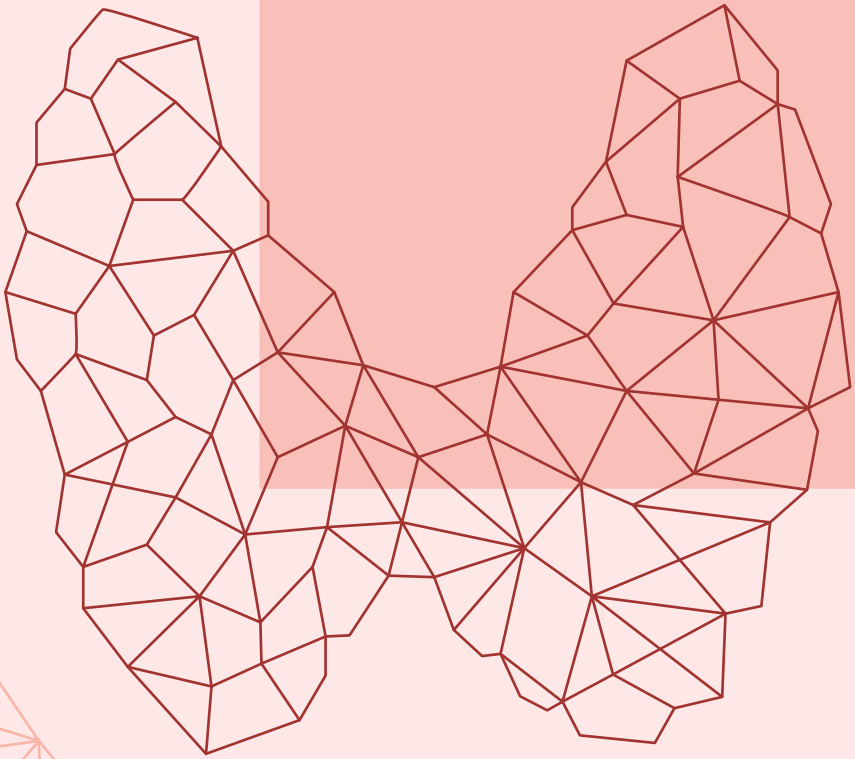

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Thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer: a systematic review

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Submitted

Highlights

- Childhood cancer patients treated with systemic antineoplastic drugs are at risk for the development of thyroid dysfunction.
- Primary hypothyroidism is seen in up to 18% of children during treatment with high dose interferon-α (HDI-α) or tyrosine kinase inhibitors (TKIs).
- The Euthyroid Sick Syndrome (ESS) is common in children treated with systematic multi-agent chemotherapy (occurring in 42-100%).
- Prospective high-quality studies including large study samples are needed to longitudinally assess the prevalence, risk factors and possible consequences of thyroid dysfunction during childhood cancer treatment.

Abstract

Thyroid dysfunction is known to occur following radiotherapy or chemotherapy for childhood cancer. Thyroid dysfunction during treatment for childhood cancer has, however, not been studied extensively, although thyroid hormones are of utmost importance during childhood. This information is needed to develop adequate screening protocols and may be of special importance with upcoming drugs, such as checkpoint inhibitors, which are highly associated with thyroid dysfunction in adults.

In this systematic review we have evaluated the occurrence and risk factors for thyroid dysfunction in children during treatment with systemic antineoplastic drugs, up to three months after the end of therapy. Two review authors independently performed the study selection, data extraction and risk of bias assessment of included studies. After an extensive search (January 2021), in total six heterogeneous articles were included, reporting on 91 childhood cancer patients with a thyroid function test during treatment with systemic antineoplastic therapy for childhood cancer. All studies had risk of bias issues.

Primary hypothyroidism was found in 18% of children treated with high dose interferon-α (HDI-α) and in 0-10% after tyrosine kinase inhibitors (TKIs). Transient euthyroid sick syndrome (ESS) was common (in 42-100%) during treatment with systematic multi-agent chemotherapy. Only one study addressed possible risk factors, showing different types of treatment to increase the risk. However, the exact prevalence, risk factors and clinical consequences of thyroid dysfunction remain unclear. Prospective high-quality studies including large study samples are needed to longitudinally assess the prevalence, risk factors and possible consequences of thyroid dysfunction during childhood cancer treatment.

Introduction

Thyroid hormones are essential for normal development and growth in children and may be essential for adequate recovery from cancer treatment (1). In children with thyroid dysfunction energy level, height, weight, defecation, liver function, cardiac function, daily well-being and quality of life may all be affected. Symptoms of thyroid dysfunction may be non-specific and mimic complaints regularly observed by children (whether or not treated for cancer), such as fatigue and loss of energy, and may therefore be overlooked (2). In childhood cancer survivors, primary hypothyroidism has been reported after radiotherapy to the neck and after chemotherapy(3–6). However, during cancer treatment in children, much less studies have been performed on fluctuating thyroid hormone parameters while awareness of fluctuating thyroid hormone parameters during treatment may be relevant as an adequate thyroid hormone state is essential for daily quality of life. In addition, if cancer treatment is given for a prolonged period, optimal thyroid hormone levels are important for longitudinal growth, BMI and (in the young) cognitive development. Also, low thyroid hormones may be of influence on chemotherapy related toxicity such as vincristine-induced constipation or anthracycline-induced cardiotoxicity.

In children receiving cancer treatment, the hypothalamic-pituitary-thyroid system may be disrupted by the tumor itself (e.g. thyroid cancer or a brain tumor in the hypothalamic-pituitary region), by therapy such as systemic antineoplastic drugs and radiotherapy, by autoimmunity, and by ill-being or as consequence of “supportive care” drugs, such as steroids or anti-epileptics. The change in thyroid hormone parameters caused by “ill-being” is known as the euthyroid sick syndrome (ESS) (7). ESS is considered to be an adaptive state, explained by downregulation of the hypothalamic-pituitary axis resulting in a decrease of thyroid releasing hormone (TRH) and a decrease of deiodinases (D1 and D2), resulting in a decreased conversion of T4 to T3, without an increase in plasma TSH concentrations (8). Weight loss and caloric deprivation, as frequently observed during severe illness, may also cause ESS (9).

To distinguish “true” central hypothyroidism from ESS, the concentration of reverse T3 can be measured, which is lowered in case of hypothyroidism, but will be increased in case of ESS (10). Changes in thyroid hormone parameters as a consequence of ESS are correlated with the degree of illness; low levels of T3 may be predictive for poor prognoses in several diseases (11).

Systemic antineoplastic therapy (e.g. HDI-α, TKIs, multi-agent chemotherapy, immuno-therapy) may target the function of the thyroid gland directly due to toxicity or autoimmunity or target pathways which secondarily influence thyroid function (12). New antineoplastic drugs, such as checkpoint inhibitors, target cancer cells by enhancing the immune system which can lead to immune related adverse events. Checkpoint inhibitors are associated with a variety of thyroid hormone abnormalities in adult and childhood cancer patients: transient thyrotoxicosis due to thyroiditis; primary hypothyroidism as well as central hypothyroidism due to hypophysitis (13–15).

Insight into the changes of thyroid hormone parameters and the occurrence of hypothyroidism, hyperthyroidism or ESS during treatment with systemic antineoplastic therapy is important to develop adequate screening and treatment protocols. True hypothyroidism and hyperthyroidism can be treated with medication, while the presence of ESS in children with cancer may aid the oncologist in improving supportive care or be related to illness itself. For this reason, we conducted a systematic literature review to identify studies on the prevalence of thyroid dysfunction, the dynamics of thyroid hormone parameters over time, and risk factors for thyroid dysfunction during treatment with systemic antineoplastic drugs for childhood cancer.

Methods

Search strategy, inclusion criteria, data extraction, risk of bias assessment and analyses

We searched Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE in Pubmed (January 14, 2021). In addition, we hand searched several conference proceedings and searched the reference lists of included articles and reviews. Search strategies are shown in appendix A. We included all study designs measuring thyroid hormone parameters during childhood cancer (age 0-21 years at tumor diagnosis) and up to three months after the end of therapy (i.e. systemic antineoplastic drugs), except case reports and case series. Childhood cancer patients with known risk factors for thyroid dysfunction (131-I-MIBG, radiotherapy exposing the thyroid or pituitary gland, thyroid carcinoma, suprasellar intracranial tumors or Down syndrome) were excluded (16,17). Studies which included both children and adults were only included if >90% were children. Searches, data extraction and risk of bias assessment (appendix B) were performed by two independent reviewers. If discrepancies between reviewers could not be solved by discussion, final resolution was achieved by using a third-party arbitrator. We used the Wilson method to calculate the corresponding 95% confidence intervals (CIs) of the prevalences (18).

Outcomes and definitions

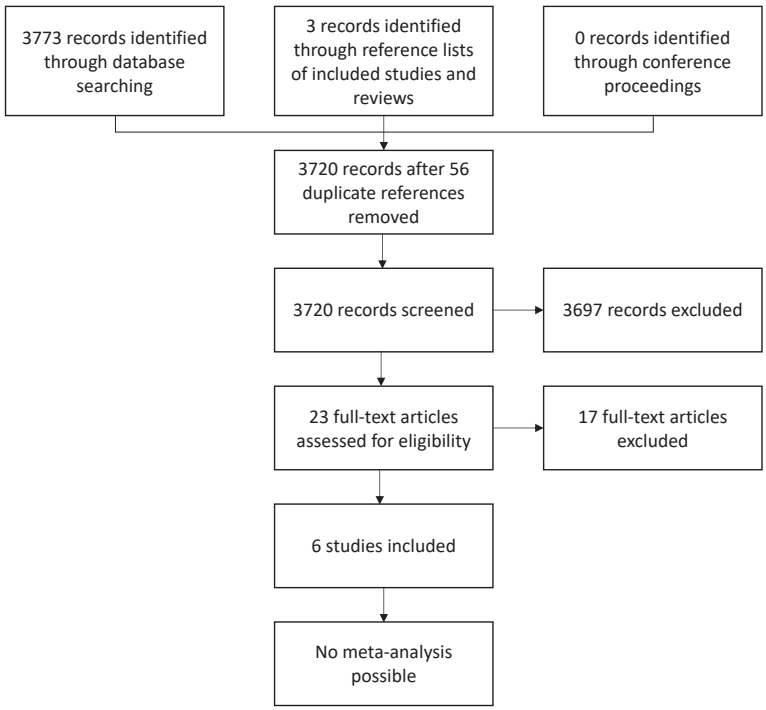
Our primary outcomes were the percentage of patients who developed thyroid dysfunction (i.e., hyper-, hypothyroidism or ESS) and the percentage of patients treated with thyroid hormone. Our secondary outcomes were the change in thyroid hormone parameters (ΔTSH, ΔFT4, ΔT4, ΔT3, ΔrT3, ΔTBG (thyroxine-binding globulin) and IGF-1) and the change in anti-thyroid antibody (anti-thyroid peroxidase, thyroglobulin antibody and TSH receptor antibody). Our definitions were based on biochemistry reports. The exact definitions are shown in appendix C.

Results

Our search revealed 3720 studies after deduplication. We screened titles and abstracts and excluded 3697 references clearly not meeting the eligibility criteria for this review. We

assessed the remaining 23 references in full text of which six fulfilled all criteria for inclusion (figure 1). Reasons for exclusion of the 17 references are mentioned in appendix D. There might be overlap between two studies (19,20). Both studies included chronic myelogenous leukemia (CML) patients treated with imatinib in the same medical centre and they were written by partly the same authors. However, the study periods do not overlap, so both were included.

Figure 1. Flowchart for inclusion and exclusion of studies



Of the six included studies, four studies described a cohort (19,21–23) and two studies were cross-sectional studies (20,24). None of the studies had a control group. The total number of participants with thyroid function test in the studies was 91 (range nine to 20 participants per study). Patients were diagnosed with different types of childhood cancer.

In three studies, patients were treated with different kinds of multi-agent chemotherapy (21–23). Patients were treated with TKIs (imatinib) in two studies (19,20) and with HDI-α in one study (24). In two studies patients did not receive previous systemic antineoplastic therapy (21,22). In two studies patients were treated with imatinib for at least six months, no information on other previous treatment was provided (19,20). In the other studies no information on previous treatment was provided.

Pre-existing thyroid disease was reported absent at study entry in two studies (20,22) One study reported a low serum T3 level before study entry in 22% of the patients (21). The remaining three studies did not report on this.

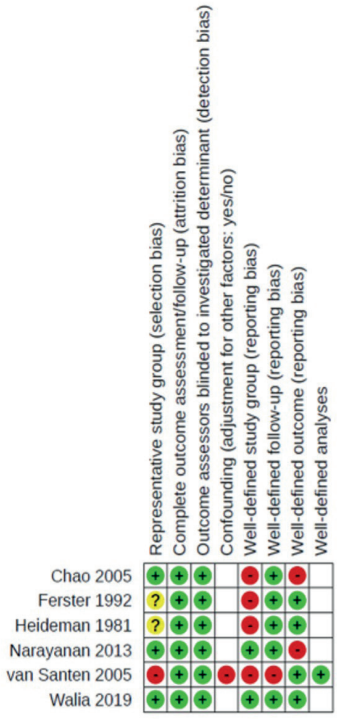
The studies were heterogeneous regarding for example cancer type, therapy, and definitions of thyroid dysfunction. Therefore, pooling of the results was not possible. We report outcomes separately for three categories of systemic antineoplastic drugs: HDI-α, TKIs and systemic multi-agent chemotherapy. More detailed study information is shown in appendix E.

Risk of bias in included studies

Internal validity

In one study (17%), the risk of selection bias was high (23), in three (50%) it was low (19,20,24) and in the two remaining studies (33%), it was unclear (21,22). In all studies, the risk of attrition and detection bias was low. Only one study conducted a multivariable analyses of risk factors for thyroid dysfunction (23); the risk of confounding was high (figure 2 and appendix E).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



External validity

Study groups were only well defined in two studies (19,20). Follow-up and outcome definitions were properly defined in five (19–22,24) and four (19,21–23) studies, respectively. The multivariable analysis in the study of van Santen (23) was well defined.

Primary (thyroidal) hypothyroidism

The prevalence of primary hypothyroidism was reported in five studies (19–22,24) (table 1). The study of Chao et al. reported hypothyroidism in two of the 11 patients (18%; 95%CI 5-48%) treated with HDI-α (24). One patient was diagnosed with hypothyroidism immediately after starting HDI-α, while the other was diagnosed at the end of therapy. The study did not provide any data about clinical symptoms of hypothyroidism, and we were unable to determine if the hypothyroidism was overt or subclinical.

Two studies reported primary hypothyroidism in patients treated for at least six months with the TKI imatinib (19,20). In the study of Narayanan et al., none of the 18 patients (0%; 95%CI 0-18%) developed hypothyroidism (mean duration of treatment with imatinib 3.6 years) (20). In the study of Walia et al. subclinical hypothyroidism was reported in two of the 20 patients (10%; 95%CI 3-30%) (mean duration of treatment with imatinib 6.1 years) (19).

In the three studies with systemic multi-agent chemotherapy none of the patients developed primary hypothyroidism. In the study of Ferster et al. none of the nine patients (0%; 95%CI 0-30%) developed overt primary hypothyroidism after chemotherapy induction consisting of vincristine, daunorubicin, prednisolone and L-asparaginase (21) and none of the seven patients (0%, 95%CI 0-35%) developed overt primary hypothyroidism during intensification therapy consisting of dexamethasone, vincristine, adriamycin and L-asparaginase. However, it was impossible to determine the incidence of subclinical hypothyroidism during chemotherapy because only mean TSH levels were available. In the study of Heidemann et al. none of the 14 patients (0%; 95%CI 0-22%) developed primary hypothyroidism during chemotherapy and none of the 13 patients (0%; 95%CI 0-23%) developed primary hypothyroidism after one to two weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase.

In the study of van Santen et al. the prevalence of primary hypothyroidism during and shortly after different kinds of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) could not be calculated because only mean TSH levels were reported (23). However, the fact that mean TSH level decreased (mean TSH level before chemotherapy 1.4 mU/L versus 0.77 mU/L after chemotherapy) makes the development of primary hypothyroidism unlikely. Furthermore, this decrease of TSH was accompanied by an increase of rT3 (mean rT3 before chemotherapy 0.18 nmol/l versus 0.39 nmol/l after chemotherapy) suggesting the presence of ESS. In one of the 19 patients (5%; 95%CI

1-25%) TSH level was elevated after treatment with vincristine and asparaginase. However, this elevated TSH level was accompanied by an elevated T3 level and was therefore not considered a reflection of subclinical hypothyroidism.

Primary hyperthyroidism

The prevalence of hyperthyroidism was reported in four studies (19–22) (table 1). None of the 18 patients (0%; 95%CI 0-18%) treated with TKIs developed hyperthyroidism during imatinib treatment (mean duration of 3.6 years) in the study of Narayanan et al. (20). Furthermore, none of the 20 patients (0%; 95%CI 0-16%) developed hyperthyroidism during treatment with imatinib (mean duration of 6.1 years) in the study of Walia et al. (19).

In the three studies with systemic multi-agent chemotherapy, none of the nine patients (0%, 95%CI 0-30%) developed primary overt hyperthyroidism during induction chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase and none of the seven patients (0%; 95%CI 0-35%) developed overt hyperthyroidism during intensification therapy consisting of dexamethasone, vincristine, adriamycin and L-asparaginase in the study of Ferster et al. Because only mean TSH levels were available, it was impossible to determine the prevalence of subclinical hyperthyroidism.

In the study of Heidemann et al. none of the 14 patients (0%; 95%CI 0-22%) developed primary hyperthyroidism during chemotherapy and none of the 13 patients (0%; 95%CI 0-23%) developed primary (overt or subclinical) hyperthyroidism after one to two weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase.
In the study of van Santen et al. the prevalence of primary hyperthyroidism could not be determined because only mean TSH and mean total T4/T3 levels were available (23). However, after chemotherapy mean TSH levels showed a decline of 53% which was accompanied by a stable mean total T4 and a decline of 67% in mean total T3 concentration. Therefore, it is unlikely that patients developed primary hyperthyroidism.

Table 1. Overview of the prevalence of thyroid dysfunction (%)

Study	Patients	Treatment	Thyroid dysfunction	Prevalence (95%CI)
Chao 2005	Melanoma (n= 11)	High dose interferon-α	Primary hypothyroidism Subclinical Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	18% (95%CI 5-48%) NM NM NM 0% (95%CI 0-26%)
Narayanan 2013	CML (n= 18)	TKIs (imatinib)	Primary hypothyroidism Subclinical Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	0% (95%CI 0-18%) 0% (95%CI 0-18%) 0% (95%CI 0-18%) 0% (95%CI 0-18%) 0% (95%CI 0-18%)
Walia 2019	CML (n= 20)	TKIs (imatinib)	Primary hypothyroidism - Subclinical - Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	10% (95%CI 3-30%) NM 0% (95%CI 0-16%) 0% (95%CI 0-16%) 10% (95%CI 3-30%)
Heidemann 1981	ALL (n= 14, during multiagent chemotherapy; n= 13, after 1-2 weeks multiagent chemotherapy)	Multiagent chemotherapy Vincristine, daunorubicin, prednison L-asparaginase	Primary hypothyroidism Subclinical Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	0% (95%CI 0-23%) during and after 1-2 weeks of multiagent chemotherapy 0% (95%CI 0-23%) during and after 1-2 weeks of multiagent chemotherapy 0% (95%CI 0-23%) 1-2 weeks after multiagent chemotherapy 64% (95%CI 39-84%) during multiagent chemotherapy NM

Study	Patients	Treatment	Thyroid dysfunction	Prevalence (95%CI)
Fester 1992	ALL (n= 9, during induction n=7, during intensification)	Multiagent chemotherapy Induction Vincristine, daunorubicin, prednisone, L-asparaginase Intensification Vincristine, dexamethasone, adriamycin, L-asparaginase	Primary hypothyroidism Subclinical Overt Primary hyperthyroidism Subclinical Overt ESS/central hypothyroidism Thyroid hormone treatment	NM, only mean TSH 0% (95%CI 0-30%) during induction 0% (95%CI 0-35%) during intensification NM, only mean TSH 0% (95%CI 0-30%) during induction 0% (95%CI 0-35%) during intensification 100% (95%CI 70-100%) on day 28 of induction 86% (95%CI 49-97%) on day 16 of intensification NM
Van Santen 2005	Solid tumors or leukemia (n= 19; 46 courses of chemotherapy)	Multiagent chemotherapy Alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinating compounds, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids	Primary hypothyroidism Subclinical Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	NM, only mean TSH NM, only mean TSH NM, only mean TSH NM, only mean TSH 42% (95%CI 1-64%) 0% (95%CI 0-18%)

Abbreviations: ALL, acute lymphoblastic leukaemia; CML, chronic myelogenous leukemia; ESS, euthyroid sick syndrome; TKIs, tyrosine kinase inhibitors; TSH, thyroid stimulating hormone; CI, confidence interval; NM, not mentioned

Euthyroid sick syndrome (ESS) or central (secondary/hypothalamic-pituitary) hypothyroidism

In five of the six studies (19–23), it was possible to calculate the percentage of patients with a decrease in thyroid hormones without an adequate increase in plasma TSH (table 1). In the study of Narayanan et al. none of the 18 patients (0%; 95%CI 0-18%) treated with imatinib developed ESS or central hypothyroidism. In the study of Walia et al. none of the 20 patients (0%; 95%CI 0-16%) treated with imatinib developed ESS or central hypothyroidism (19).

In the study of Fester et al, in all nine patients (100%; 95%CI 70-100%) low levels of T3 and T4 were seen accompanied by a low TBG level suggesting TBG deficiency on day 28 of induction therapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase. Isolated low T3 or low T3 and low T4 was reported in six of the seven patients (86%; 95%CI 49-97%) on day 16 of intensification therapy consisting of dexamethasone, vincristine, adriamycin and L-asparaginase. In three out of these seven patients the TBG level was below the reference range. TSH levels were normal during the study.

In the study of Heidemann et al. nine of the 14 patients (64%; 95%CI 9-84%) developed a low FT4 compatible with ESS or central hypothyroidism within three weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase (22). In six of these nine patients with FT4 levels below the reference range the pituitary-thyroid axis was evaluated by TRH stimulation. All six patients had a normal TSH response after TRH administration before starting chemotherapy. However, after chemotherapy the TSH peak after administration of TRH was absent in all six patients suggesting central hypothyroidism. The prevalence of patients with a low total T4 and T3 could not be calculated because only mean T4 and T3 were mentioned. However, mean total T4, total T3 and TBG declined to below the reference range without a significant change in the TSH level during three weeks of chemotherapy consisting of vincristine, daunorubicin, prednisone and L-asparaginase.

In the study of van Santen et al. ESS (or central hypothyroidism) developed in eight of the 19 patients (42%; 95%CI 23-64%) after different types of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) (23). ESS only developed after the administration of dexamethasone.

Treatment with thyroid hormone

Treatment with thyroid hormone was mentioned in four studies (table 1) (19,20,23,24). Only the study of Walia et al. actually reported two patients out of 20 (10%; 95%CI 3-30%) who were diagnosed with subclinical hypothyroidism and received thyroid hormone treatment. In the three other studies, no patients received treatment.

Change in thyroid hormone parameters or antithyroid antibodies

Three studies reported on the change in thyroid hormone parameters during treatment with systemic multi-agent chemotherapy for childhood cancer (table 2) (21–23). A decrease in thyroid hormone parameters was reported in the study of Ferster et al. including nine patients: change in total T4 of -61% (mean T4 10.1 to 3.96 ug/100ml; $p<0.001$), total T3 of -53% (mean T3 134 to 57 ng/100ml; $p<0.001$), FT4 of -51% (mean FT4 of 1.4 to 0.7 ng/100 ml; $p<0.001$) and TBG of -63% (mean 2.14 to 0.79 mg/100 ml; $p<0.001$) between day one and day 28 of induction therapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase. Total T4, total T3 and TBG level were below the lower limit of normal on day 28 of the induction therapy in all patients. All thyroid hormone parameters reverted towards normal on day 35 of the chemotherapy course, after withdrawal of L-asparaginase and during tapering of prednisone. TSH levels were normal before the start of induction therapy and did not change during the study.

A decrease in thyroid hormone parameters was reported in the study of Heidemann et al. including 14 patients: change in total T4 of -73% (mean 10.7 to 2.9 ug/100ml; $p<0.001$), total T3 of -65% (mean 0.99 to 0.35 ng/ml; $p<0.001$), FT4 of 47% (mean 1.77 to 0.94 ng/100 ml; $p<0.001$) and TBG of -73% (mean 29.4 to 8.0 ug/ml; $p<0.001$) during 3 weeks of

chemotherapy consisting of vincristine, daunorubicin, prednisone and L-asparaginase (22). TSH levels remained within the reference ranges throughout the study. All thyroid hormone levels normalized one week after the last prednisone and two to three weeks after the last L-asparaginase.

The study of van Santen et al., including 19 patients reported a change in thyroid hormone parameters: decrease in TSH of -53% (mean TSH 1.45 to 0.77 mU/l; p≤0.0001), T3 of -67% (mean T3 2.4 to 1.6 nmol/l; p≤0.0001), rT3 + 217% (mean rT3 0.18 to 0.39 nmol/l; p≤0.0001) after a course of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) (23). Total T4, TBG, and IGF-1 were not affected. FT4 was not determined because of the possible interaction with the assay using heparin in the central venous catheters. Appendix E shows a complete overview of the reported changes in thyroid function parameters**.**

None of the studies reported on change of anti-thyroid antibodies. In the study of van Santen et al., in none of the 19 patients elevated concentrations of anti-TPO or anti-TG were found at baseline (23).

Table 2. Change in thyroid hormone parameters

Study	Patients	Multiagent chemotherapy	ΔTSH, ΔFT4, ΔT4, ΔT3, ΔrT3, ΔTBG, ΔIGF-1
Heidemann 1981	ALL (n= 14)	Vincristine, daunorubicin, prednisolone, L-asparaginase	*Before versus during 3 weeks of therapy* **TSH**: within reference range (no significant change) **T4:** **-73%** (mean 10.7 to 2.9 ug/100ml; p<0.001) **T3:** **-65%** (mean 0.99 to 0.35 ng/ml; p<0.001) **TBG:** **-73%** (mean 29.4 to 8.0 ug/ml; p<0.001) On day 35 (after withdrawal L-asparaginase + tapering prednisolone) all thyroid hormone levels reverted towards normal
Fester 1992	ALL (n= 9)	Vincristine, daunorubicin, prednisolone, L-asparaginase	*Day 1 versus day 28 therapy* **TSH:** percentage not mentioned (not significant) **T4:** **-61%** (mean T4: 10.1 to 3.96 ug/100ml; p<0.001) **T3:** **-53%** (mean T3: 134 to 57 ng/100ml; p<0.001) **TBG:** **-63%** (mean TBG: 2.14 to 0.79 mg/100 ml; p<0.001) 2-3 weeks after L-asparaginase all thyroid hormone levels normalized
Van Santen 2005	Solid tumor or leukemia (n= 19, 46 courses of chemotherapy)	Alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinating compounds, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids	*After course of chemotherapy* **TSH:** **-53%** (mean TSH: 1.45 to 0.77 mU/l; p≤0.0001) **T4:** no significant change **T3:** **-67%** (mean T3: 2.4 to 1.6 nmol/l; p≤0.0001) **TBG** no significant change **rT3:** **+217%** (mean rT3: 0.18 to 0.39 nmol/l; p≤0.0001) **IGF-1:** no significant change

Abbreviations: ALL, acute lymphoblastic leukaemia; CML, chronic myelogenous leukemia; ESS, euthyroid sick syndrome; TKIs, tyrosine kinase inhibitors; TSH, thyroid stimulating hormone; free T4, FT4; total T4, T4; total T3, T3; thyroxine binding globulin, TBG; reverse T3, rT3.

Multivariable risk factor analyses

Possible risk factors for change in thyroid hormone parameters were analysed in the study of van Santen et al. for the different subgroups of chemotherapy; for therapy schedules with or without dexamethasone and per by cancer type (solid tumor versus leukemia) (23). Cancer type did not influence the thyroid hormone parameters during chemotherapy treatment. The study analysed the presence of anti-TPO and anti-TG concentrations, in none of the 19 participants elevated concentrations were found at baseline, therefore this could not be included in the model.

In 39 courses of chemotherapy in which dexamethasone was administered the baseline TSH was significantly lower and the concentrations of rT3 and T4 were significantly higher at baseline compared to chemotherapy courses without dexamethasone. No differences were seen in baseline T3 and TBG level. After administration of dexamethasone significantly lower concentrations of plasma TSH and T3 and an increase in plasma rT3 were found. In the chemotherapy courses with administration of dexamethasone, T3 was lower after alkylating chemotherapy (β -2.246 with 95%CI -1.06 to -0.59, p 0.000), antineoplastic agents (β -0.447 with 95%CI -0.29 to -0.02, p 0.027), antimetabolites (β -2.808 with 95%CI -1.26 to -0.68, p 0.000), cisplatin (β -1.968 with 95%CI -1.15 to -0.54, p 0.000) and topoisomerase inhibitors (β -0.385 with 95%CI -0.22 to -0.05 p=0.002). The TBG level was lower in patients treated with topoisomerase inhibitors (β -0.478 with 95%CI -0.16 to -0.22, p 0.012).

In seven courses of chemotherapy without dexamethasone administration an increase in plasma rT3 was found after the course of chemotherapy. The mean rT3 was lower in patients treated with asparaginase (β -0.936 with 95%CI -1.52 to -0.92, p 0.000).

Discussion

This systematic review is, to our knowledge, the first review to analyse the change in thyroid hormone parameters in childhood cancer patients treated with systemic antineoplastic therapy. While the number of studies is small, the six studies included report on 91 childhood cancer patients and illustrate that changes in thyroid hormone parameters are seen in children treated with systemic antineoplastic therapy, although the exact number varies.

Primary hypothyroidism was reported in 18% treated with HDI-α and in up to 10% of patients treated with TKIs, but it is rare in children treated with systemic multi-agent chemotherapy. However, ESS (or central hypothyroidism) was reported in 42-100% of patients treated with systemic multi-agent chemotherapy. The consequences of these changes in thyroid hormone parameters in children receiving chemotherapy have been studied insufficiently.

The wide variation in prevalence of thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer, especially ESS, is related to the differences in definitions used for thyroid dysfunction and it may reflect the large heterogeneity of included

studies mainly regarding the type of childhood cancer and type of systemic antineoplastic therapy. Antineoplastic therapy can affect thyroid hormone parameters in different ways. Antineoplastics can target the thyroid gland directly or indirectly by affecting TSH, TBG and deiodinase enzymes. Because of the heterogeneity in systemic antineoplastics and the different underlying mechanism in affecting the thyroid hormone parameters we reported the outcomes separately for HDI-α, TKIs and multi-agent systemic chemotherapy.

Only one study performed a multivariate analysis to identify risk factors for aberrant thyroid function parameters (23). Cancer type (solid tumour versus leukemia) did not influence the thyroid function parameters during chemotherapy treatment. In the chemotherapy courses with administration of dexamethasone the mean T3 levels were lower after alkylating agents, antineoplastic antibiotics, antimetabolites, cisplatin and topoisomerase inhibitors. In the chemotherapy courses without administration of dexamethasone an increase in mean rT3 was found after the course of chemotherapy. The mean rT3 was lower after treatment with asparaginase.

Unfortunately, an international definition of ESS is lacking and the wide biochemical criteria for ESS overlap the criteria for central hypothyroidism. Low thyroid hormones without an adequate TSH increase can thus biochemically fit both the diagnosis ESS as well as central hypothyroidism. There may also be a TBG deficiency if the low total thyroid hormones are accompanied by low levels of TBG. The distinction between ESS and central hypothyroidism can be made by determining rT3 or performing a TRH test (5,20). In the clinical setting, the distinction between ESS and central hypothyroidism is based on the clinical pre likelihood by identifying risk factors for ESS or central hypothyroidism (e.g., malnourishment or admission to intensive care versus (supra)sellar tumor or cranial radiotherapy) whether or not in combination with the rT3 level. Due to lack of rT3 measurements, it was impossible to distinguish ESS from central hypothyroidism in most of the reviewed studies. Only in the study of van Santen et al. rT3 was analysed and in the study of Heidemann et al. a TRH test was performed making differentiation between ESS and central hypothyroidism possible (22,23).

In the study of van Santen et al. the mean concentration of rT3 increased to 217% after a course of chemotherapy suggesting ESS (23). However, the prevalence of ESS in this study was solely based on low thyroid hormones without an adequate TSH response and the percentage of patients with an increased rT3 was not separately reported. In the study of Heidemann et al. in six of the nine patients with ESS or central hypothyroidism an additional TRH test was performed (22). All six patients had a normal TSH response after TRH administration before starting chemotherapy. After three weeks of systemic multiagent chemotherapy all six patients had a blunted TSH response after TRH administration. The authors hypothesised that L-asparaginase and corticosteroids can result in transient central hypothyroidism.

Even though differentiation between ESS and central hypothyroidism was biochemically not possible in all studies it is likely that in most cases the aberrant thyroid parameters are caused by ESS because patients at risk for central hypothyroidism (e.g. cranial radiotherapy, (supra)

sellar tumors) were excluded in our review. The fact that ESS only developed in chemotherapy courses in which dexamethasone was administered is suggestive for an important role for corticosteroids in the development of ESS. Corticosteroids are known to have different effects on thyroid hormone parameters: administration of glucocorticosteroids suppress the secretion of TSH, inhibits the synthesis of TBG and inhibits the conversion of T4 into T3 (10).

Because the effect of antineoplastic drugs may be different in children and adults, we specifically sought studies performed in children with cancer. However, in adults, primary hypothyroidism has been reported in 2.4-19% of patients treated with HDI-α and the incidence is higher in patients with pre-existing thyroid autoimmunity (25,26). The prevalence of thyrotoxicosis, mostly due to mild transient thyroiditis, is 2-3% and is mostly seen in the first weeks to months of treatment with HDI-α. Thyroiditis with thyrotoxicosis may be followed by hypothyroidism. Graves hyperthyroidism has also been described. Thyroid dysfunction may recover after withdrawal of HDI-α, although hypothyroidism is persistent in most patients (25,26). In our reviewed study (24) the prevalence of HDI-α-induced hypothyroidism of 18% is comparable to the adult literature.

In adult patients, TKIs may induce primary thyroid dysfunction or worsen pre-existent hypothyroidism (increased thyroid hormone demand). The prevalence of TKI-induced primary hypothyroidism in adult patients ranges between 0-85% depending on the type of TKIs. Transient thyrotoxicosis due to destructive thyroiditis is seen in 0-24% of adult patients and is often followed by hypothyroidism. It is unclear if hypothyroidism is reversible after withdrawal of TKIs (26,27). The range in prevalence of TKI-induced primary hypothyroidism in adult patients is larger than the prevalence of 0-10% in our reviewed studies and our reviewed studies did not report any patient with thyrotoxicosis probably due to the small number of patients (19,20). Remarkable, in adult patients imatinib is not associated with hypothyroidism (27) in contrast to the reported 10% primary hypothyroidism in the study of Walia et al. (19).

During systemic chemotherapy it is difficult to analyse the effects of individual chemotherapeutic agents on the thyroid function because most chemotherapeutic protocols involve multiple agents including corticosteroids. In our review, primary thyroid dysfunction during systemic multi-agent chemotherapy was not identified. However, it should be noted that although studies reported a prevalence of 0%, primary thyroid dysfunction cannot be excluded because of the small numbers of patients in the reviewed studies and as the 95% confidence intervals includes a higher prevalence. The literature regarding thyroid function during systemic chemotherapy in adult patients is limited. In the study of Sutcliffe et al., 20 adult patients with advanced Hodgkin lymphoma were treated with chemotherapy consisting of mechlorethamine, vinblastine, procarbazine and prednisolone (28). During treatment none of the patients developed thyroid dysfunction. However, after a median follow-up of 35 months 44% of patients developed subclinical hypothyroidism.

In the study of Stuart et al., analysing thyroid function in adult patients with advanced testicular carcinoma 10% (two of 20 patients) developed subclinical hypothyroidism after treatment with chemotherapy consisting of cisplatin, bleomycin, vinblastine, etoposide and dactinomycin (29). The mean level of TSH was positively associated with the cumulative dose of cisplatin and vinblastine. However, this study only evaluated thyroid function after and not during treatment with systemic chemotherapy. Based on these studies and the results of our reviewed studies primary thyroid dysfunction during systemic multi-agent chemotherapy seems to be rare.

The effect of L-asparaginase on TBG levels is described by Garnick et al. (30). In this study with adult ALL patients treated with monotherapy L-asparaginase a transient reduction in TBG-level was seen. In the studies of Ferster et al. and Heidemann et al. the decline in thyroid hormones was also accompanied by a decline in TBG levels suggesting TBG deficiency (21,22). Because thyroid hormones and TBG levels trend to normalize after withdrawal of L-asparaginase but still during treatment with corticosteroids and because of the known effects of monotherapy L-asparaginase on the TBG levels it is likely that L-asparaginase is responsible for the TBG deficiency (30).

The clinical relevance of aberrant thyroid function during childhood cancer is unclear. In the study of van Santen et al. no significant changes were found between complaints and thyroid hormone parameters at baseline or during the administration of multi-agent chemotherapy in a period of three months (23). In the study of Heidemann et al. no obvious clinical symptoms of hypothyroidism were observed (22). The other reviewed studies did not provide any information on clinical functioning of patients. Thyroid hormone treatment was indicated in two of the 20 patients (10%) diagnosed with subclinical hypothyroidism during treatment with TKIs (19). Because of the important role of thyroid hormone in the growth and development of children, systemic antineoplastic therapy-induced primary thyroid disorders should be considered being clinically relevant.

In contrast to primary thyroid disorders, ESS is seen as an adaptive state in critical ill patients and is postulated to be protective by preventing excessive tissue catabolism in the acute setting. However, the clinical effects of chemotherapy-induced ESS, especially if these effects are prolonged (e.g., for a period of one- or two-years during leukaemia treatment), are still unknown (8,10). The fact that systemic chemotherapy-induced thyroid dysfunction is transient in the reviewed studies is reassuring.

It remains difficult to extrapolate our findings to individual childhood cancer patients being treated with systemic antineoplastics drugs because of the continuous development of new treatment protocols in oncology. However, with upcoming new therapies, such as checkpoint inhibitors, with a prevalence of primary thyroid dysfunction up to 20% and hypophysis's (with potential central hypothyroidism) in up to 17% of adult patients, it is important to understand the effects of the current systemic antineoplastic therapy on thyroid hormone parameters (13,14,31).

Limitations of the included studies

The six included studies were heterogeneous regarding for example childhood cancer, systemic antineoplastic therapy, and definitions of thyroid dysfunction. Because of this heterogeneity, pooling of the results was not possible. Also, the quality of the studies varied, on many occasions due to a lack of reporting. In 50% of the studies, selection bias could not be ruled out. This may have led to an overestimation of the prevalence of thyroid dysfunction if participants with a higher risk of thyroid function were included in the study or to an underestimation when participants with a lower risk were selected. In addition, if important information is missing (as the exact treatment patients received or prior thyroid dysfunction) it is difficult to interpret the results correctly and extrapolate them to individual patients. This was the case in almost all included studies.

Finally, only one study performed a multivariable risk assessment, so knowledge regarding patients who are at highest risk remains limited. Furthermore, in this study, confounding could not be ruled out which could lead to an over- or underestimation of the real effect of the risk factors.

Conclusions

The exact prevalence, risk factors and clinical consequences of thyroid dysfunction during antineoplastic therapy remain unclear. Before definitive conclusions can be made, high quality studies with a sufficient number of patients are needed. Future trials should preferably be prospective cohort studies that longitudinally assesses the prevalence and risk factors for thyroid dysfunction and include valid outcome definitions. In addition, to distinguish ESS from central hypothyroidism, rT3 and risk factors (e.g., cranial radiotherapy, supra(sellar) tumors) for central hypothyroidism should be noted.

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Supplementary materials

Appendix A. Search strategies

Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1) For thyroid function:
euthyroid Sick Syndromes OR euthyroid sick syndrom* OR Hyperthyroidism OR Hypothyroidism OR Thyroiditis OR Insulin-Like Growth Factor I OR hyperthyroid* OR hypothyroid* OR thyroid-stimulating hormone deficienc* OR thyroid stimulating hormone deficienc* OR TSH deficienc* OR sick euthyroid syndrome OR non-thyroidal illness syndrome OR non thyroidal illness syndrome OR low T3 low T4 syndrome OR low T3 low T4 syndrome OR low T3 and low T4 syndrome OR low T3 high T4 syndrome OR low T3 high T4 syndrome OR high T4 syndrome OR low T3 syndrome OR rT3 OR reversed T3 OR TBG OR thyroxine binding globuline OR thyroxine binding globulin* OR IGF-1 OR insulin like growth factor OR thyroid diseas* OR hypothyroxinemia OR hyperthyroxinemia OR hypothyrotropinemia OR hyperthyrotropinemia OR anti-thyroid antibod* OR "anti thyroperoxidase" OR thyroglobulin antibody OR TSH receptor antibody

2) For children/young adults:
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR school OR school* OR prematur* OR preterm*

3) For childhood cancer:
(leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric

oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR cancer or neoplasms or tumor or cancers or neoplasm or tumors)

4) For cancer:
cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato

oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

5) For antineoplastic systemic therapy:
antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap* OR Topoisomerase Inhibitors OR Protein Kinase Inhibitors OR Antibodies, Monoclonal OR antigens, neoplasm OR antineoplastic agents, immunological OR immunotherapy OR immunotherapy* OR checkpoint inhibitor* OR checkpoint block*

Combinations:
1 AND 2 AND (3 OR 4) AND 5
The search was performed in title, abstract or keywords.

Search strategy for PubMed/MEDLINE

1) For thyroid function:
euthyroid Sick Syndromes OR euthyroid sick syndrom* OR Hyperthyroidism OR Hypothyroidism OR Thyroiditis OR Insulin-Like Growth Factor I OR hyperthyroid* OR hypothyroid* OR thyroid-stimulating hormone deficienc* OR thyroid stimulating hormone deficienc* OR TSH deficienc* OR sick euthyroid syndrome OR non-thyroidal illness syndrome OR non thyroidal illness syndrome OR low T3-low T4 syndrome OR low T3 low T4 syndrome OR low T3 and low T4 syndrome OR low T3-high T4 syndrome OR low T3 high T4 syndrome OR high T4 syndrome OR low T3 syndrome OR rT3 OR reversed T3 OR TBG OR thyroxine binding globuline OR thyroxine binding globulin* OR IGF-1 OR insulin like growth factor OR thyroid diseas* OR hypothyroxinemia OR hyperthyroxinemia OR hypothyrotropinemia OR hyperthyrotropinemia OR anti-thyroid antibod* OR “anti thyroperoxidase” OR thyroglobulin antibody OR TSH receptor antibody

2) For children/young adults:
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school [tiab] OR school*[tiab] OR prematur* OR preterm* OR young adult[mh] OR young adult

3) For childhood cancer:
leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing’s OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR

rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR Pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR Central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain

neoplasm* OR intracranial neoplasm* OR leukemia lymphocytic acute OR leukemia, lymphocytic, acute[mh]

4) For cancer:
cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

5) For antineoplastic systemic therapy:
antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap* OR Topoisomerase Inhibitors OR Protein Kinase Inhibitors OR Antibodies, Monoclonal OR antigens, neoplasm OR antineoplastic agents, immunological OR immunotherapy OR immunotherapy* OR checkpoint inhibitor* OR checkpoint block*

Combinations:
1 AND 2 AND (3 OR 4) AND 5
[mh = MeSH term; * = zero or more characters]

Search strategy for conference proceedings (2015-2020)

Pdf files of SIOP, ASPHO, PES, ESPE, BSPED, Endocrine Society, ATA, ETA, LATS, and AOTA conference proceedings were assessed using these terms: thyroid, insulin-like growth factor, TSH, T3, rT3, T4, TBG, thyroxine, IGF-1, TPOAb, TgAb, and TRAb

Appendix B. 'Risk of bias' assessment criteria for observational studies*

	Internal validity	External validity
Study group	Selection bias (representative: yes/no/unclear): If the described study group consisted of more than 90% of the childhood cancer patients treated with systemic antineoplastic therapy included in the original cohort Or If it was a random sample of these patients with respect to the cancer treatment and important prognostic factors for thyroid function (i.e. age, prior thyroid dysfunction, genetic syndromes with predisposition to thyroid disease, familial history).	Reporting bias (well-defined: yes/no): If the type of cancer and type and dose of systemic antineoplastic therapy were mentioned *and* If the inclusion and exclusion criteria are described *and* If information on pre-existing thyroid disease (i.e. number of patients and definition) was provided.
Follow-up	Attrition bias (adequate: yes/no/unclear): If the outcome was assessed for more than 90% of the study group of interest.	Reporting bias (well-defined: yes/no): If the length of follow-up was mentioned.
Outcome	Detection bias (blind: yes/no/unclear): If the outcome assessors were blinded to the investigated determinant.	Reporting bias (well-defined: yes/no): If the method of detection and the definition of an abnormal outcome were provided.
Risk assessment**	Confounding (adjustment for other factors: yes/no): If important prognostic factors (age, prior thyroid dysfunction, genetic syndromes with predisposition to thyroid disease, familial history) and follow-up were adequately taken into account.	Analyses (well-defined: yes/no): If a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference, or Chi2 was calculated.

* based on previously described checklists according to evidence-based medicine criteria (32,33)
** only applicable when risk factor analyses have been performed.

Appendix C. Definitions thyroid dysfunction
Primary (thyroidal) hypothyroidism was defined as a TSH-level above the reference range with either FT4/total T4 below the reference range (overt hypothyroidism) or FT4/total T4 within the reference range (subclinical hypothyroidism).

Primary hyperthyroidism was defined as a suppressed TSH with either FT3/FT4 or total T3/T4 above the reference range (overt hyperthyroidism) or FT3/FT4 or total T3/T4 within the reference range (subclinical hyperthyroidism).

ESS was defined as the combination of low to normal TSH with low FT4, FT3, total T4 or total T3 and high rT3 or was defined as the combination of low to normal TSH with isolated low total T3 or with low total T4 and total T3.

Central (secondary/hypothalamic-pituitary) hypothyroidism was defined as the combination of low to normal TSH with FT3/FT4 or total T3/T4 below the reference range. Definitions for ESS and central hypothyroidism are overlapping, and therefore described collectively in the results section.

Appendix D. Characteristics of excluded studies

Study	Reason for exclusion
Bossi 1997	Radiotherapy
Fox 2010	Radiotherapy
Garnick 1979	Only 2 non-consecutive patients described
Gaspar 2017	Patients treated with MIBG
Ghavamzadeh 2003	Systemic chemotherapy in malignant and benign disorders, no separate results for malignant disorders
Hummel 1997	Only adult patients described
Ihara 2019	Review
Krawczuk-Rybak 1999	Full text was not available, but publication was labelled in MEDLINE as editorial
Lodish 2010	Review
Lodish 2013	Review
Merchant 2016	Radiotherapy
Pansy 2012	Radiotherapy
Reismüller 2010	Cranial radiotherapy
Sutcliffe 1981	Adult patients
Vialettes 1993	Children were not the majority of patients; no separate data on children reported
Waguespack 2019	Review
Willemse 1982	Children were not the majority of patients; no separate data on children reported

Appendix E. Characteristics of included studies

Chao et al. (2005)

Study characteristics	
Methods	Study design: cross-sectional study Time period: January 1989 -July 2003 Setting: Single center, USA Inclusion criteria study: high-risk surgically resected melanoma Exclusion criteria study: (nm) not mentioned Control group (general pediatric population or other) available: no control group
Patients	Original cohort n= 14 of which 12 received high dose interferon Study group of interest n= 11 Patients with a thyroid function test n= 11 Age at time of primary cancer diagnosis: mean 9.4 yrs, median 8.5 yrs (range 5-18 years) Sex: 6 boys (43%), 8 girls (57%) Type of malignancy: primary melanoma (AJCC stage IIB/C or III) Pre-existing thyroid disease: nm Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): nm Renal failure: nm
Interventions	Previous antineoplastic therapy: not reported, but n=1 medulloblastoma in history Name treatment protocol: nm Systemic antineoplastic therapy: high-dose interferon (HDI) alfa-2b: 20 million IU/m^2/day IV 5 times per week for 4 weeks followed by 10 million IU/m^2/day SC 3 times per week for 48 weeks. Cumulative dosage 1840 million IU/m^2, but 1 out of 11 patients had dose reduction because of neutropenia (exact dose reduction nm). Stem cell transplantation: no Theranostics: no Other treatment interventions: surgery primary tumor and regional lymph node dissection, no radiotherapy Other medication: nm Use of steroids: nm
Outcomes	Number of blood samples including thyroid hormone parameters n= nm Assay type for the different thyroid hormone parameters: nm Reference values thyroid hormone parameters: nm Blood sample taken from a central venous catheter containing heparin: nm Time-points of blood samples: nm **Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* Hypothyroidism (subclinical or overt nm) developed in 2 of the 11 (18%; 95%CI 5% to 48%) patients (n= 1 immediately after starting HDI, n= 1 at the end of therapy). Definitions thyroid dysfunction according to study: nm *Percentage of patients who developed thyroid dysfunction*: No information about percentage of patients with primary (subclinical) hypo- or hyperthyroidism, secondary hypothyroidism or ESS because aberrant thyroid parameters were not mentioned. *Thyroid hormone treatment:* no (0%; 95%CI 0% to 26%) **Secondary outcomes** *Thyroid hormone parameters*: nm *Change in thyroid hormone parameters*: nm *Change in anti-thyroid antibodies*: nm *Multivariable risk factor analyses*: no

Study characteristics		
Notes	Partial overlap with other included studies: not likely Details of funding sources: no funding details Declaration of interest primary investigators: nm	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Representative study group (selection bias)	Low risk	Original cohort 14 patients with high risk melanoma, of which 12 received high dose interferon. 11 out of these 12 patients included (92%).
Complete outcome assessment/ follow-up (attrition bias)	Low risk	Complete study group of interest had a thyroid function test.
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used.
Well-defined study group (reporting bias)	High risk	Protocol described, actually received cumulative dose not mentioned. Inclusion criteria described. Exclusion criteria not mentioned. Pre-existing thyroid disease was not described.
Well-defined follow-up (reporting bias)	Low risk	Follow-up period per patients was described.
Well-defined outcome (reporting bias)	High risk	Assay and definition not mentioned

Ferster et al. (1992)

Study characteristics	
Methods	Study design: prospective, cohort study Time period: 1991 Setting: Single center, Belgium Inclusion criteria study: children with acute lymphoblastic leukemia (ALL) treated according to EORTC protocol number 58831 Exclusion criteria study: CNS involvement, cranial or craniospinal irradiation during an early stage of therapy Control group (general pediatric population or other) available: no control group
Patients	Original cohort n= nm Study group of interest n= 9 Patients with a thyroid function test n= 9 Age (at time of primary cancer diagnosis): nm, a range of 2-14 years of age is reported (but not stated to what time those data refer) Sex: nm Type of malignancy: primary disease, acute lymphoblastic leukemia Pre-existing thyroid disease: not clearly described; 7/9 (78%) had normal thyroid hormone levels and 2/9 (22%) had low serum T3 levels before therapy Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): nm Renal failure: nm
Interventions	Previous antineoplastic therapy: no Name treatment protocol: EORTC (58831, modified BFM protocol) Systemic antineoplastic therapy: actual received cumulative dose not reported, but according to protocol Patients should have received the following agents: Induction therapy: • Vincristine (1.5 mg/m^2/week) during 4 weeks (cumulative dose: 6 mg/m^2) • Daunorubicin (30 mg/m^2/week) during 4 weeks (cumulative dose: 120 mg/m^2) • Prednisolone (60 mg/m^2/day) during 4 weeks subsequently tapered over a period of 2 weeks (cumulative dose at least 1680 mg/m^2 but no information about tapering schedule) • L-asparaginase (5,000 U/m^2/day) during 21 days (cumulative dose: 105000U/m^2) Followed by a 4-week chemotherapy course of: • Cyclophosphamide (no information on dose) • Cytosine arabinoside (no information on dose) • 6-mercaptopurine (6-MP) (no information on dose) • Followed by interval therapy containing: • Methotrexate (no information on dose) • 6-MP (no information on dose) Late intensification: • Dexamethasone (10mg/m^2/day), 2 weeks in low risk patients , 4 weeks in medium to high risk patients (cumulative dose 140-280 mg/m^2) • Vincristine (1.5 mg/m^2/week), 2 weeks in low risk patients , 4 weeks in medium to high risk patients (cumulative dose 3-6 mg/m^2) • Adriamycin (30 mg/m^2/week), 2 weeks in low risk patients, 4 weeks in medium to high risk patients (cumulative 60-120 mg/m^2) • L-Asparaginase (10.000U/m^2) 4 times, interval of 4 days (cumulative dose according to protocol 40.0000U/m^2) Stem cell transplantation: no SCT Theranostics: no Other treatment interventions: no surgery or radiotherapy Other medication: nm Use of steroids: dexamethasone and prednisolone according to the protocol, otherwise not specified.

Study characteristics	
Outcomes	Number of blood samples including thyroid hormone parameters: Total n= 8 blood samples per patient according to protocol, but 2 patients were not tested during late intensification Assay type for the different thyroid hormone parameters: Analog free T4 method (Amerlex) Reference values thyroid hormone parameters (not adjusted for age): • TSH <6 mcU/100ml • FT4 0.8-21 ng/100ml • T4 6-12 ug/100ml • T3 125-275 ng/100ml • TBG 1.2-2.1 mg/100ml Blood sample taken from a central venous catheter containing heparin: nm Time-points of blood samples: Induction therapy: day 1, 10, 28, 35 Late intensification: day 1, 10, 16, 22 **Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* On day 28 induction: • n= 9/9 (100%; 95%CI 70% to 100%) T4 and T3 below the lower limit of the normal ranges • n= 4/9 (44%; 95%CI 19% to 73%) FT4 below reference ranges Day 16 intensification: • n = 6/7 (86%; 95%CI 49% to 97%) T3 or T3 and T4 below reference ranges • n = 3/7 (43%; 95%CI 16% to 75%) TBG decreased Definitions thyroid dysfunction according to study: nm *Percentage of patients who developed thyroid dysfunction:* 0% (95%CI 0% to 30%) of 9 patients during induction chemotherapy and 0% (95%CI 0% to 35%) of 7 patients during intensification treatment developed primary overt hypothyroidism. Primary subclinical hypothyroidism impossible to determine because only mean TSH available. 0% (95%CI 0% to 30%) primary overt hyperthyroidism (FT4 within reference ranges) in 9 patients during induction chemotherapy and 0% (95%CI 0% to 35%) in 7 patients during intensification treatment. Primary subclinical hyperthyroidism impossible to determine because only mean TSH available. 9/9 (100%; 95%CI 70% to 100%) patients had low T3 and low T4 on day 28 of induction without a significant change in TSH. This could be compatible to ESS or central hypothyroidism. 6/7 (86%; 95%CI 49% to 97%) patients had an isolated low T3 or low T3 and low T4 on day 16 of intensification without a significant change in TSH. This could be compatible to ESS or central hypothyroidism. *Thyroid hormone treatment*: nm

Study characteristics	

Outcomes	**Secondary outcomes**
	Thyroid hormone parameters (n= 9 at induction; n= 7 at late intensification):
	• Thyroid hormone parameters at day 1 of induction therapy (mean ± SD)
	  • TSH (mcU/100ml): 3.1±1.5
	  • FT4 (ng/100ml): 1.4±0.3
	  • T4 (ug/100ml): 10.1± 2.3
	  • T3 (ng/100ml): 134 ± 32
	  • TBG (mg/100ml): 2.14 ±0.59
	• Thyroid hormone parameters at day 10 of induction therapy) (mean ± SD)
	  • TSH (mcU/100ml): 1.5±1.1
	  • FT4 (ng/100ml): 1.0±0.3
	  • T4 (ug/100ml): 6.16±2.3
	  • T3 (ng/100ml): 69±12
	  • TBG (mg/100ml): 1.61±0.19
	• Thyroid hormone parameters at day 28 of induction therapy (mean ± SD)
	  • TSH (mcU/100ml): 2.3±1.7
	  • FT4 (ng/100ml): 0.7±0.2
	  • T4 (ug/100ml): 3.96± 0.97
	  • T3 (ng/100ml): 57±21
	  • TBG (mg/100ml): 0.79±0.27
	• Thyroid hormone parameters at day 35 of induction therapy (mean ± SD)
	  • TSH (mcU/100ml): 2.7±1.5
	  • FT4 (ng/100ml): 1.1±0.1
	  • T4 (ug/100ml): 5.64± 1.41
	  • T3 (ng/100ml): 88±32
	  • TBG (mg/100ml): 1.22±0.44
	• Thyroid hormone parameters at day 1 of intensification (mean ± SD)
	  • TSH (mcU/100ml): 2.4±1.1
	  • FT4 (ng/100ml): 1.4±0.2
	  • T4 (ug/100ml): 9.03± 1.8
	  • T3 (ng/100ml): 180±26
	  • TBG (mg/100ml): 1.86±0.50
	• Thyroid hormone parameters at day 10 of intensification (mean ± SD)
	  • TSH (mcU/100ml): 1.9±1.1
	  • FT4 (ng/100ml): 1.4±0.12
	  • T4 (ug/100ml): 8.06 ± 1.4
	  • T3 (ng/100ml): 107±27
	  • TBG (mg/100ml): 1.51±0.28
	• Thyroid hormone parameters at day 16 of intensification (mean ± SD)
	  • TSH (mcU/100ml): 2.2±1.3
	  • FT4 (ng/100ml): 1.3±0.18
	  • T4 (ug/100ml): 7.07± 1.9
	  • T3 (ng/100ml): 93±40
	  • TBG (mg/100ml): 1.13±0.45
	• Thyroid hormone parameters at day 22 of intensification (mean ± SD)
	  • TSH (mcU/100ml): 3.2±1.9
	  • FT4 (ng/100ml): 1.5±0.3
	  • T4 (ug/100ml): 9.34± 2.29
	  • T3 (ng/100ml): 143±31
	  • TBG (mg/100ml): 1.31±0.36

Study characteristics

Outcomes

Change in thyroid hormone parameters:

- Day 1 versus day 28 of induction therapy (mean difference)
  - TSH (mcU/100ml): -0.8 (not significant)
  - FT4 (ng/100ml): -0.7 (p<0.001)
  - T4 (ug/100ml): -6.14 (p<0.001)
  - T3 (ng/100ml): -77 (p<0.001)
  - TBG (mg/100ml): -1.35 (p<0.001)
- Day 1 versus day 35 of induction therapy (mean difference)
  - TSH (mcU/100ml): -0.4 (significance level nm)
  - FT4 (ng/100ml): -0.3 (significance level nm)
  - T4 (ug/100ml): -4.46 (significance level nm)
  - T3 (ng/100ml): -46 (significance level nm)
  - TBG (mg/100ml): -0.92 (significance level nm)
- Day 1 versus day 16 of intensification (mean difference)
  - TSH (mcU/100ml): -0.2 (not significant)
  - FT4 (ng/100ml): -0.1 (not significant)
  - T4 (ug/100ml): -0.8 (not significant)
  - T3 (ng/100ml): -87 (p<0.01)
  - TBG (mg/100ml): -0.73 (p<0.05)
- Day 1 versus day 22 of intensification (mean difference)
  - TSH (mcU/100ml): 0.8 (significance level nm)
  - FT4 (ng/100ml): 0.1 (significance level nm)
  - T4 (ug/100ml): 0.31 (significance level nm)
  - T3 (ng/100ml): -37 (significance level nm)
  - TBG (mg/100ml): -0.55 (significance level nm)

On day 28 of induction therapy total T4 decreased by 61%, total T3 decrease by 53%, FT4 decreased by 51% and TBG decreased by 63%. On day 28 of the induction therapy 9 of the 9 patients (100 %) had total T4, total T3 and TBG level below the lower limit of normal. On day 35 after withdrawal of L-asparaginase and during tapering of prednisone all thyroid parameters reverted towards normal. There was no significant change in TSH level during the study.

Change in anti-thyroid antibodies: nm

Multivariable risk factor analyses: no

Notes

Partial overlap with other included studies: not likely
Details of funding sources: no funding details
Declaration of interest primary investigators: nm

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Original cohort not described
Complete outcome assessment/ follow-up (attrition bias)	Low risk	9/9 (100%) during induction; 7/9 (77.8%) during intensification, however no further treatment in these 2 children
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used

Study characteristics		
Well-defined study group (reporting bias)	High risk	Protocol described, actually received cumulative dose not mentioned. In- and exclusion criteria described. 7/9 patients had normal parameters at start, pre-existing thyroid disease was not clearly described
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up reported
Well-defined outcome (reporting bias)	Low risk	Assay mentioned; % of patients below normal described

Heidemann et al. (1981)

Study characteristics	
Methods	Study design: prospective cohort study Time period: 1980 Setting: single center, Germany Inclusion criteria study: acute lymphoblastic leukemia (ALL) Exclusion criteria study: nm Control group (general pediatric population or other) available: no control group
Patients	Original cohort n= nm Study group of interest n= 14 Patients with a thyroid function test: before treatment n= 14, after L-asparaginase for 3 weeks n= 14, 2-3 weeks after L-asparaginase n= 13 (93%) Age at time of primary cancer diagnosis: range 9 months – 18 years Sex: nm Type of malignancy: primary disease acute lymphoblastic leukemia Pre-existing thyroid disease: all thyroid values were normal before treatment Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): nm Renal failure: nm
Interventions	Previous antineoplastic therapy: no Name treatment protocol: modified protocol according to the Berlin study group Systemic antineoplastic therapy (actual received cumulative dose not reported but according to protocol patients should have received the following agents): • L-asparaginase 200 U/kg/day for 3 weeks (cumulative 4200 U/kg) • Prednisone 60 mg/m^2/day for 4 weeks (cumulative 1680 mg/m^2) • Daunorubicin (25mg/m^2/week) during 4 weeks (100 mg/m^2) • Vincristine (1.5mg/m^2/week) during 4 weeks (6 mg/m^2) Stem cell transplantation: no Theranostics: no Other treatment interventions: no surgery or radiotherapy Other medication: no Use of steroids: prednisone 60 mg/m^2 for 4 weeks followed by gradual reduction within 1-2 weeks, cumulative dose or tempering schedule not mentioned

Study characteristics	
Outcomes	Number of blood samples including thyroid hormone parameters: Before treatment: n= 14 After systemic antineoplastic therapy including L-asparaginase for 3 weeks: n= 14 1-2 weeks after antineoplastic therapy including L-asparaginase with prednisone tempering schedule: n= 13 Assay type for the different thyroid hormone parameters: • TSH: RIA-mat-TSH-Kit, Byk-Mailinckrodt • FT4: free T4-RIA-Immunophase-Kit, Corning • T4: T4-RIA-Kit, Amersham-Buchler • T3: RIA-gnost-T3-Kit, Behringwerke • TBG: RIA-gnost-TBG-Kit, Behringwerke For concentrations within the euthyroid range the intra assay coefficients of variation were: • TSH: ± 14.0% • FT4: ± 7.4%3 • T4: ± 2.7% • T3: ± 5.0% • TBG: ± 4.5% Reference values thyroid hormone parameters: normal range (not reported if adjusted for age): • TSH: <5 (uU/ml) • FT4: 1.0-2.3 (ng/100ml) • T4: 4.7-13.2 (ug/100ml) • T3: 0.47-2.0 (ng/ml) • TBG: 24.1±6.5 (mean±SD) (ug/ml) Blood sample taken from a central venous catheter containing heparin: nm Time-points of blood samples: Before treatment During systemic antineoplastic therapy including L-asparaginase for 3 weeks 1-2 weeks after antineoplastic therapy including L-asparaginase with prednisone tempering schedule **Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* Within 3 weeks of systemic antineoplastic therapy 9 out of 14 (64%; 95%CI 39% to 84%) patients had secondary hypothyroidism. TSH levels were normal during the study. Definitions thyroid dysfunction according to study: secondary hypothyroidism defined as FT4 below the reference range and TSH in the normal range. *Percentage of patients who developed thyroid dysfunction:* 0% (95%CI 0% to 22%) of 14 patients developed primary (subclinical or overt) hypothyroidism during chemotherapy for 3 weeks and 0% (95%CI 0% to 23%) of 13 patients developed primary (subclinical or overt) hypothyroidism after 1-2 weeks of chemotherapy consisting of L-asparaginase, prednisone, daunorubicin and vincristine. 0% (95%CI 0% to 22%) of 14 patients developed primary (subclinical or overt) hyperthyroidism during chemotherapy for 3 weeks or after 1-2 weeks of chemotherapy consisting of L-asparaginase, prednisone, daunorubicin and vincristine. 64% (95%CI 39% to 84%), 9 out of 14 patients developed FT4 levels below the reference ranges within 3 weeks of chemotherapy consisting of L-asparaginase, prednisone, daunorubicin and vincristine therapy. In 6 of these 9 patients with FT4 levels below the reference range, the pituitary-thyroid axis was evaluated by TRH stimulation. All 6 patients had a normal TSH response after TRH administration before chemotherapy. During chemotherapy the TSH peak after TRH was absent in all 6 patients suggesting central hypothyroidism. The mean of T4, T3 and TBG were below the reference range during chemotherapy without a significance change in TSH level. It was not possible to calculate the percentage of patients with a low total T4/T3 and TBG because only mean levels were reported. *Thyroid hormone treatment: nm*

Study characteristics	

Outcomes	**Secondary outcomes**
	Thyroid hormone parameters:
	• At diagnosis (mean ± SD)
	  • TSH (uU/ml): 2.4±1.3
	  • FT4 (ng/100ml): 1.77± 0.4
	  • T4 (ug/100ml); 10.7 ± 1.6
	  • T3 (ng/ml): 0.99 ± 0.23
	  • TBG (ug/ml): 29.4±3.6
	• During chemotherapy treatment (mean ± SD) for 3 weeks
	  • TSH (uU/ml): 2.9±1.8
	  • FT4 (ng/100ml): 0.94± 0.35
	  • T4 (ug/100ml); 2.9± 1.8
	  • T3 (ng/ml): 0.35 ± 0.2
	  • TBG (ug/ml): 8.0±3.8
	• 1-2 weeks after chemotherapy treatment (mean ± SD)
	  • TSH (uU/ml): 2.7±1.4
	  • FT4 (ng/100ml): 1.7± 0.28
	  • T4 (ug/100ml); 9.1 ± 1.33
	  • T3 (ng/ml): 1.11 ± 0.4
	  • TBG (ug/ml): 26.7±4.8
	
	Change in thyroid hormone parameters:
	Change in thyroid parameters at diagnosis and during systemic antineoplastic therapy including L-asparaginase for 3 weeks (mean difference)
	• TSH (uU/ml): 0.5 (no information on significance level)
	• FT4 (ng/100ml): -0.83 (p<0.001)
	• T4 (ug/100ml); -7.8 (p<0.001)
	• T3 (ng/ml): -0.64 (p<0.001)
	• TBG (ug/ml):-21.4 (p<0.001)
	Change in thyroid parameters during systemic antineoplastic therapy for 3 weeks and 1-2 weeks after antineoplastic therapy with prednisone tempering schedule (mean difference)
	• TSH (uU/ml): -0.2 (no information on significance level)
	• FT4 (ng/100ml): 0.76 (no information on significance level)
	• T4 (ug/100ml); 6.2 (no information on significance level)
	• T3 (ng/ml): 0.76 (no information on significance level)
	• TBG (ug/ml): 18.7 (no information on significance level)
	Change in thyroid parameters at diagnosis and 1-2 weeks after antineoplastic therapy with prednisone tempering schedule (mean difference)
	• TSH (uU/ml): 0.3 (no information on significance level)
	• FT4 (ng/100ml): -0.07 (no information on significance level)
	• T4 (ug/100ml); -1.6 (no information on significance level)
	• T3 (ng/ml): 0.12 (no information on significance level)
	• TBG (ug/ml): -2.7 (no information on significance level)
	After 3 weeks of systemic antineoplastic therapy total T4 decreased by 73%, total T3 decrease by 65%, free T4 decreased by 47% and TBG decreased by 73%. One week after the last prednisone dose and 2 to 3 weeks after the last L-asparaginase injection all values were normal and remained in the euthyroid range. TSH levels
	remained within the reference level throughout the study.
	
	Change in anti-thyroid antibodies: nm
	
	Multivariable risk factor analyses: no

Notes	Partial overlap with other included studies: not likely Details of funding sources: no funding details Declaration of interest primary investigators: nm

Study characteristics		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Representative study group (selection bias)	Unclear risk	Original cohort not described
Complete outcome assessment/ follow-up (attrition bias)	Low risk	14/14 (100%); 13/14 (92.6%)
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used
Well-defined study group (reporting bias)	High risk	Protocol described, actually received cumulative dosage not described. Inclusion criteria mentioned. Exclusion criteria not described. All patients had normal thyroid parameters at start.
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up 2-3 weeks after L-asparaginase
Well-defined outcome (reporting bias)	Low risk	Assay and definition mentioned

Narayanan et al. (2013)

Study characteristics	
Methods	Study design: cross-sectional study Time period: January 2011 to June 2012 Setting: single center, India Inclusion criteria study: children <18 yrs with CML and receiving imatinib > 6 months Exclusion criteria study: accelerated/blast phase of disease, height for age standard deviate score < -2 prior to imatinib, co-existing liver and kidney disease, poor compliance. Control group (general pediatric population or other) available: no control group
Patients	Original cohort: n=18 Study group of interest n= 18 Patients with a thyroid function test n= 18 Age at time of primary cancer diagnosis: median age 10 years (range 4.5-12 years) Median age at study enrolment: 12.9 years (range 6.5-17 years) Sex: 12 boys (67%), 6 girls (33%) Type of malignancy: chronic myelogenous leukemia Pre-existing thyroid disease: normal thyroid function at study entry Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): 2/18 (11%) underweight, no further information provided Renal failure: no
Interventions	Previous antineoplastic therapy: nm, treatment > 6 months with imatinib at study entry Name treatment protocol: nm Systemic antineoplastic therapy: imatinib mean dose 314 mg/m^2/day (SD 56 mg), mean duration of imatinib therapy was 43.7 months (SD 32.8 months) Stem cell transplantation: no Theranostics: no Other treatment interventions: nm Other medication: nm Use of steroids: nm
Outcomes	Number of blood samples including thyroid hormone parameters n= 18 (all patients at entry study) Assay type for the different thyroid hormone parameters: immuno analyzer (Roche diagnostics) Reference values thyroid hormone parameters: nm Blood sample taken from a central venous catheter containing heparin: nm Time-points of blood samples: thyroid function only at entry of study, the mean duration of Imatinib was 43.7 months SD +/- 32.8 months (range 6-89 months) **Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* 0/18 (0%; 95%CI 0% to 18%) hyperthyroidism, 0/18 (0%; 95%CI 0% to 18%) hypothyroidism Definitions thyroid dysfunction according to study: nm *Percentage of patients who developed thyroid dysfunction:* 0% (95%CI 0% to 18%) primary (subclinical or overt) hypothyroidism 0% (95%CI 0% to 18%) primary (subclinical or overt) hyperthyroidism 0% (95%CI 0% to 18%) ESS or central hypothyroidism. No information about aberrant thyroid parameters. However, all patients were euthyroid. *Thyroid hormone treatment:* no (0%; 95%CI 0% to 18%)

Study characteristics		
Outcomes	**Secondary outcomes** *Thyroid hormone parameters:* At diagnosis: nm Thyroid hormone parameters at entry of study during treatment with Imatinib: TSH, T4, T3 normal Mean IGF-1 z-score in pubertal patients -2.41 SD and in pre-pubertal group -0.156 SD *Change in thyroid hormone parameters:* nm *Change in anti-thyroid antibodies:* nm *Multivariable risk factor analyses:* no	
Notes	Partial overlap with other included studies: yes, potentially same cohort as Walia et al. Details of funding sources: funded by Glivec and The Max foundation Declaration of interest primary investigators: nothing to declare	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Representative study group (selection bias)	Low risk	All eligible patients without growth retardation included
Complete outcome assessment/ follow-up (attrition bias)	Low risk	Thyroid function measured in all patients
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used
Well-defined study group (reporting bias)	Low risk	Normal thyroid function at study entry
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up reported
Well-defined outcome (reporting bias)	High risk	No definition of thyroid dysfunction available.

Van Santen et al. (2005)

Study characteristics	
Methods	Study design: prospective cohort study Time period: March to June 2003 Setting: single center, the Netherlands Inclusion criteria study: all patients admitted to the pediatric oncology ward for chemotherapy Exclusion criteria study: brain tumor, neuroblastoma, history of radiotherapy in head and neck region, use of dexamethasone before first blood withdrawal Control group general pediatric population or other available: no control group
Patients	Original cohort: n= 51 Study group of interest: n= 19 Patients with a thyroid function test: n= 19 Age at time of primary cancer diagnosis: median 11.0 yrs (range 2-16 years) Sex: 12 boys (63%), 7 girls (37%) Type of malignancy: primary disease or recurrence: osteosarcoma (n= 4), Ewing sarcoma (n= 2), rhabdomyosarcoma (n= 1), ALL (n= 11), glioma of the spinal cord (n= 1), primary disease or recurrence nm Pre-existing thyroid disease: nm Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): vital parameters were assessed but nm Renal failure: no renal failure
Interventions	Previous antineoplastic therapy: nm Name treatment protocol: nm Systemic antineoplastic therapy: alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids. No further information available. Stem cell transplantation: no Theranostics: no Other treatment interventions: nm Other medication: nm Use of steroids: in 85% of chemotherapy courses dexamethasone 6–15 mg/m^2 was administered
Outcomes	Number of blood samples including thyroid hormone parameters: n= 123 For analysis of changes in hormone concentrations, only paired blood samples, before and after chemotherapy were used. Assay type for the different thyroid hormone parameters: T4, T3, rT3 and TGAb, TBG by radioimmunoassay, TSH fluoroimmunoassay, TPOAb luminescence immunoassay, IGF-1 nm. Reference values thyroid hormone parameters (age adjusted reference values nm): • T4: 70-150 nmol/L • T3: 1.3-2.7 nmol/L • rT3: 0.11-0.44 nmol/L • TBG: 200-650 nmol/ml • TSH: 0.4-4.0 mU/L • IGF-1: nmol/L age and sex specific* • TPOAb nm, TGAb nm Blood sample taken from a central venous catheter containing heparin: yes, free T4 measurements were not used because of possible interaction with heparin use in central venous catheters Time-points of blood samples: on day 0 (before course of chemotherapy: at least 7 days prior to blood sample no chemotherapy) and day ≥1 (after course of chemotherapy)

Study characteristics	
Outcomes	**Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* ESS in 2.1-21.7% (95%CI 0% to 11% and 95%CI 12% to 36%, respectively) of courses depending on the definition of ESS (2.1% if ESS defined as a combination of low to normal TSH with low T3 and low T4 and high rT3 or 21.7% if ESS defined as low T3 and low T4 or isolated low T3) ESS developed in 1 to 8 of the 19 patients (5%; 95%CI 1% to 25% and 42%; 95%CI 23% to 64%, respectively) defined according to study as (low T3 + low T4 + low–normal TSH + high rT3 or low T3 + low T4 or a low T3 only) *Percentage of patients who developed thyroid dysfunction:* No information about percentage of patients with primary (subclinical or overt) hypothyroidism because only the mean TSH level was reported. However, 1 out of 19 patients developed in one course an elevated TSH level (but this was accompanied by an elevated T3 level) (5%; 95%CI 1% to 25%). 1 to 8 of the 19 (5%; 95%CI 1% to 25% and 42%; 95%CI 23% to 64%, respectively) patients developed ESS or central hypothyroidism dependent on the definition used. The prevalence of ESS solely based on low thyroid hormones without an adequate TSH response and an increased rT3 was not separately reported In 10/46 (21.7%; 95%CI 12% to 36%) of courses ESS or central hypothyroidism occurred. The timing of development of ESS after the course of chemotherapy was reported as > day 1. *Thyroid hormone treatment:* no (0%; 95%CI 0% t0 17%) **Secondary outcomes** *Thyroid hormone parameters:* At baseline, in 28/46 (61%) courses, at least one thyroid function determinant was already aberrant. Mean concentration on day 0 (before course of chemotherapy at least 7 days prior to blood sample no chemotherapy) • TSH: 1.45 mU/l • T4: 115 nmol/l • T3: 2.4 nmol/l • rT3: 0.18 nmol/l • TBG: 398 nmol/l • IGF-1: 31 nmol/l Mean concentration on day ≥1 (after course of chemotherapy): • TSH: 0.77 mU/l • T4: 111 nmol/l • T3: 1.6 nmol/l • rT3: 0.39 nmol/l • TBG: 425 nmol/l • IGF-1: 28 nmol/l *Change in thyroid parameters:* Before and after one course of chemotherapy: TSH: decrease to 53% of baseline level (p≤0.0001) T4: not significantly affected, no further information provided T3: decrease to 67% of the baseline level (p≤0.0001) rT3: increased to 217% of baseline level (p≤0.0001) TBG: not significantly affected, no further information provided IGF-1: not significantly affected, no further information provided *Change in anti-thyroid antibodies*: nm, none of the 19 patients had elevated concentrations of anti-TPO or anti –TG at baseline (extra information about timing of measurement was obtained from the first author of this study)

Study characteristics	
Outcomes	*Multivariable risk factor analyses:* Difference in the geometric mean of the concentration of day ≥1 and the log of the concentration of day 0 per course per patient for the different subgroups of chemotherapy, with or without dexamethasone and divided by cancer type (solid tumor versus leukemia). Type of cancer had no influence on thyroid hormone parameters during treatment with chemotherapy (no further information provided) All courses in which dexamethasone was administered (n = 39) T3 alkylating agents β - 2.246 (CI -1.06 to -0.59, p<0.001) T3 antineoplastic agents β -0.447 (CI -0.29 to -0.02, p=0.027) T3 antimetabolites β -2.808 (CI -1.26 to -0.68, p<0.001) T3 Cisplatin β -1.968 (CI -1.1 to -0.54, p <0.001) T3 topoisomerase inhibitors β -0.385 (CI 0.22 to -0.05, p=0.002) TBG topoisomerase inhibitors β -0.478 (CI -0.16 to -0.22, p=0.012) All courses without dexamethasone (n = 7) rT3 Asparaginase β -0.936 (CI -1.52 to -0.92, p<0.001)
Notes	Partial overlap with other included studies: no Details of funding sources: no funding details Declaration of interest primary investigators: nm

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	Original cohort described. Out of 51 patients 11 were not eligible because of risk factors for thyroid dysfunction (radiotherapy (n= 3), MIBG (n= 3), brain tumor (n = 5)). Not all the remaining patients were included as a result of: lack of informed consent (n = 12), only one blood sample obtained (n = 3), no admission for chemotherapy (n = 2), later excluded because blood test were only eligible after chemotherapy (n = 2), because of the use of dexamethasone at home (n = 2). Less than 90% of the original eligible cohort included.
Complete outcome assessment/follow-up (attrition bias)	Low risk	In all patients thyroid function measured before and after chemotherapy.
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used
Confounding (adjustment for other factors: yes/no)	High risk	Age, prior thyroid dysfunction, genetic syndromes, familial history not in multivariate analysis
Well-defined study group (reporting bias)	High risk	Inclusion and exclusion criteria described. Type of systemic therapy described. No information about (cumulative) dose of systemic antineoplastic therapy. Pre-existing thyroid disease not mentioned.
Well-defined follow-up (reporting bias)	High risk	Exact timing of blood sample after chemotherapy unclear
Well-defined outcome (reporting bias)	Low risk	Assay and definition provided
Well-defined analyses	Low risk	Linear regression analyses to assess effect of cytotoxic agents and to assess effect of solid tumors versus leukemia.

Walia et al. (2020)

Study characteristics	
Methods	Study design: prospective cohort study Time period: January 2013 to June 2014 Setting: single center, India Inclusion criteria study: patients with CML < 21 years receiving Imatinib for > 6 months with growth retardation, hematological and molecular remission Exclusion criteria study: coexisting systemic illness (kidney/liver disease, celiac disease), poor compliance with Imatinib, common causes of short stature including malnutrition, hypothyroidism and celiac disease Control group general pediatric population or other available: no control group
Patients	Original cohort: n=20 Study group of interest: n= 20 Patients with a thyroid function test: n= 20 Age at time of primary cancer diagnosis: median 10 years (range 4.5-12.5), median age at inclusion 14.7 years (range 8-20.75). Sex: 15 boys (75%), 5 girls (25%) Type of malignancy: chronic myelogenous leukemia Pre-existing thyroid disease: nm Familial history of thyroid disease: nm Clinical condition at blood measurement (vital parameters, weight (SDS)): nm Renal failure: no, renal function tests were in range
Interventions	Previous antineoplastic therapy: nm, at study entry imatinib for > 6 months Name treatment protocol: nm Systemic antineoplastic therapy: Imatinib, median cumulative dose until inclusion 632 mg/m^2 (range 70.4-1,424.8 mg/m^2). The median duration of treatment was 6.11 years (range 0.5–10 years). No information provided on imatinib dose during this study. Stem cell transplantation: no Theranostics: nm Other treatment interventions: nm Other medication: nm Use of steroids: nm
Outcomes	Number of blood samples including thyroid hormone parameters: nm Assay type for the different thyroid hormone parameters: electro chemiluminescence assay (Roche diagnostics) Reference values thyroid hormone parameters: nm Blood sample taken from a central venous catheter containing heparin: nm Time-points of blood samples: entry of study (median duration of imatinib at entry of study 6.11 years) and 3 months after entry of study. **Primary outcomes** *Percentage of patients who developed thyroid dysfunction:* At study entry: 2 out of 20 (10%; 95%CI 3% to 30%) patients had subclinical hypothyroidism. 18/20 (90%; 95%CI 70% to 97%) patients were euthyroid, but clinical hypothyroidism was an exclusion criterium for the study. Definitions according to study: subclinical hypothyroidism defined as elevated TSH, normal FT4 and T3 (reference values not mentioned). *Percentage of patients who developed thyroid dysfunction:* 2 out of 20 (10%; 95%CI 3% to 30%) developed primary subclinical hypothyroidism 0% (95%CI 0% to 16%) primary (subclinical or overt) hyperthyroidism 0% (95%CI 0% to 16%) ESS or central hypothyroidism: No information about aberrant thyroid hormone parameters. However, all patients except the 2 patients with subclinical hypothyroidism were euthyroid. Thyroid hormone treatment: yes, in 2 out of 20 patients (10%; 95%CI 3% to 30%)

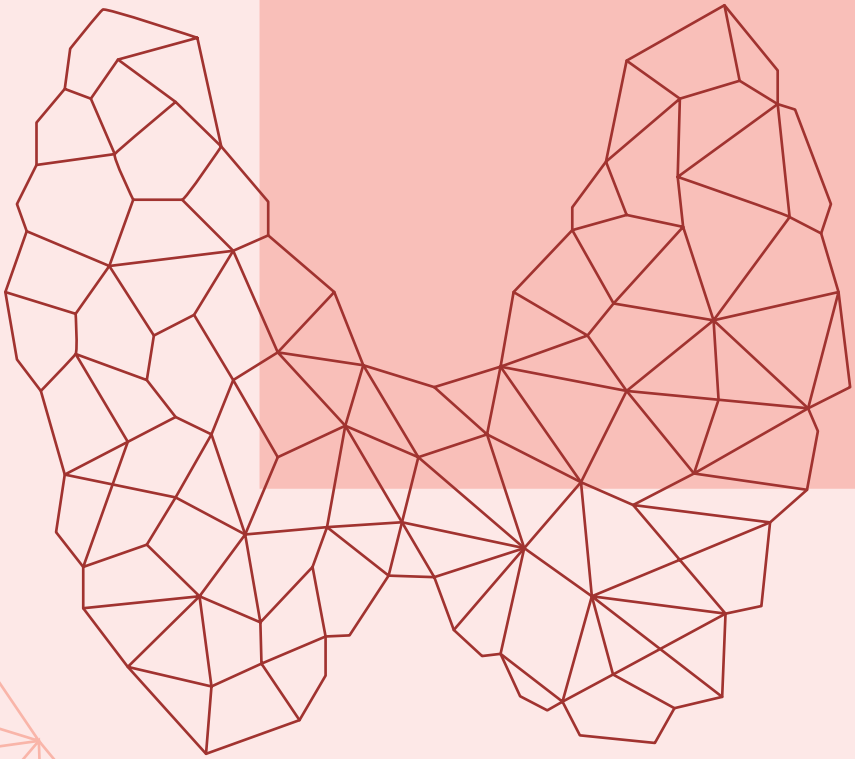
Study characteristics	
Outcomes	**Secondary outcomes** *Thyroid hormone parameters:* nm *Change of thyroid hormone parameters:* nm *Change in anti-thyroid antibodies*: nm *Multivariable risk factor analyses:* no
Notes	Partial overlap with other included studies: yes, potentially same cohort as Narayanan et al. Details of funding sources: no funding details Declaration of interest primary investigators: nothing to declare Clinical hypothyroidism was an exclusion criterion for this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	All eligible patients without growth retardation and hypothyroidism included.
Complete outcome assessment/follow-up (attrition bias)	Low risk	All patients in cohort were screened for thyroid dysfunction on entry of the study and at 3 months follow up
Outcome assessors blinded to investigated determinant (detection bias)	Low risk	Outcome measurement is not likely to be influenced by lack of blinding; laboratory test was used
Well-defined study group (reporting bias)	Low risk	Study group defined, and systemic therapy reported (including cumulative dose until inclusion/thyroid function test)
Well-defined follow-up (reporting bias)	Low risk	Duration of follow-up reported
Well-defined outcome (reporting bias)	Low risk	Assay and definition mentioned

Abbreviations: ALL, acute lymphoblastic leukaemia; CML, chronic myelogenous leukemia; ESS, euthyroid sick syndrome; TKIs, tyrosine kinase inhibitors; TSH, thyroid stimulating hormone; free T4, FT4; total T4, T4; total T3, T3; thyroxine binding globulin, TBG; reverse T3, rT3. nm; not mentioned

*Rikken B, van Doorn J, Ringeling A, Van den Brande JL, Massa G, Wit JM. Plasma levels of insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein-3 in the evaluation of childhood growth hormone deficiency. Horm Res. 1998 Sep;50(3):166-76



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Thyroid function parameters in the first three months after starting treatment in children with newly diagnosed cancer

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Submitted

Abstract

Background

Thyroid dysfunction during childhood may affect daily energy, growth, BMI and bone development. Thyroid dysfunction (hypo- or hyperthyroidism) may occur during childhood cancer treatment, although its prevalence is unknown. Thyroid function parameters may also change as adaptation during illness, called the euthyroid sick syndrome (ESS). In children with central hypothyroidism, a decline in FT4 of >20% has been shown to be clinically relevant. We aimed to quantify the percentage, severity and risk factors of changing thyroid function parameters in the first three months of childhood cancer treatment.

Methods

In 284 children with newly diagnosed cancer, a prospective evaluation was performed of thyroid function parameters at diagnosis and three months after starting treatment.

Results

Subclinical hypothyroidism was found in 8.2% and 2.9% and subclinical hyperthyroidism in 3.6% and in 0.7%, at diagnosis and after three months, respectively. ESS was present in 1.5% of children after three months. In 28% of children, FT4 concentration decreased with ≥20%.

Conclusions

Children with cancer are at low risk to develop hypo- or hyperthyroidism in the first three months after starting treatment but may develop significant decline in FT4 concentrations. Future studies are needed to investigate the clinical consequences thereof.

Introduction

Thyroid hormones are essential during childhood for adequate mental development, linear growth, bone development and metabolic regulation (1,2). Signs and symptoms of thyroid dysfunction can be fatigue, overweight, declining linear growth, mental retardation in the young, constipation (hypothyroidism) or tachycardia, growth acceleration, and emotional imbalances. In children with cancer, thyroid dysfunction may present with symptoms that are regularly observed during childhood cancer treatment and therefore may be overlooked.

The thyroid gland can be damaged by the tumor itself, by chemotherapy (e.g. busulphan), by radiation exposure or immunotherapy resulting in thyroidal hypo- or hyperthyroidism (3). In several small studies, the prevalence of primary hypothyroidism during cancer treatment varied between 0-18% (4–9). Next to damage of the thyroid gland, thyroid hormone metabolism in children with cancer may also be distorted due to damage of the hypothalamic-pituitary region as a consequence of a brain tumor or cranial irradiation (central hypothyroidism). Moreover, specific drugs may influence thyroid function parameters without actual thyroid- or pituitary gland damage, as is seen for example after administration of asparaginase with a decrease in thyroxine binding globulin (TBG) concentration (8) or after administration of corticosteroids with lowered thyroid stimulating hormone (TSH), triiodothyronine (T3) and TBG concentrations and increased reverse T3 (rT3) concentrations (8,9).

Lastly, thyroid hormone metabolism may change during childhood cancer treatment as a consequence of an adaptive mechanism during illness, called the 'euthyroid sick syndrome' (ESS) (10). In this case, concentrations of thyroxine (T4) and T3 decrease, due to two mechanisms: (1) downregulation of hypothalamic TRH secretion and (2) changed activity of the liver deiodinases resulting in decreased conversion of T4 to T3 and increased conversion of T4 into rT3 (11). In children, EES has been described during severe illness and anorexia, and is thus not associated with the underlying disease per se, but with its severity (12). For the presence of ESS, different definitions are used and in the few small studies that have been done, the prevalence of ESS during childhood cancer treatment, depending on its definition, varied between 0-100% (4–9). When children with cancer have hypo- or hyperthyroidism due to pituitary or thyroidal damage, this is considered a pathophysiological state and needs treatment. However, in case of acute illness, changes in thyroid function parameters (ESS) are considered as "physiological" and may even be protective. Therefore, it is not recommended to treat children who develop a low thyroid hormone concentration during acute illness with thyroid hormone (13).

In children who develop mild central hypothyroidism after treatment for a brain tumor, a decline in FT4 of >20%, even within reference ranges, was shown to be clinically relevant (14). Although mild central hypothyroidism may not be comparable with ESS, it may be hypothesized that a prolonged decline of the FT4 concentration of >20% in children who are not acutely but "chronically" ill (such as during a two-year treatment period for childhood

leukemia) does impact bone, muscle and BMI development or daily energy (15). This has thus far not been studied. Because there is lack of studies reporting on thyroid hormone metabolism in large cohorts of children treated with cancer and thus uncertainty on the percentage, severity, and risk factors of changing thyroid function parameters in children during treatment for cancer, we performed a prospective observational cohort study.

Methods and patients

Patients

During a two-year period (January 2020 to December 2021), thyroid function parameters were measured at diagnosis and three months after starting chemotherapy or radiotherapy, in newly diagnosed children (<21 years) with leukemia, lymphoma, sarcoma, or a non-pituitary brain tumor, at the Princess Máxima Center for Pediatric Oncology. Children known with previous thyroid disease, Down syndrome, a thyroid cancer predisposition syndrome, a history of neck irradiation or meta-iodobenzylguanidine (MIBG) treatment or a brain tumor in the hypothalamic-pituitary region were excluded.

Ethics

The research protocol was approved by the medical ethical committee of the Princess Máxima Center (NedMec NL69960.041.19). For ethical reasons, blood samples for the study were only taken if, simultaneously, sampling for clinical reasons was performed. Informed consent was obtained of all children and/or their parents and/or legal representatives.

Data collection

Thyroid function parameters TSH, FT4 and rT3 were measured at time of diagnosis (range ±35 days from diagnosis) and three months later (range 60-160 days after diagnosis). Anti-thyreoperoxidase (anti-TPO) concentrations were measured at diagnosis. Blood results were interpreted by the treating physician. In case of aberrant thyroid function tests (FT4 < reference range or TSH >10mU/L) children were referred to the pediatric endocrinologist and treated if needed.

Clinical data on anthropometrics (height, weight, body mass index (BMI)) and general well-being (body temperature, vomiting, nutritional status, and overall physical condition) were extracted from patients' electronic medical records on the day of blood sampling. Physical condition was scored as "good" (no complaints), "medium" (moderate complaints, 'not feeling well' or 'feeling tired') or "poor" (severe complaints or 'feeling ill') as reported by the health care provider in the electronic patient chart.

Laboratory assays

A description of the laboratory assays is shown in appendix I.

Definitions and statistics

Thyroidal hypothyroidism was defined as present if the plasma TSH concentration was above the reference range (5.0 mU/L) combined with a plasma FT4 concentration below the reference range. Thyroidal subclinical hypothyroidism was defined as present if the plasma TSH concentration was above the reference range (5.0 mU/L) combined with a plasma FT4 concentration within the reference range. Subclinical hyperthyroidism was defined as present if the plasma TSH concentration was below the reference range (5.0 mU/L) with a plasma FT4 concentration within the reference range. Central hypothyroidism was defined as present if the plasma FT4 concentration was below the reference range with non-elevated TSH concentration in combination with non-elevated rT3 concentration. ESS was defined as present if the plasma FT4 concentration was below the reference range with a non-elevated TSH concentration in combination with an elevated rT3 concentration.

Data are presented as mean ±SD or median (range) for continuous data variables, depending on the distribution. Data are presented as percentages for categorical variables. Differences between groups were examined by unpaired Student's t tests for normally distributed continuous data and Mann-Whitney U tests for continuous data with a skewed distribution. For categorical data, χ^2 tests or Fisher's exact tests (if the assumptions for chi-square were violated) were used. Between time point differences were evaluated by paired Student's t test for continuous data with a normal distribution, Wilcoxon matched-pair signed rank test for continuous data with a skewed distribution. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro-Wilk's test were used. For statistical analysis of changes in thyroid hormone concentrations, only paired blood samples per patient were used. The Pearson correlation coefficient was estimated to study the strength of a linear association between two continuous variables.

Multivariable logistic regression analyses were used to estimate the association between covariates and two outcomes: elevated rT3 concentrations and a ≥20% decline in FT4 concentrations. Independent variables included in the multivariable logistic regression were selected by estimating the univariate model and by considering the clinical relevance of each variable. Therefore, in the final regression model, not only variables that were significant in the univariate analysis were included, but also factors that were clinically relevant. Odds ratios (ORs) along with 95% Cis are reported. Analyses were performed by using SPSS version 27.0. P-values of <0.05 were considered as statistically significant.

Results

General patient characteristics

Of 519 children assessed for eligibility, 284 were included (figure 1). Of the included children, 141 (50%) were diagnosed with leukemia, 74 (26%) with lymphoma, 38 (13%) with sarcoma, and 31 (11%) with a brain tumor (table 1). Median age at diagnosis was 9.4 years (range 0.0-19 years) and 127/284 (45%) children were female.

Figure 1. Inclusion Flowchart THYRO-Dynamics study

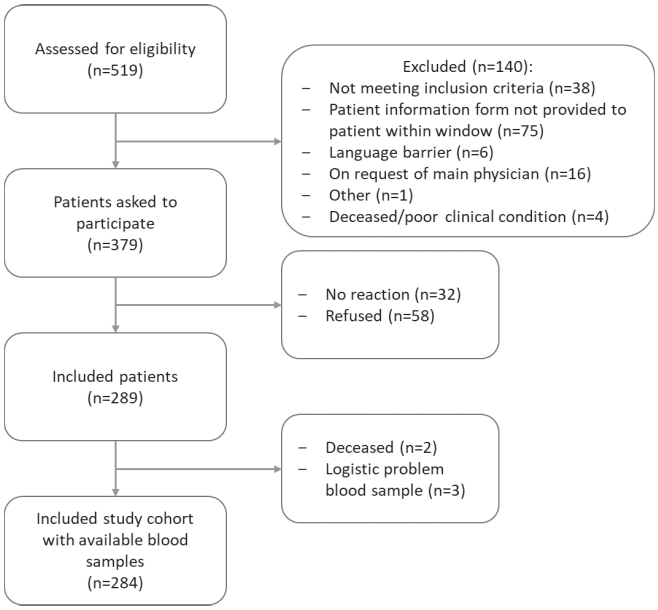


Table 1. Baseline patient characteristics (n=284)

Characteristics	
Age at diagnosis (yrs) (median, range)	9.4 (0.0-19.7)
# of females (%)	127/284 (45%)
Diagnosis	
Leukemia	141 (50%)
ALL	118 (42%)
AML	20 (7.0%)
CML	2 (0.7%)
Other	1 (0.4%)
Lymphoma	74 (26%)
Hodgkin lymphoma	35 (12%)
B-NHL/B-ALL	25 (8.8%)
Non-B NHL	12 (4.2%)
ALCL	2 (0.7%)
Sarcoma	38 (13%)
Bone tumor (osteosarcoma/Ewing sarcoma)	22 (7.7%)
Rhabdomyosarcoma	11 (3.9%)
Non-rhabdomyosarcoma	4 (1.4%)
Other	1 (0.4%)
Brain tumor	31 (11%)
ATRT	1 (0.4%)
Ependymoma	5 (1.8%)
Low grade glioma	3 (1.0%)
High grade glioma	10 (3.5%)
Germ cell tumor	2 (0.7%)
Medulloblastoma	9 (3.2%)
Optic glioma	1 (0.4%)
Physical condition	
At diagnosis	
Good	76 (38%)
Medium	112 (57%)
Poor	10 (5.1%)
Unknown	22
After three months	
Good	186 (69%)
Medium	74 (28%)
Poor	8 (3.0%)
Unknown	8

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; B-NHL, B-cell non-Hodgkin lymphoma; B-ALL, B-cell acute lymphoblastic leukemia; non-B cell non-Hodgkin lymphoma; ALCL, anaplastic large cell lymphoma; ATRT, atypical teratoid rhabdoid tumor

Thyroid function parameters

At diagnosis, TSH and FT4 were both measured in 220 children, of which in 81% (179/220) both were within reference ranges (table 2). Three months after diagnosis, in 91% (252/276) both TSH and FT4 concentrations were found within reference ranges. In two children (1.2%) elevated anti-TPO antibodies were detected, both were euthyroid.

Table 2. Median plasma concentration of thyroid determinants in children with cancer measured at diagnosis and three months after diagnosis

	All children (n=284)			Analysis only of children who had not received corticosteroids or chemotherapy before first measurement (n=202)		
Thyroid hormone determinants	**At diagnosis Concentration mIU/L Median (range) (# samples)**	**Three months after diagnosis Concentration mIU/L Median (range) (# samples)**	**P-value**	**At diagnosis before start of chemotherapy or corticosteroids Concentration mIU/L Median (range) (# samples)**	**Three months after diagnosis Concentration mIU/L Median (range) (# samples)**	**P-value**
TSH (0.30-5.00 mIU/L)	2.00 (0.07-11.0) (n=222)	1.90 (0.31-8.00) (n=276)	0.334	2.30 (0.34-9.40) (n=141)	1.90 (0.31-11.00) (n=199)	<0.001
FT4 (10-22 pmol/L)*	16 (10-29) (n=220)	14 (8-23) (n=276)	<0.001	16 (10-29) (n=139)	14 (8-24) (n=199)	<0.001
rT3 (0.098-0.218 ng/mL)	0.18 (0.09-0.58) (n=148)	0.22 (0.10-2.36) (n=265)	<0.001	0.16 (0.09-0.58) (n=90)	0.22 (0.10-2.26) (n=191)	<0.001

*****Dependent on age: 20 days - 3 years: 12 - 21 pmol/L, 3 - 5 years: 10 – 19 pmol/L, 5 - 19 years: 11 – 20 pmol/L, > 19 years: 10 - 22 pmol/L.
P-value: for analysis of changes in thyroid hormone concentrations, only paired blood samples (diagnosis and three months after diagnosis) were used.

(Subclinical) hypo- and hyperthyroidism

At diagnosis, 8.2% (18/220) of children had subclinical hypothyroidism with a median TSH concentration of 6.30 mIU/L (range 5.00-11.00). In 3.6% (8/220) of children subclinical hyperthyroidism was found (median TSH 0.21 mIU/L (range 0.07-0.34)).

Three months after diagnosis, 2.9% (8/276) of children had subclinical hypothyroidism (median TSH 6.75 mIU/L (range 5.30-11.00)). None of these children required treatment with thyroxine. Two of 276 children (0.7%) had subclinical hyperthyroidism (TSH 0.31-0.33 mIU/L) after three months.

ESS (low FT4 in combination with low to normal TSH with elevated rT3)

At diagnosis none of the children had ESS. After three months, 1.5% (4/265) of children had developed ESS. In 33% (49/148) of children an isolated rT3 elevation was found at diagnosis (median rT3 concentration 0.25 ng/mL (range 0.22-0.58)) which increased to in 50% (133/265) after three months (median 0.27 ng/mL (range 0.22-2.36)). A significant, weak positive correlation was found between the FT4 and the rT3 concentrations three months after diagnosis (r=0.18, 95%CI 0.06-0.29). Children with an isolated elevated rT3 concentration after three months were slightly younger (7.7 compared to 9.6 years), more frequently had a brain tumor (74% versus 48%; p=0.009) and were less often treated with

anthracyclines (65% versus 80%; p=0.006) than those without. No association was found between corticosteroid use <48 hours or physical condition and having an elevated rT3. In a multivariable analysis, brain tumor diagnosis was the only significant risk factor for developing an elevated rT3 concentration three months after diagnosis (OR 3.17, 95% CI 1.19 to 8.41) (table 3).

Table 3. Risk factor analyses

Risk factors associated with ≥20% FT4 decline

Covariate/categories	≥ 20% FT4 decline	
	Univariable OR (95% CI)	**Multivariable OR (95% CI)**
Age at diagnosis, years	0.95 (0.89 to 1.02)	0.97 (0.90 to 1.04)
Administration of antimetabolites	2.59 (0.98 to 6.81)	2.37 (0.78 to 7.18)
Use of corticosteroids <48 hours before thyroid hormone measurement after three months	1.11 (0.27 to 4.55)	1.55 (0.35 to 6.97)
Radiotherapy before thyroid hormone measurement after three months	0.54 (0.11 to 2.67)	0.93 (0.15 to 5.65)

NOTE. Multivariable logistic regression for risk factors of children with a ≥20% FT4 decline from diagnosis to three months after diagnosis (n=38) compared to children without ≥20% FT4 decline from diagnosis to three months after diagnosis (n=98).
Abbreviations: FT4, free thyroxine; OR, odds ratio.

Risk factors associated with elevated rT3 concentrations

Covariate/categories	Elevated rT3 concentrations	
	Univariable OR (95% CI)	**Multivariable OR (95% CI)**
Age at diagnosis, years	0.96 (0.92 to 1.00)	0.97 (0.92 to 1.01)
Brain tumor vs others[a]	3.16 (1.29 to 7.76)	3.17 (1.19 to 8.41)[b]
Physical condition three months after diagnosis Medium/poor vs good	1.54 (0.90 to 2.64)	1.42 (0.80 to 2.53)
Use of corticosteroids <48 hours before thyroid hormone measurement	1.68 (0.67 to 4.20)	1.72 (0.67 to 4.43)
Underweight (<-2 SDS)	0.51 (0.12 to 2.08)	0.57 (0.13 to 2.45)

NOTE. Multivariable logistic regression for risk factors of children with elevated rT3 concentrations three months after diagnosis (n=133) compared to children without elevated rT3 concentrations three months after diagnosis (n=132).
Abbreviations: FT4, free thyroxine; OR, odds ratio; SDS, standard deviation score.
[a]Brain tumor diagnosis versus other diagnoses.
[b]Statistically significant

Central hypothyroidism (low FT4 in combination with low to normal TSH without elevated rT3)

After three months, 1.9% (5/265) of children were suspected of having central hypothyroidism with lowered FT4 (median FT4 8 pmol/L (range 8-9)), non-elevated TSH (median TSH 2.80 mIU/L (range 1.80-4.00)) and non-elevated rT3 concentrations (median 0.17 ng/mL (range 0.11-0.20)). All five had been diagnosed with leukemia at a median age of 5.4 years (range 4.4-13.4). None were started on thyroxine treatment, but thyroid function parameters were followed in time.

Decline of FT4 in time

Overall, the median FT4 concentration declined significantly in three months' time from a median of 16 to 14 pmol/l ($p<0.001$), with no change in TSH ($p=0.334$). Median rT3 concentrations significantly increased (0.18 to 0.22 ng/ml; $p<0.001$) (table 2, figure 2).

At time of diagnosis, 29% (82/284) of children had received corticosteroids <48 hours or chemotherapy before the first measurement. In this group, at diagnosis, a lower median TSH and a higher median FT4 concentration were found when compared to those who had not (TSH 1.20 (range 0.07-11.00) versus 2.30 mIU/L (range 0.34-9.40); $p<0.001$ and FT4 17 (range 11-28) versus 16 pmol/L (range 10-29); $p=0.017$). In the 22 children who had received corticosteroids <48 hours before the blood withdrawal after three months, no differences were found in either TSH or FT4 concentration. (appendix II).

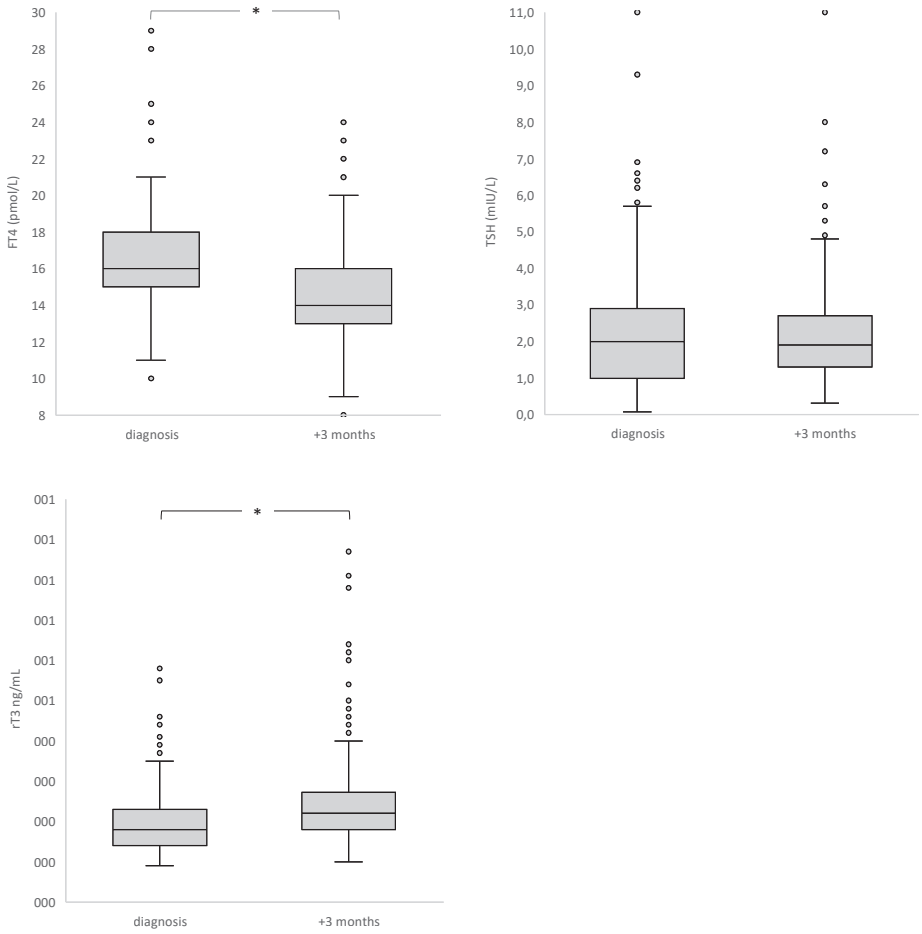
Due to the differences found in median plasma TSH and FT4 concentration in the children who had already received corticosteroids <48 hours or chemotherapy before their first thyroid hormone measurement at diagnosis, these children were excluded from the analysis of the changes in thyroid function in time. TSH and FT4 concentrations were found to significantly decline in three months' time (median TSH from 2.35 to 1.90 mIU/L; $p<0.001$, median FT4 from 16 to 14 pmol/L; $p<0.001$). Median rT3 concentrations increased significantly (0.16 to 0.22 ng/ml; $p<0.001$) (table 2).

The median overall change in FT4 concentration in children who had not received corticosteroids <48 hours or chemotherapy before the first measurement was -11% (range -47% to +100%). A FT4 decline of ≥10%, ≥20% or ≥30% was found in 41% (69/136), 28% (38/136) and 7.4% (10/136), respectively.

In children with a FT4 decline ≥20%, the median FT4 concentration declined from 17 (range 10-29) to 12 pmol/L (range 8-16), with no change in median TSH and rT3 concentrations. Of these children, 36.1% had an elevated rT3 concentration after three months. Univariate analysis showed that children with a ≥20% FT4 decline had similar age (7.7±5.1 years versus 10.0 ± 5.7; $p=0.200$), received more often antimetabolites (84% versus 67%; $p=0.049$)) and showed a trend towards more frequent treatment with vinca-alkaloids (92% versus 80%;

p=0.081) compared to those with no or a decline <20%. Multivariable analysis however did not show risk factors for a ≥20% FT4 decline (table 3). No clinical significant effect of a ≥20% FT4 decline from baseline was found on BMI SDS or linear growth.

Figure 2. Median concentrations and interquartile ranges of TSH, FT4 and rT3 in children at diagnosis and three months after diagnosis (n=284)



Radiotherapy

Radiotherapy had been given to 21 (7.4%) children in the three months; in seven possibly including the thyroid gland and in 20 possibly including the hypothalamic-pituitary region in the radiation field. Eighteen of the 21 children were irradiated for a brain tumor of whom seven craniospinal (medulloblastoma n=5 (total dose 54.0 Gray) and ependymoma n=2 (total dose 59.4 Gray)), and 11 cranial (high grade glioma n=10 (total dose 13-60 Gy) and germ cell tumor n=1 (total dose 40.0 Gray)). Three children were irradiated for a sarcoma (2/3 orbit, total dose 45-50 Gray). Median FT4 in children with radiotherapy changed from 15

(range 13-24) to 14 pmol/L (range 8-23) (p=0.034) while median TSH remained unchanged. Revere T3 concentrations after three months were significantly higher in children who had received radiotherapy compared to those who had not (0.28 (range 0.14-0.62) and 0.21 ng/mL (range 0.10-2.36); p=0.015)).

Discussion

In this large prospective study investigating the percentage and severity of thyroid dysfunction in children treated for newly diagnosed cancer, we found a low percentage of (subclinical) hypo- and hyperthyroidism in the first three months after starting treatment, which may be considered reassuring. Also the percentage of children that developed ESS, in this study defined having a lowered FT4, normal TSH and increased rT3, was low. However, in a considerable percentage of children, thyroid function parameters were found to change, with an individual decline of FT4 concentration ≥20% in 28% of children after three months. We did not detect clinical consequences of this change in FT4 in this relative short period of time and future studies are needed with prolonged follow-up.

Based on these results, we suggest that, with the current treatment protocols, surveillance for hypo- and hyperthyroidism is unnecessary at this stage of treatment. However, our results do illustrate that thyroid function parameters can severely change during cancer treatment in children, which may reflect adaptation to an altered metabolic state during illness or may be iatrogenic (16–18).

In ESS, adaptive downregulation of TRH secretion may result in low to normal TSH concentrations with lowered thyroid hormone concentrations. Apart from this, in ESS, alteration of liver deiodinases decreases conversion of T4 to T3 and increases the conversion of T4 to rT3. In case of doubt between central hypothyroidism or ESS, determination of rT3 may be used to differentiate; in true central hypothyroidism rT3 will be low while in ESS this will be increased. The high percentage of isolated elevated rT3 concentration in our cohort, may thus illustrate presence of (mild) ESS, which may not be surprising as these children undergo intensive treatment (19). We could not correlate the rT3 increase to corticosteroid use, although 90% of children had received any kind of corticosteroids within the three months.

Brain tumor diagnosis was found as risk factor for elevated rT3. Although no association was found between poor physical state, corticosteroids and elevated rT3, it must be considered that brain tumor patients may have been in worse physical state when compared to others, amongst others caused by cranial radiotherapy. No central hypothyroidism was found, as expected, because radiotherapy is unlikely to cause pituitary dysfunction after such a short period of time (20).

Van Iersel et al. showed that a FT4 decline of >20% during prolonged follow-up, although within reference ranges, was associated with weight gain, reduced linear growth and less improvement of intelligence scores over time in childhood brain tumor survivors (14). This

FT4 decline was regarded as reflection of mild central hypothyroidism. Even though the etiology of declining FT4 as result of mild central hypothyroidism and (mild) ESS may not be comparable, we hypothesize that prolonged lowered thyroid hormone concentrations in (non-acutely ill) children with cancer may contribute to adverse late effects such as short stature, weight gain, dyslipidemia, fatigue or the pathogenesis of early frailty in childhood cancer survivors (14,21–23). Therefore, we aim to follow thyroid hormones parameters in relation to these possible adverse late effects until the end of cancer treatment in this large prospective cohort.

It is not recommended to treat children with thyroid hormone for ESS during acute illness (13). When FT4 declines in time and remains lowered for a prolonged period in "chronically" ill children, this disease state may however be compared to adaptation of the hypothalamic-pituitary axes which is also encountered in children with other chronic diseases. Examples of such diseases are cystic fibrosis or chronic kidney disease, whereby affected children develop low insulin-like growth factor-1 concentrations or delayed puberty due chronical illness (24,25). In these situations, treatment with sex steroids or growth hormone to improve bone development and final height are considered (26,27). With this in mind, thyroid hormone treatment might be beneficial in the situation of prolonged lowered thyroid hormones in children with chronic illness or prolonged disease. This question needs to be addressed in future studies.

Our study also has several limitations. At first, the results might not be applicable to all children with cancer because for this study we only included children treated for leukemia, lymphoma, sarcoma or a non-pituitary brain tumor. Future studies may be performed to investigate changing thyroid function parameters in children with other types of childhood cancer. Secondly, although we aimed to measure thyroid function parameters before any drugs had been administered, 29% of the children had already received corticosteroids <48 hours or chemotherapy before the first thyroid hormone measurement. For optimal analysis we therefore excluded these children from analysis on changes in TSH and FT4 concentration. Moreover, data on physical condition was scored by the researchers in three categories, based on the notes of the health care provider in the electronic patient chart, which may be considered a subjective way of physical condition scoring and thus a limitation.

Conclusions

Children with cancer, treated within current treatment protocols, do not seem to be at risk for hypo- and hyperthyroidism in the first three months of cancer treatment. In 28% of children, however, the median FT4 concentration significantly decreases during cancer treatment. The long-term clinical consequences thereof have to be investigated in future studies.

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Supplementary materials

Appendix I. Laboratory assays

FT4 and TSH concentrations were measured using the Atellica IM analyzer ®, (Siemens Healthcare Diagnostics Inc., Erlagen, Germany). Serum reverse T3 was measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (TECAN IBL International, Hamburg, Germany). For determination of antibodies against thyroid peroxidase (anti-TPO) the 'Phadia250' immunoassay analyzer was used (Thermo Fisher Scientific Inc., Waltham, United States).

Appendix II.

A. Overview of groups of chemotherapeutic agents and corticosteroids administered in children three months after diagnosis.

Chemotherapy groups	**Three months after diagnosis N=276**	
	Total N (%)	<7 days N (%)
Alkylating agents	216 (79)	16 (5.8)
Antimetabolites	192 (70)	34 (12)
Anthracycline antibiotics	197 (71)	3 (1.1)
Asparaginase	128 (46)	19 (6.9)
Oncolytica	4 (1.4)	2 (0.7)
Protein kinase inhibitors	8 (2.9)	7 (2.5)
Topo-isomerase inhibitors	86 (31)	1 (0.4)
Vinca-alkaloids	235 (85)	18 (6.5)
Corticosteroids	Total N (%)	<48 hours N (%)
Treatment protocol	243 (89)	2 (0.7)
Other^	5 (1.8)	20 (7.2)

Chemotherapeutic agents or corticosteroids administered three months after diagnosis.
^Including corticosteroids used as supportive care drugs e.g. as anti-emetic drugs.

B. Group Classification of Chemotherapeutic Agents and Corticosteroids

Alkylating agents: Cyclofosfamide, Dacarbazine, Ifosfamide. Lomustine, Thiotepa, Busulfan, Temozolomide, Melfalan, Bendamustine, Carmustine, Treosulfan

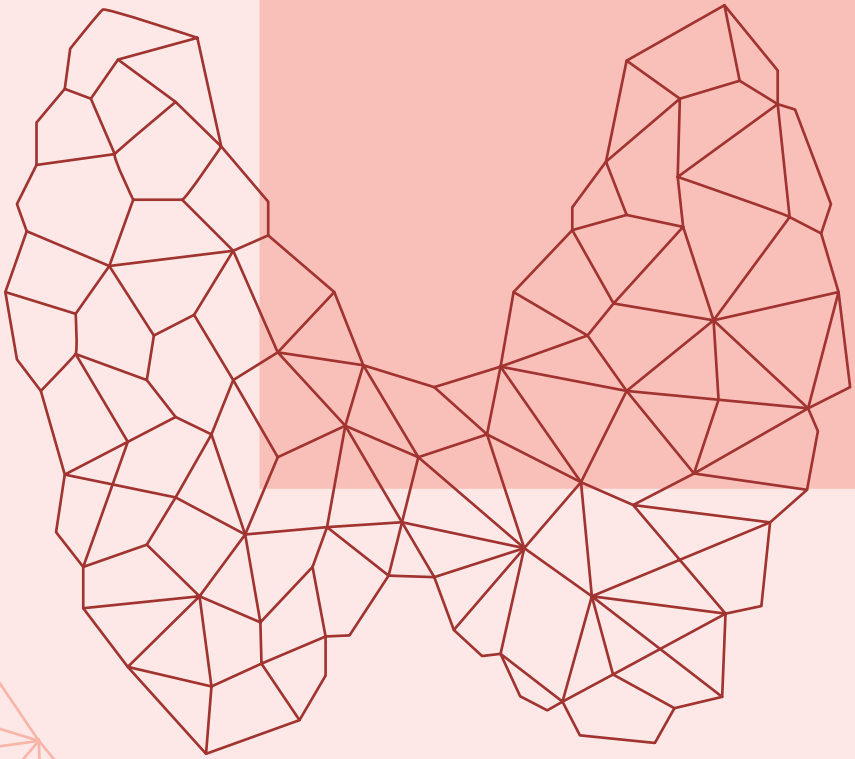
Antimetabolites: **Cytarabine,** Fludarabine, Fluorouracil, Mercaptopurine, Methotrexaat, Tioguanine, Azacitidine, Clofarabine, Gemcitabine, Nelarabine 5 mg/ml

Anthracycline antibiotics: Bleomycine, Dactinomycine, Daunorubicine, Doxorubicine, Mitoxantrone, Daunorubicin+Cytarabin, Daunorubicine, Idarubicine

Asparaginase: Pegasparaginase (Oncaspar), Spectrila, Erwinase, Asparaginase, E.Coli (Spectrila) Asparaginase, Erwinia (Crisantaspase)

Oncolytica: Arseentrioxide

Protein kinase inhibitor: Bortezomib, Imatinib, Quizartinib, Brigatinib, Dasatinib, Ruxolitinib, Ponatinib, Crizotinib
Topo-isomerase inhibitor: Etoposide, Irinotecan, Topotecan
Vinca-alkaloids: Vinblastine, Vincristine, Vindesine, Vinorelbine
Corticosteroids: Dexamethason, Methylprednisolon, Prednisolon, Hydrocortison



11

Changes in thyroid function parameters three months after allogenic and autologous hematopoietic stem cell transplantation in children

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Submitted

Abstract

Thyroid dysfunction (hypo- and hyperthyroidism) has been reported as a late effect after hematopoietic stem cell transplantation (HSCT) in children. Short term effects of HSCT on thyroid function parameters are, however, unclear. Therefore, we prospectively evaluated thyroid function parameters before and three months after HSCT in all children (<21 years) who underwent HSCT during a two-year period in the Princess Máxima Center, the Netherlands.

Among 72 children, none had thyroidal hypothyroidism or hyperthyroidism three months after HSCT. Changes in thyroid function parameters (either aberrant TSH or FT4 concentrations) were found in 16% before and in 10% three months after HSCT. Reverse T3 was found elevated in 9.3% before and in 37% three months after HSCT, which could be related to poor physical condition. An individual decline in FT4 concentration of ³20% was found in 10.5% (6/57) three months after HSCT.

In conclusion, thyroidal hypo- and hyperthyroidism are very rare three months after HSCT. These results indicate that surveillance for hypo- and hyperthyroidism may start later in time. The changes in thyroid function parameters found three months after HSCT might reflect the euthyroid sick syndrome.

Introduction

Hematopoietic stem cell transplantation (HSCT) has become an important treatment modality to improve prognosis for several benign and malignant childhood diseases (1). Adverse effects of HSCT however, have been described on the endocrine system, including thyroid dysfunction (1,2). Thyroid hormones are essential during childhood (3,4). Hypothyroidism may result in fatigue, declining growth, mental retardation in the young, constipation and it has cardiovascular consequences (5). Hyperthyroidism may cause tachycardia, growth acceleration, fatigue, diarrhea, and emotional imbalances (6).

Hypo- and hyperthyroidism have been reported to occur as adverse late effect of childhood cancer treatment, as well as following HSCT (6), especially after treatment with busulphan or melphalan (7,8), radiotherapy (9), or due to auto-immune disease following allogeneic HSCT (10). Signs and symptoms of thyroid dysfunction can be overlooked in children, therefore surveillance for thyroid function is advocated after cancer treatment and HSCT. In this regard, not only thyroid function parameters outside the reference ranges may be of clinical importance, but, as was shown in childhood cancer survivors following cranial irradiation, a decline in free thyroxine (FT4) concentration of >20% can be clinically relevant (11,12), even when FT4 is still within normal reference ranges.

Previous studies showed a prevalence of hypothyroidism after HSCT ranging from 10.0-22.3%, occurring after a median of 1.8 to 5.3 years (8,13–15), with increased risk after total body irradiation (TBI) as conditioning and younger age at time of HSCT (9). Prevalence of hypo- or hyperthyroidism was reported in 12.6%, 22.5% and 34.0% at five, 10 and 15 years post-HSCT, respectively (13). The minimum time between HSCT and the occurrence of hypo- or hyperthyroidism is uncertain. Some studies already reported thyroid dysfunction four months after HSCT (10,16). Currently, there is no agreement on timing of surveillance of thyroid dysfunction after HSCT, as screening has been advised starting from three months to one year after HSCT (8,17–19). In children undergoing HSCT, thyroid hormone metabolism may also change due to supportive care drugs (e.g., decrease in thyroid stimulating hormone (TSH) concentration due to corticosteroids) or as consequence of an adaptation mechanism of the body to severe illness, called the 'euthyroid sick syndrome' (ESS) (20). In this situation, secretion of other pituitary hormones may also be distorted such as the gonadotrophins (leading to amenorrhea) and growth hormone (leading to low insulin like growth factor (IGF-1) concentrations) (21). In ESS, changes in thyrotropin-releasing hormone (TRH) metabolism and deiodinase activity (22,23) result in a low-normal TSH, low FT4 and free triiodothyronine (FT3) with increased reverse triiodothyronine (rT3) concentration. ESS is considered to be a physiological adaptation mechanism which does not require thyroxine treatment (24). It may be hypothesized that having aberrant thyroid function parameters for a prolonged time during recovery from HSCT in childhood has clinical consequences.

As euthyroidism is important for optimal recovery after HSCT, we firstly questioned whether thyroid dysfunction occurs shortly after HSCT. Secondly, we questioned whether thyroid

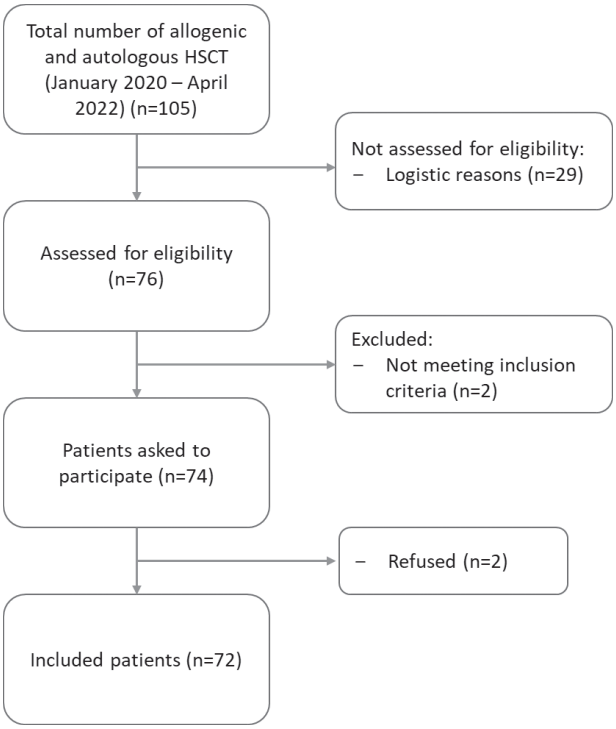
function parameters are aberrant three months after HSCT, and, if so, its relation to clinical well-being and whether such changes have clinical relevance. These questions prompted us to perform a prospective study evaluating thyroid function parameters before and three months after HSCT in children.

Methods

Patients

During a two-year period (January 2020 to April 2022), thyroid function parameters in all children (<21 years) who underwent HSCT (allogenic or autologous) in the Princess Máxima Center for Pediatric Oncology were measured before and 3 months after HSCT. Children known with previous thyroid disease, Down syndrome, a thyroid cancer predisposition syndrome, a history of neck irradiation, meta-iodobenzylguanidine (MIBG) treatment and children with a brain tumor in the hypothalamic-pituitary region were excluded from this study. In total 76 children were assessed for eligibility; two children were excluded and two children did not consent to the study (figure 1). Informed consent was obtained from 72 children (97% of eligible children).

Figure 1. Flowchart included children THYRO-Dynamics study



Ethics

The research protocol was approved by the medical ethical committee of the Princess Máxima Center (NedMec, NL69960.041.19). For ethical reasons, blood samples for the study were only taken if, simultaneously, sampling for clinical reasons was necessary. Informed consent was obtained of all children and/or their parents and/or legal representatives.

Data collection

Thyroid function parameters TSH, FT4, rT3 and IGF-1, anti-thyreoperoxidase (anti-TPO) concentrations) were measured before HSCT (-100 to 0 days before HSCT) and at three months after HSCT (+60 days to +160 days after HSCT). Results of the laboratory investigations were interpreted by the treating physician. As this was a descriptive study, no interventions were done. However, in case of aberrant thyroid function tests requiring further evaluation or intervention (FT4 concentrations below the reference range or TSH values >10mU/L) children were referred to the pediatric endocrinologist.

Clinical data on anthropometrics (height, weight, body mass index (BMI)) and general well-being (body temperature, vomiting, nutritional status, and overall physical condition) were abstracted from children's electronic medical records on the day of blood sampling. Physical condition was categorized into "good" (no complaints), "medium" (moderate complaints, "not feeling well" or "feeling tired') or "poor" (severe complaints or "feeling ill") as noted by the health care provider/nurse.

Laboratory assays

A description of the laboratory assays is shown in appendix I. Reference values are shown in table 1.

Table 1. Median plasma concentration of thyroid function parameters measured before HSCT and three months after HSCT

Thyroid function parameters	Before HSCT Concentration mIU/L median (range) (# samples)	3 months after HSCT Concentration mIU/L Median (range) (# samples)	P-value
TSH (0.30-5.00 mIU/L)	2.20 (0.44-5.20) (n=68)	2.50 (0.49-5.80) (n=60)	0.206
FT4 (10-22 pmol/L)*	15 (9-20) (n=69)	15 (8-24) (n=59)	0.143
rT3 (0.098-0.218 ng/mL)	0.15 (0.08-1.65) (n=44)	0.20 (0.11-0.40) (n=39)	0.012
IGF-1 (nmol/L, age and sex specific)	22.50 (2.30-53.60) (n=66)	21.80 (2.30-74.20) (n=60)	0.119
IGF-1 SDS^	0.06 (-2.22-2.41) (n=62)	0.03 (-2.47-3.03) (n=53)	0.196

*Dependent on age: 20 days - 3 years: 12 - 21 pmol/L, 3 - 5 years: 10 – 19 pmol/L, 5 - 19 years: 11 – 20 pmol/L, >19 years: 10 - 22 pmol/L.
^IGF-1 SDS of children < 6 months of age are not presented electronic patient chart; data could not automatically be retrieved.
P-value: for analysis of changes in thyroid hormone concentrations, only paired blood samples (diagnosis and three months after diagnosis) were used (TSH: n=58; FT4: n=57; rT3: n=24; IGF-1: n=55; IGF-1 SDS: n=48).

Definitions and Statistics

Definitions of thyroid dysfunction are described in appendix II. Data are presented as mean ±SD or median (range) for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Differences between groups were examined by unpaired Student's t tests for normally distributed continuous data and Mann-Whitney U tests for continuous data with a skewed distribution. For categorical data, χ^2 tests or Fisher's exact tests (if the assumptions for chi-square were violated) were used. Between time point differences were evaluated by paired Student's t test for continuous data with a normal distribution, Wilcoxon matched-pair signed rank test for continuous data with a skewed distribution. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro-Wilk's test were used. For analysis of changes in thyroid hormone concentrations, only paired blood samples were used. The Pearson correlation coefficient was calculated to measure the strength of a linear association between two continuous variables. Analyses were performed by using SPSS version 27.0. P-values of <0.05 were considered as statistically significant.

Results

Patient characteristics

Among 72 included children, 42 (58%) were diagnosed with leukemia (table 2). Sixty-eight (94%) children underwent allogeneic HSCT, five had already undergone ≥ 1 previous HSCT. Median age at HSCT was 10.2 years (0.2-20.4 years) and 60% was male. Three children (4.2%) were deceased within three months after HSCT.

Table 2. Baseline characteristics of 72 children undergoing HSCT

Baseline characteristics	
Age at HSCT (yrs) (median, range)	10.2 (0.2-20.4)
Male/female (%)	43/29 (60/40)
Diagnosis	
Leukemia	42 (58%)
ALL	21 (29%)
AML	16 (22%)
CML	2 (2.8%)
Other[a]	3 (4.2%)
Myelodysplastic syndrome	6 (8.3%)
Lymphoma	4 (5.6%)
Severe aplastic anemia	4 (5.6%)
Fanconi anemia	5 (6.9%)
Hurler Syndrome	5 (6.9%)
Other[b]	6 (8.3%)
Type of stem cell transplantation	
Autologous	4 (5.6%)
Allogenic	68 (94%)
TBI (conditioning regimen)	22/72 (31%)
Mean BMI SDS (± SD)	
before HSCT	0.52 (1.37)
three months after HSCT	0.21 (1.41)

[a]Including: juvenile myelomonocytic leukemia, acute bilineage leukemia

[b]Including: Wolman disease, juvenile dermatomyositis, teratoid rhabdoid tumor, Diamond Blackfan anemia, medulloblastoma, Ewing sarcoma.

Abbreviations: HSCT, hematopoietic stem cell transplantation; ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; TBI, total body irradiation

Thyroid function parameters

Hypo- and hyperthyroidism

In table 1 median plasma concentrations of the thyroid function parameters are shown. Before HSCT, TSH and FT4 were both measured in n=68 children. Of these, 84% (64/68) had both the TSH and FT4 concentrations within reference ranges. One child (1/68,1.5 %) had mild thyroidal hypothyroidism before HSCT. None were found to have hyperthyroidism before HSCT. Three (4.4%; 3/68) showed decreased FT4 concentrations (9, 10 and 11 pmol/L) with non-elevated TSH concentrations. Reverse T3 in combination with TSH and FT4 had been measured in 43 children before HSCT. In two out of 43 patients (2.8%) FT4 was below reference range with non-elevated TSH and non-elevated rT3; they were considered to have central hypothyroidism (diagnoses: ALL (n=1), AML (n=1)). In one patient with decreased FT4 and non-elevated TSH concentrations, rT3 was not measured. All values were discussed with the pediatric endocrinology department. None of the children were started on thyroid hormone.

Three months after HSCT, TSH and FT4 combined were measured in 59 children. TSH and FT4 concentrations within reference ranges were found in 90% (53/59) of children. None had thyroidal hypo- or hyperthyroidism. Two (3.4%; 2/59) children (with normal FT4 before HSCT) showed decreased FT4 concentrations (10 and 8 pmol/L) with non-elevated TSH concentrations. Four children (6.8%; 4/59) showed elevated FT4 concentrations (median 23 pmol/L, range 21-24 pmol/L) with TSH concentrations within the reference range.

ESS

Prevalence of ESS was be determined in children in whom simultaneously measurements of TSH, FT4 and rT3 were available. Before HSCT, no ESS was found in 43 children in whom these measurements were available. Three months after HSCT, in one of 38 patients in whom FT4, TSH and rT3 had been measured simultaneously (2.6%; 1/38) (moderate) ESS was found.

Overall, three months after HSCT, the median concentration of rT3 significantly increased (0.15 ng/ml (0.08-1.65) to 0.20 ng/ml (range 0.11-0.40); p=0.012) (table 1). No significant correlation was found between the FT4 and rT3 concentrations before or three months after HSCT (before HSCT: r=0.16, 95%CI -0.95 to 0.97; after HSCT: r=0.30, 95%CI -0.95 to 0.97). However, a significant negative correlation was found between TSH and rT3 (r=-0.37, 95%CI -0.61 to -0.06) three months after HSCT. Additionally, no significant correlation was found between age at HSCT and FT4 or rT3 concentrations three months after HSCT.

An isolated rT3 elevation (with no decrease in FT4 and non-elevated TSH was found in 9.3% (4/43) and 37% (14/38) of the children before and three months after HSCT, respectively. Children with isolated elevated rT3 concentrations three months after HSCT showed a median increase of FT4 in this period of +27% compared to +5.9% in others (p=0.077). No other differences were found between children with elevated rT3 levels three months after HSCT compared to those without in underlying disease or any administered chemotherapy groups, corticosteroids (table 3) or BMI (table 1).

Table 3. Overview of groups of chemotherapeutic agents and corticosteroids administered in children undergoing HSCT

Chemotherapy groups	Thyroid hormone measurement before HSCT N=68		Thyroid hormone measurement +3 months after HSCT N=59	
	Cumulative N (%)	<7 days N (%)	Cumulative N (%)	<7 days N (%)
Alkylating agents	29 (43)	0 (0)	57 (97)	0 (0)
Busulphan	3 (4.4)	0 (0)	21 (37)	0 (0)
Melphalan	0 (0)	0 (0)	3 (5.3)	0 (0)
Antimetabolites	47 (69)	1 (1.5)	57 (97)	0 (0)
Antracyclines/antineoplastic antibiotics	35 (52)	0 (0)	28 (48)	0 (0)
Asparaginase	22 (32)	0 (0)	19 (33)	0 (0)
Platinum agents	2 (2.9)	0 (0)	1 (1.7)	0 (0)
Protein kinase inhibitors	10 (15)	8 (12)	5 (8.5)	2 (3.4)
Topo-isomerase inhibitors	30 (44)	0 (0)	33 (56)	0 (0)
Vinca-alkaloids	26 (38)	1 (1.5)	21 (36)	0 (0)
Immunotherapy	19 (28)	2 (2.9)	22 (37)	1 (1.7)
CAR-T cell infusion	11 (16)	0 (0)	11 (19.3)	NA
	<48 hours N (%)		**<48 hours N (%)**	
Corticosteroids^	1 (1.5)		17 (29)	

Chemotherapeutic agents or corticosteroids (appendix III) administered prior to transplant and first measurement as well as at second measurement three months after HSCT (the latter including the conditioning regimen).
^Including corticosteroids used as GVHD prophylaxis, anti-inflammatory drug, or anti-emetic drugs.
Abbreviations: HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor (CAR) T cell-therapy; NA, not applicable

Dynamics of thyroid function parameters

Overall, no significant differences were found in median FT4, TSH or IGF-1 concentrations three months after HSCT when compared to before HSCT (table 1). No correlation between IGF-1 SDS and rT3 concentrations was found three months after HSCT (r=0.13, 95%CI 0.22 to 0.44).

A paired TSH and FT4 measurement was available for 57 children. The median difference in FT4 concentration between the two time points was +5.0%. A decline in FT4 in the three months after HSCT of 10%, 20%, 30% was found in 30% (17/57), 11% (6/57) and 3.5% (2/57) of children, respectively.

Anti-TPO concentrations

Two children (3.4%) had elevated anti-TPO concentrations before HSCT, compared to none of the children after HSCT. One of the two children with elevated pre-transplant anti-TPO concentrations had a decreased FT4 concentration after three months with a normal TSH concentration.

Chemotherapy, corticosteroids and TBI

Table 3 provides an overview of the groups of chemotherapy that had been administered to the children in whom thyroid hormones were measured. Three months after HSCT, 21 (37%) and three (5.3%) children had received busulphan or melphalan, respectively. Corticosteroids had been administered to one child <48 hours before the first thyroid hormone measurement; while three months after HSCT, 17/59 (29%) children had received corticosteroids <48 hours. In these 17 children, FT4 concentrations were higher ($p<0.001$) and TSH concentrations were lower ($p<0.001$), compared to those not receiving corticosteroids <48 hours before thyroid hormone measurement. Reverse T3 concentrations did not differ between the two groups. TBI (12 Gy) had been part of the conditioning regimen in 31% of the children. FT4, TSH and rT3 concentrations of these irradiated children were comparable with non-irradiated children three months after HSCT.

General well-being and anthropometrics

Before HSCT 15%, 16% and 13% of the children reported symptoms of pain, symptoms of nausea/vomiting and presence of fever on day of blood sampling, respectively. Physical condition was scored as “medium” in 35% of the children and “poor” in one child. Three months after HSCT, symptoms of nausea/vomiting, pain and fever were reported in 24%, 25% and 3.5%, respectively. Physical condition “medium” and “poor” were scored in 49% and 1.7% of the children three months after HSCT. Children with elevated rT3 concentrations three months after HSCT scored significantly more often “medium” or “poor” on physical condition compared to those without elevated rT3 concentrations (11/14 (79%) versus 10/24 (42%; $p=0.043$)). Mean BMI SDS before HSCT was 0.52 ± 1.37 which significantly decreased to 0.21 ± 1.41) ($p=0.004$). No correlation was found between the BMI SDS and TSH, FT4 or rT3 at both time points.

Discussion

This prospective study of a 2-year cohort of children treated with HSCT in the Princess Máxima Center enabled us to evaluate thyroid function parameters after the first three months following HSCT. We did not find any clinically relevant hypo- or hyperthyroidism after three months requiring intervention. These results are reassuring and may imply that surveillance for hypo- and hyperthyroidism may be unnecessary shortly after HSCT. However, we did find an individual decline in FT4 of ³20% after three months in 11% of the children. The period of time of this FT4 decline and whether such a severe FT4 decline has clinical consequences on e.g. growth, bone health or muscle development in these children is uncertain and may be studied in future cohorts with longer follow-up time.

The high percentage of children developing elevated rT3 concentrations in combination with the significant negative correlation between TSH and rT3 three months after HSCT, underlines the possible presence of ESS in this group (25). The presence of ESS can be

expected in the light of the intensive treatment that these patients have undergone, and in the setting of immune dysregulation with an inflammatory milieu that may impair organ functions and tissue damage with, amongst others, mucositis and feeding problems. In line with this, we found that elevated rT3 concentrations were associated with “medium and poor” physical condition.

Our results illustrate that determination of rT3 in such situations may serve as an objective marker of physical condition. Furthermore, determination of rT3 may be helpful in clinical care when thyroid function tests suggest central hypothyroidism with low FT4 and non-elevated TSH concentrations. In such situations, rT3 will be normal-low in case of central hypothyroidism but will be elevated in case of ESS. In case of ESS it is not recommended to treat with thyroid hormone (26).

Children suffering from prolonged severe illness have shown to present with low total T4 and FT4 concentrations (27). For this reason, we had expected that, since higher rT3 concentrations and “medium and poor” physical condition were associated, the FT4 concentrations of children with elevated rT3 concentrations would have been lower. No significant correlation between rT3 and FT4 was, however, found in children with elevated rT3 concentrations. This may be explained by the fact that circulating FT4 concentrations may transiently rise during the acute phase of illness and normalize during recovery (28). Another explanation for the non-decreased FT4 concentrations might be that the TRH metabolism had already been restored, but, during severe illness, the deiodinase activity was altered resulting in elevated rT3 concentrations. Unfortunately, T3 concentrations were not available, thus the T3/rT3 ratio, used to define ESS (24), could not be determined.
Next to illness, age is also known to influence rT3 and FT4 concentrations with higher rT3 and FT4 concentrations in younger children (29). In our cohort, no significant correlation of age with rT3 or FT4 concentrations could be found.

The changes in thyroid function parameters may, alternatively to ESS, be explained by the administration of drugs, such as corticosteroids (30). In our cohort 29% of the children had received corticosteroids <48 hours of thyroid hormone measurement three months after HSCT. Although no significant difference in median rT3 concentration was found between children given corticosteroids <48 hours before thyroid hormone measurement and those not.

During severe illness the body is in a catabolic state (31). This catabolic state has not only been linked to changes in thyroid function parameters but also to other pituitary hormones, such as ACTH and GH. Due to reduced pulsatile secretion of GH, IGF-1 levels may diminish. In our cohort, as well as in the children with elevated rT3 concentrations, IGF-1 SDS remained stable three months after HSCT. Administration of corticosteroids might have influenced these results, since corticosteroids have been described to increase IGF-1 concentrations due to corticosteroid induced insulin resistance (32). Alternatively, IGF-1 levels may already have improved after catabolic state due to illness, with more prolonged time for recovery of rT3.

In this unique cohort, we studied the short term effects of HSCT on thyroid function parameters in children. The strengths of this study are the relatively large cohort of children and the systematic biochemical measurements before and three months after HSCT. Also, measurement of rT3 concentrations in addition to TSH and FT4, has given insight in the relation between poor physical condition and the dynamics of thyroid function parameters.

The fact that only 72% of all the patients undergoing HSCT were assessed for eligibility, may be considered a limitation. However, this seemed to be due to logistic reasons, making selection bias unlikely. Secondly, although thyroid function parameters were evaluated in 72 children, a paired TSH and FT4 measurement at before and after three months was only available for 80% of the children, due to ethical reasons (blood samples were only taken if simultaneously sampling for clinical reasons was necessary). Also, rT3 concentrations were only available in 65% of the children and T3 measurements were not available. Lastly, the scoring of physical condition was done using three categories, which may have been subjective and not detailed.

In conclusion, this study shows that hypo- and hyperthyroidism are exceedingly rare in children three months after HSCT and surveillance for thyroid dysfunction may start later in time, e.g. at six months after HSCT (8). Starting surveillance earlier may even result in a large number of false positive results, as children may have aberrant thyroid function parameters caused by ESS in which thyroid hormone treatment is not indicated. The fact that both a decline in FT4 concentration ^{3}20 % was seen in 11% of patients and elevated rT3 concentrations were frequently found three months after HSCT, may reflect presence of ESS and poor physical condition. Re-evaluation of these findings one year after HSCT might give insight in the trend of thyroid function parameters and clinical consequences.

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Supplementary Materials

Appendix I. Laboratory assays

FT4, TSH concentrations were measured using the Atellica IM analyzer® (Siemens Healthcare Diagnostics Inc., Erlagen, Germany) and IGF-1 was measurend using the LIAISON® analyzer (DiaSorin, Saluggia, Italy). The IGF-1 blood sample was stored and used for measurement of serum reverse T3 (Enzyme-Linked Immunosorbent Assay (ELISA) kit (TECAN IBL International, Hamburg, Germany)). For determination of antibodies against thyroid peroxidase (anti-TPO) the 'Phadia250' immunoassay analyzer was used (Thermo Fisher Scientific Inc., Waltham, United States).

Appendix II. Definitions thyroid dysfunction

Thyroidal hypothyroidism: TSH concentration > reference interval (5.0 mU/L) at diagnosis or 3 months after diagnosis. Severity of thyroidal hypothyroidism was defined as mild (TSH >5, FT4 within the reference range), moderate (TSH >10 mU/L, FT4 within reference ranges) or severe (TSH >10 mU/L, FT4 < reference range).

Thyroidal hyperthyroidism: suppressed TSH in combination with FT4 within the reference range (mild) or suppressed TSH in combination with FT4 above the reference range (severe).

Hypothalamic-pituitary (HP) hypothyroidism (central hypothyroidism): non-elevated TSH concentration in combination with a FT4 concentration below the reference range and a non-elevated rT3.

Euthyroid sick syndrome (ESS): FT4 concentration <reference range in combination with an elevated rT3 concentration. Severity of ESS was defined as mild (FT4 9-10 pmol/L), moderate (FT4 7-9 pmol/L), or severe (FT4 <7 pmol/L).

Appendix III. Group Classification of Chemotherapeutic Agents and Corticosteroids

Alkylating agents: Cyclofosfamide, Dacarbazine, Ifosfamide. Lomustine, Thiotepa, Busulphan, Temozolomide, Melfalan, Bendamustine, Carmustine, Treosulfan

Antimetabolites: **Cytarabine,** Fludarabine, Fluorouracil, Mercaptopurine, Methotrexaat, Tioguanine, Azacitidine, Clofarabine, Gemcitabine, Nelarabine 5 mg/ml

Antracyclines/antineoplastic antibiotics: Bleomycine, Dactinomycine, Daunorubicine, Doxorubicine, Mitoxantrone, Daunorubicin+Cytarabin, Daunorubicine, Idarubicine

Asparaginase: Pegasparaginase (Oncaspar), Spectrila, Erwinase, Asparaginase, E.Coli (Spectrila) Asparaginase, Erwinia (Crisantaspase)

Immunotherapy: Bevacizumab, Gemtuzumab ozogamicin, Rituximab, Blinatumomab, Pembrolizumab, Blinatumomab, Dinutuximab, Inotuzumab ozogamicine, Alemtuzumab, Brentuximab, Daratumumab, Inotuzumab ozogamicine, Isatuximab, Nivolumab,

Platinum agents: Carboplatin, Cisplatine, Oxaliplatin

Protein kinase inhibitor: Bortezomib, Imatinib, Quizartinib, Brigatinib, Dasatinib, Ruxolitinib, Ponatinib, Crizotinib

Topo-isomerase inhibitor: Etoposide, Irinotecan, Topotecan

Vinca-alkaloids: Vinblastine, Vincristine, Vindesine, Vinorelbine

Corticosteroids: Dexamethason, Methylprednisolon, Prednisolon, Hydrocortison

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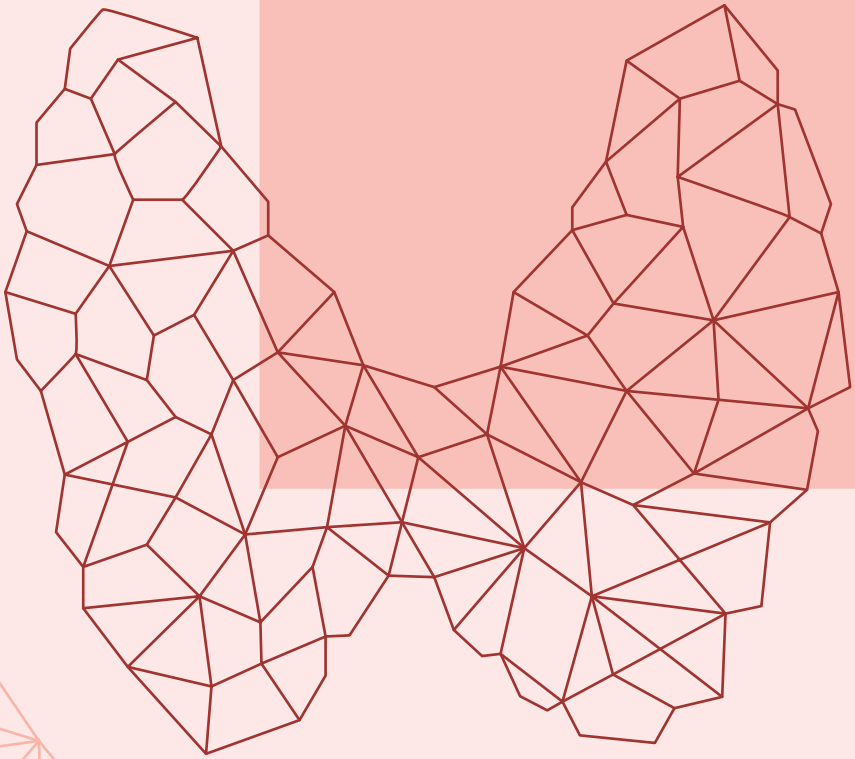

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Summary and general discussion

The aim of this thesis was to improve the outcome of pediatric DTC by developing evidence based national and international harmonized recommendations for care. After identifying gaps in research, new studies were performed on imaging techniques and surveillance strategies for pediatric DTC (part I). Furthermore, we aimed to explore disturbances in thyroid function parameters during childhood oncology treatment (other than thyroid cancer) (part II).

In this chapter the main findings are summarized, and the implications of our studies are discussed. Additionally, directions for future research are suggested.

Summary

Part I. Differentiated thyroid carcinoma in children

Thyroid carcinoma is the most common endocrine malignancy in children, with a worldwide rising incidence. In chapter 2 the incidence and survival rates of differentiated thyroid carcinoma (DTC) (including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC)) and MTC in Dutch children, adolescents, and young adults (0-24 years) over a 30-year life span are described. A total of 839 patients aged 0-24 years were diagnosed with thyroid carcinoma in the Netherlands, between 1990-2019. We found an increased incidence rate of PTC over time; the incidence rate of FTC remained stable, while the incidence rate of MTC had decreased. Lymph node metastases were found in a substantial part (40%) of the patients with DTC, distant metastases were found in relatively few (3%) patients with DTC. We could confirm that, even though children often present with advanced disease, survival rates for DTC are excellent, with a 10-year overall survival of >98.5%.

In chapter 3 we summarized literature on DTC in children with PTEN hamartoma tumor syndrome (PHTS). Its incidence ranges from 4-12%, with a median age of onset of 12 years. The youngest age in which DTC had been reported in the included studies was four years. No evidence was found for different clinical behavior of DTC in PHTS versus sporadic DTC. Consensus was reached to recommend surveillance for DTC in all children with PHTS by means of annual neck palpation and triennial neck ultrasound from the age of 10 years onwards. However, in counseling of such patients and their families, the importance of individual considerations and shared decision making with the child and caregivers to start surveillance for DTC in high-risk patients should be emphasized. Additionally, reconsideration over time whether to start or stop surveillance for DTC is also of importance.

Because DTC is a rare disease, national and international harmonization of care for children with DTC is necessary to improve the outcome. Up till now neither Dutch nor European pediatric recommendations for thyroid nodules and DTC were available. Although the American Thyroid Association (ATA) had already developed such recommendations, due to cultural differences and differences in medical regulations between countries, specific national and European recommendations were required.

In chapter 4 the first national recommendations for the treatment of pediatric DTC in the Netherlands are presented. Using the 2015 ATA Pediatric Guideline as starting point, the Dutch expert panel for pediatric DTC appraised the newest evidence and formulated national recommendations. Subsequently, a European expert panel was formed. Consensus was achieved to also use the 2015 ATA Pediatric Guideline 2015 as framework; in combination with thorough grading of all available evidence and consensus on discussion points, harmonized European guidelines were developed. These first European Thyroid Association (ETA) guidelines for management of pediatric DTC are presented in chapter 5. The recommendations in this thesis for management of pediatric thyroid nodules and DTC provide guidance for health care professionals to make well-considered decisions.

In chapter 6 we investigated the value of routine cervical US surveillance in follow-up of pediatric DTC after total thyroidectomy and we assessed the contribution of cervical US findings to the identification of structural residual or recurrent disease as compared to other surveillance modalities. Based on our findings we suggest to continue to endorse an initial post-operative cervical US for all patients to identify structurally residual disease. Additionally, in children where the initial post-operative cervical US is clearly reassuring and for those with undetectable or low-detectable Tg concentrations during subsequent follow-up, without elevated TgAbs, it may be reasonable to restrict subsequent surveillance to a 'Tg-first' approach (chapter 6). With the 'Tg-first' approach cervical US is limited to the context of rising Tg concentrations. Structural residual or recurrent disease was found in a few patients with declining TgAb titres, therefore following the trend of TgAbs as 'alternative' tumor marker for Tg might not be accurate enough in this setting.

In chapter 7 we retrospectively evaluated the results of FDG PET/CT imaging as a first-line nuclear imaging modality in adult patients suspected of residual or recurrent DTC without first performing a radioactive iodine whole body scan (RAI WBS).

We found FDG positive lesions, suspect of lymph node metastases, in more than half of the patients with elevated Tg concentrations. DTC was confirmed in 93% of these patients. However, also in 70% of patients without FDG positive lesions, DTC was confirmed within three months after FDG PET/CT. In this case series we showed that FDG PET/CT imaging might be of additional value to detect residual or recurrent DTC in adult patients with low detectable Tg. However, DTC cannot be ruled out when no lesions are found on FDF PET/CT imaging.

In chapter 8 we investigated the clinical presentation, treatment, and outcome of subsequent DTC (DTC following previously treatment for a different type of cancer) among CCS in The Netherlands. In accordance with previous studies, we found that subsequent DTC seems to present with smaller tumors and more frequent bilateral disease (1,2). Tumor behavior and outcome of DTC in CCS does not seem to differ significantly from sporadic DTC.

Radiotherapy is known as the major risk factor developing subsequent DTC, however, in our cohort one third of the patients with subsequent DTC had not received radiotherapy but only received chemotherapy for their childhood cancer. In a large pooled-analysis, alkylating agents were described to increase the risk of developing subsequent DTC (3). Alkylating agents have also been reported to increase the overall risk of other subsequent malignancies (4). In addition, the fact that an individual already has had cancer during childhood and subsequently develops thyroid carcinoma may indicate a germline genetic susceptibility to develop cancer.

Part II. Thyroid dysfunction during childhood cancer treatment

Thyroid dysfunction is known to occur as late effect in childhood cancer survivors. Thyroid dysfunction during childhood cancer treatment has not been studied extensively so far, however. In chapter 9 we systematically reviewed all current available studies on thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer. We found primary hypothyroidism to be described in up to 18% of children during treatment with high dose interferon-α (HDI-α) or tyrosine kinase inhibitors (TKIs). Euthyroid sick syndrome (ESS) was commonly described in children treated with systematic multi-agent chemotherapy, with a prevalence ranging from 42-100%.

In chapter 10 and 11 we present the first results of a prospective cohort study in the largest European pediatric oncology center: the THYRO-Dynamics study. In chapter 10, we reported the prevalence and risk factors for thyroid dysfunction during childhood cancer treatment in children with newly diagnosed cancer. A low percentage of hypo- and hyperthyroidism was found three months after diagnosis. ESS was present in 1.5% after starting cancer treatment although in 50% of children after three months an isolated rT3 concentration was measured. An individual FT4 decline of greater than 20% was found in 28% of children. Future studies are needed to investigate the clinical implications of such changes during childhood cancer treatment.

In chapter 11, we evaluated thyroid function parameters before and three months after autologous or allogenic HSCT in children. We also studied the dynamics of and risk factors for changes in thyroid function parameters over time. We found aberrant TSH or FT4 concentrations in 16% before HSCT and in 10% three months after HSCT, however, hypo- and hyperthyroidism were uncommon in the first three months after HSCT. These results indicate that surveillance for hypo- and hyperthyroidism may start later in time. An individual decline in FT4 concentration greater than 20% was found in 10.5% three months after HSCT. Whether such a FT4 decline has clinical consequences on e.g. growth, bone health or muscle development is uncertain and may be studied in future cohorts with longer follow-up time.

General discussion

Part I. Differentiated thyroid carcinoma in children

Organization of care for pediatric DTC

The Dutch expert panel developed an organogram for the organization of care in the Netherlands (chapter 4). The panel reached consensus that care for a child presenting with a thyroid nodule may be delivered at four 'health care levels' including the general practitioner *(level 1)*, a pediatrician in a general hospital *(level 2)*, a pediatric endocrinologist working in a (academic) hospital with an experienced pediatric or thyroid radiologist and pathologist with experience in ultrasound guided FNB in children and with the interpretation of cytological results *(level 3)* and a pediatric endocrinologist working in a specialized thyroid expertise center, with a multidisciplinary team specialized in the diagnostics, treatment and follow-up of pediatric DTC *(level 4)* (chapter 4). A child can present at each level but should be referred to the next level when indicated. Consensus was reached that a child with DTC should always be referred to and treated in a level 4 hospital. A level 4 hospital must have a multidisciplinary team, including a pediatric and adult endocrinologist, pediatric radiologist, ('high volume') pediatric thyroid cancer surgeon, ('high volume') pediatric surgeon experienced in thyroid surgery, pathologist, nuclear medicine physician, clinical geneticist, pediatric psychologist, and a pediatric oncologist.

The organization of care for children with DTC differs between countries across Europe (5). This includes differences over which medical specialist is ultimately responsible for the management and treatment of these children. In the Netherlands, a pediatric endocrinologist is most often the responsible medical specialist, but in the United Kingdom it may be the pediatric oncologist and in Germany the nuclear physician. In our opinion, such differences do not necessarily impact the quality of care, which more depends on the expertise of the treating physician and its team. In agreement with the Dutch recommendations, in the European guidelines it was also agreed that a child with, or suspected of having, thyroid carcinoma should be referred to an experienced multidisciplinary thyroid team, specifically with experience in pediatric thyroid cancer (chapter 5).

As DTC in children is a rare disease, centralization of care to expert centers is an important step for improving management and outcome (15). However, while a reduction in the number of hospitals might not drastically harm accessibility at a population level, it may present challenges for children living in rural areas. If centralization is not possible for whatever reason, consultation with the expert team is mandatory which can be done by online meetings. In the Netherlands, for example, we have started a 3-monthly online multidisciplinary board meeting where all Dutch patients are discussed. This seems already to improve national collaboration and harmonized treatment.

If centralization of care if further centralized, it will be important to evaluate its outcome. National outcome of treatment for DTC may be expressed in terms of surgical complications

(6) or other adverse effects of treatment. It may be interesting to compare to outcome of DTC in the Netherlands to other countries, including evaluation of centralization. The current European initiative for prospective international data registration of children with DTC will be very useful for this evaluation within as well as between countries (Development of A Pediatric Differentiated Thyroid Carcinoma Registry Within the EuRRECa Project: Rationale and Protocol, Clement et al, under review). The results of this evaluation should (inter) nationally be discussed; if improvement in outcome is deemed necessary, further national, or even international centralization could be initiated.

How to distinguish the benign thyroid nodule from the malignant thyroid nodule?

Prevalence of the thyroid nodule

In chapter 5 we questioned the prevalence of non-clinically relevant thyroid nodules during childhood. The largest data resource comes from surveillance programs in Fukushima and other parts of Japan that were not contaminated by radioactivity (Aomori, Nagasaki and Yamanashi). In Japan, the prevalence of ultrasound-detected thyroid nodules of >5 mm or cysts of >20 mm was reported to be around 1.0% (7). In two other studies, the prevalence of non-clinically relevant thyroid nodules in childhood was found to vary between 0.6-2% (8,9). Because the prevalence of thyroid nodules can greatly differ between countries depending on the iodine status or perhaps racial differences (10,11), prospective studies are needed in several populations to provide more certainty on the prevalence of non-clinically relevant thyroid nodules in childhood. However, it is of great importance that, when conducting such a study, the potential harm caused by over-diagnosis associated should be outweighed by the benefit of detection (12).

Diagnostic work-up of the thyroid nodule in a child

Evidence regarding the optimal diagnostic work-up of the thyroid nodule in children is limited. The ETA expert panel has designed a flowchart on initial evaluation, treatment, and follow-up of the pediatric thyroid nodule based upon the best available evidence and expert opinion. The first diagnostic step is to perform a neck ultrasound to assess the risk of cancer in the thyroid nodule. In chapter 5 we questioned the state of evidence using neck ultrasound to distinguish a benign thyroid nodule from a thyroid cancer. Several specific ultrasound characteristics as hypoechogenicity, calcifications, taller-than-wide shape, irregular margin and increase vascularization may increase the risk of a thyroid nodule being malignant. Ultrasound scoring systems may help stratifying for which thyroid nodules are suspicious for thyroid carcinoma (13–15). An important limitation of these scoring systems is that they are based on adult populations. Recently, Kim et al. have compared the diagnostic performance of five adult-based ultrasound risk stratification systems in discrimination of malignant thyroid nodules in children (American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS), American Thyroid Association (ATA), American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi (AACE/ACE/AME), European Thyroid Imaging Reporting and Data

System (EU-TIRADS), and Korean Thyroid Imaging Reporting and Data System TIRADS(K-TIRADS)) (16). In this retrospective study, including 221 pediatric patients with 277 thyroid nodules, the sensitivity of the FNB criteria of the ultrasound risk stratification systems ranged from 70% to 78% and the specificity from 42% to 78%. They concluded that the diagnostic performance in pediatric patients was comparable to that in the adult population (17). However, using these adult-based ultrasound risk stratification systems on pediatric thyroid nodules resulted in an unnecessary biopsy rate of 21% to 39% and a missed malignancy rate of 32% to 39%. Although the high rates of unnecessary biopsies and missed malignancies rates are comparable with results in adults (18), these outcomes are extremely unwanted. They lead to unnecessary worry and discomfort in children and missed malignancies might lead to poorer outcome. Based on this, the current adult-based ultrasound risk stratification systems seem insufficient for the use in the pediatric population.

Thyroid cancer in patients at risk (a predisposition syndrome and childhood cancer survivors)

Since behavior and outcome of DTC in children with PHTS as well as CCS does not seem to differ significantly from sporadic DTC (chapter 3 and chapter 8), treatment of DTC in these cases should generally be the same as for children with sporadic DTC. The fact that CCS more often present with bilateral disease, however, suggests that a total thyroidectomy must be advocated for all CCS presenting with DTC as second cancer (chapter 5). In addition, special consideration of prior exposures and psychosocial context should also be included to treatment planning for CCS with subsequent DTC. For example, prior exposure to ^{131}I-MIBG or total body irradiation or bleomycin in CCS may increase the cumulative risk for adverse effects of $^{131}I^-$ in subsequent DTC treatment. Next, although infrequent, the presence of a genetic predisposition syndrome underlying a patient's multiple malignancies (such as PHTS, DICER1 syndrome), may theoretically influence the decision-making regarding adjuvant $^{131}I^-$ therapy with regards to the risk of developing another subsequent malignancy. Additionally, appropriate consideration and support must be given to the additional psychological and financial burdens of a subsequent diagnosis of malignancy, including additional hospitalizations and follow-up visits, fear of an unfavorable prognosis, and impacts on health-related quality of life. For these reasons, children with subsequent DTC should be referred to an experienced pediatric oncology center, including thyroid expertise.

Differences between guidelines

There are differences between the Dutch, European and ATA recommendations regarding diagnostic work-up, surgical approach, administration of RAI, and follow-up. In addition, there have been some shifts in management of pediatric DTC over the years. In general, a shift towards more individualized treatment with focus on neither overtreatment nor under treatment is being actively pursued. In adults, there is already a trend in de-escalating the extent of surgical resection and less use of adjuvant $^{131}I^-$ therapy for patients with DTC. For example, the ATA and Association of endocrine surgeons now allow lobectomy as an option to treat PTC <4 cm in size with no or minimal central lymph node metastasis (19,20) and

the concept of risk-based selection of candidates for postoperative $^{131}I^-$ therapy has been introduced (21). In children, although such a shift in treatment will probably prevent from (part of) the adverse effects of treatment, the high prevalence of lymph node metastases at diagnoses in children must be considered.

Evidence on management and treatment of thyroid nodules and DTC in children is limited; this was the case in 2015 when the ATA guidelines were published, and unfortunately, still is the case. In the European guidelines, 85% (53/62) of all suggestions/recommendations are based on low quality evidence (including expert opinion). Due to lack of high-quality evidence, guideline expert panels have to decide whether to base recommendations solely on the existing studies or to deviate from current literature to innovate and to address practice needs for which no (or inadequate) literature exists (22).

In the diagnostic work-up, molecular gene analysis may be helpful in cytology results currently classified as indeterminate specimen. The ATA guidelines state that a positive mutational test appears highly likely to be associated with thyroid carcinoma, but insufficient data exist in children to rely on negative genetic studies to reliably exclude malignancy. Therefore, molecular gene analysis in FNB specimen is not routinely recommended in clinical practice. The Dutch expert panel, however, concluded in the year of 2020 that a *BRAF* V600E mutation in a FNB specimen is 100% specific for PTC presence. For this reason, a total thyroidectomy is recommended when a *BRAF* V600E mutation is found in a FNB specimen categorized as Bethesda 5 of the Bethesda System for Reporting Thyroid Cytopathology (23). The ETA expert panel agreed that gene analysis for a *BRAF* V600E mutation in the diagnostic work-up may be considered. However, the ETA expert panel recommended that the presence of PTC must be confirmed cytologically or histologically (preoperative FNB or intraoperative frozen section) before total thyroidectomy is performed to ensure no unnecessary total thyroidectomies are performed. Both, the Dutch and ETA expert panels suggested that analyzing the presence of other oncogenic drivers and gene-fusions (e.g., RET/PTC and NTRK-fusions) could be considered, but state that the current evidence is not sufficient to incorporate this as standard care. In the upcoming years a shift towards evaluation and management of pediatric DTC using identification of oncogenic drivers and gene-fusions in the diagnostic work-up may be expected.

Additionally, the Dutch and ETA expert panels state that molecular testing in pediatric thyroid carcinoma tissue is a rapid changing field but agree that the results of molecular testing have currently no consequences for pediatric DTC management. They suggest that molecular testing may also be performed in rare, advanced cases with ^{131}I-refractory DTC who could benefit from targeted therapies.

Differences in the regulations regarding nuclear medicine between Europe and the USA have resulted in differences in the recommendations on the use of RAI therapy. For example, the ATA 2015 guidelines suggested no iodine treatment in low-risk patients. The guidelines were evaluated by Bauer et al. and they concluded that withholding RAI therapy

does not have negative impact on remission (data not published, presented on 2022 ATA annual conference). However, the surgical approach should also be considered. The ATA guidelines recommend that, for patients with no clinical evidence of gross extrathyroidal invasion and/or locoregional metastasis, prophylactic central lymph node dissection (CLND) may be selectively considered based upon tumor focality and size, and the experience of the surgeon. But the use of prophylactic CLND is debatable in both children and adults because it may increase the risk for surgical complications, such as the occurrence of hypoparathyroidism or recurrent nerve injury. The adverse effects of prophylactic lymph node dissection (postoperative complications) must be weighed against the risk of missing clinically significant disease.

The ETA expert panel suggested that prophylactic CLND can be avoided or limited to ipsilateral lymphadenectomy in patients without features indicative of advanced thyroid cancer on neck ultrasound and be reserved for advanced thyroid cancer only. In other words, the ETA panel suggested more reluctance in prophylactic CLND, due to the potential for postoperative complications, but recommended RAI therapy for all patients, due to the high rate of lymph node metastases.

A potential innovative solution to reduce the rate of postoperative hypoparathyroidism might be the technique of fluorescence-guided surgery which may help to identify, visualize, and preserve the parathyroid glands during thyroid surgery (24). Previous studies in adults have already shown the potential benefit of fluorescence imaging in preserving parathyroid glands during thyroid surgery. Future studies should investigate the use of this technique in children.

As mentioned before, however, an individualized treatment approach, including shared decision-making with the child and caregivers is of importance. In terms of the optimal follow-up, the European approach tends to be less ‘aggressive’, recommending less imaging versus that in the USA, and no standard diagnostic whole-body scans.

The transition from pediatric to adult care is an important aspect in the follow-up of pediatric DTC but has not been addressed in the current recommendations. There is a spectrum of childhood and adult DTC, changing in the age group of 16-25 years. There are some young adults who may present with childhood DTC and who might benefit from treatment along the pediatric guideline, and vice versa. This aspect in care should receive separate attention because it is an important aspect in the care and support of the young adult DTC patient.

Imaging modalities in follow-up of pediatric DTC

In the European guidelines on management of pediatric DTC (chapter 5) we suggested that annual cervical US should be performed in the first five years of follow-up. But in low-risk patients, after the first year of follow-up, cervical US ultrasound may be omitted, with reflex cervical US limited to the context of rising Tg, rising TgAbs or suspicion of recurrence of disease to avoid false positive findings. This approach assumes that the risk of residual or recurrent

disease is dependent on risk level. In chapter 6 we investigated the rate of residual or recurrent disease among the three ATA risk levels. Surprisingly, we found a lack of separation of rates of residual or recurrent disease between those with initial low, intermediate, and high-risk DTC. In this study, we had excluded all low-risk patients who underwent lobectomy and whose *a priori* constitute the lowest risk category. Additionally, among the high-risk patients, those with distally metastatic disease and R2 resection were excluded. Exclusion of the lowest and highest risk categories might have led to potential overestimation and underestimation of recurrence risk, respectively. Moreover, differences in radioactive iodine (RAI) therapy between risk groups and underpower might have played a role.

In conclusion, based on the findings discussed in chapter 6, suggestion 23C of the European expert panel (chapter 5) might be modified to: 'We suggest an initial post-operative cervical US for all patients to identify structurally residual disease. It may be reasonable to adopt a 'Tg-first approach' in TgAb-negative patients with undetectable or low-detectable Tg concentrations and/or a reassuring initial post-operative cervical US.' Nevertheless, the importance of individual considerations and shared decision making with the patients and caregivers regarding the benefits and harms of surveillance cervical US should be emphasized.

In chapter 7 we showed that in more than half of the adult patients with elevated Tg concentrations FDG positive lesions were found, in which DTC was confirmed. Also, in children FDG PET/CT imaging might be of additional value for the detection of residual or recurrent disease in case of detectable Tg concentrations but no suspicious findings on cervical ultrasound. However, evidence on the sensitivity and specificity of FGD PET/CT in this setting in children is lacking. Prospective studies on the additional value of FDG PET/CT in children are needed to formulate evidence-based recommendations. The current experienced-based ETA recommendation on the use of FDG PET/CT in the follow-up of children with DTC suggests that FDG PET/CT in children may be considered in case of consistently rising Tg on LT4 or TgAbs (chapter 5).

Part II. Thyroid dysfunction during childhood cancer treatment

In chapter 9, our literature review demonstrated that children treated with systemic antineoplastic drugs are at risk for the development of thyroid dysfunction, although the evidence was very limited. Our prospective new data of the THYRO-dynamics study show that the prevalence of hypo- and hyperthyroidism in the first three months after starting treatment for newly diagnosed childhood cancer is low, illustrating that with the current chemotherapy regimens it is not necessary to screen for thyroid function abnormalities during the first period (chapter 10). A FT4 decline of greater than 20%, although still within the reference range, was found in a large number of children. It has been shown that, in children following cranial irradiation, a decline in FT4 of greater than 20% during follow-up may reflect mild central hypothyroidism, and this could be associated with weight gain, reduced linear growth and less improvement of intelligence scores over time (25). The latter may have been confounded by exposure to radiotherapy to the brain.

Although the etiology of the FT4 decline of more than 20% in our cohort (most probably as a reflection of ESS) may not be comparable to mild central hypothyroidism, clinical effects of lowered hormones for a prolonged time must be considered. Comparable situations exist in children with other chronic diseases and lowered other hormones, such late puberty in children with cystic fibrosis and low IGF-1 concentrations in children with renal disease resulting in short stature (26–28). We hypothesize that prolonged lower thyroid hormone concentrations in children with cancer might contribute to the short stature, weight gain, dyslipidemia, fatigue, or the pathogenesis of early frailty in childhood cancer survivors which has been reported to occur (25,29–31). This question needs to be answered in future studies

Thyroid dysfunction has been reported as a late effect after HSCT in children, however, short-term effects of HSCT on thyroid function parameters are unclear. We found a low prevalence of hypo- and hyperthyroidism in the first three months after HSCT (chapter 11). Based on these findings, we concluded that surveillance for hypo- and hyperthyroidism may start later in time, at six months after HSCT. An early start of surveillance for thyroid dysfunction may even lead to false positive results since children may have aberrant thyroid function parameters during acute illness caused by ESS in which thyroid hormone treatment is not indicated.

Directions for future research

I) Regarding DTC in childhood

International prospective data registry

Due to the rareness of the disease, we must cross borders and collaborate. An essential first step for European collaboration is the current initiative for a prospective international data registry of individual patients within the European Registries for Rare Endocrine Conditions (EuRReca). The aim of this international data registry is to (1) increase our knowledge of clinical behavior of pediatric thyroid nodules and DTC, to (2) identify risk factors for recurrence, and to (3) assess late effects of treatment.

Prevalence and clinical behavior of pediatric thyroid nodules

The main goal in management of children with a thyroid nodule is to distinguish the malignant nodule from the benign nodule because the latter does not always require treatment. However, discrimination between a thyroid nodule at risk for malignancy and a non-clinically relevant thyroid nodule is challenging. Using the current ultrasound risk stratification systems still results in a high unnecessary biopsy rate and missed malignancy rate. Risk factors for DTC, such as a history of radiation to the neck or a pre-disposition syndrome, may also influence the risk of a thyroid nodule being malignant and should be considered in determining the malignancy risk of a thyroid nodule. The role of molecular testing on FNB specimen in children appears to be promising but remains to be refined by more studies.

A second goal in management of children with a thyroid nodule is to prevent overdiagnosis and overtreatment. Overdiagnosis of thyroid nodules may lead to unnecessary additional interventions and worry. Especially in children, the psychological impact of unnecessary additional interventions should be considered.

For these reasons, future research should focus on prediction models to better determine which thyroid nodule needs treatment or follow-up and which thyroid nodule may be considered as non-clinically relevant and does not require (invasive) follow-up. In such a prediction model multiple factors as age, sex, (signs of a) pre-disposition syndrome, ultrasound characteristics, family history, BMI, iodine status and results of molecular testing on FNB specimen might be included.

To reach these goals, the following gaps in research need to be filled:

- The lack of numbers on the prevalence of thyroid nodules in the Dutch/European pediatric population.
- The lack of an accurate validated pediatric ultrasound risk stratification system to define which thyroid nodules are suspicious for thyroid carcinoma.
- The lack of evidence on the predictive value of molecular testing in an FNB specimen of a thyroid nodule for the diagnosis DTC.
- The lack of risk stratification of which thyroid nodules becomes DTC (natural history), and which thyroid nodule requires follow-up and/or treatment

Future directions for research on the thyroid nodule in childhood

To determine the prevalence of (non-clinically and clinically) relevant thyroid nodules in Dutch children. To validate the diagnostic performance of the current adult-based ultrasound risk stratification systems in bigger pediatric cohorts and to evaluate if and which modifications in the adult-based ultrasound risk stratification systems are required/needed for the pediatric population.

To determine the positive and negative predictive value of several molecular alterations in a FNB specimen of a thyroid nodule in a child for the presence of DTC. This could be done by performing an international prospective cohort study, in which molecular testing is performed on a FNB specimen during the diagnostic work-up.

To build an international data registry including children with a thyroid nodule to determine its natural history and the contribution of age, sex, pre-disposition syndrome, family history, BMI, and iodine status to the risk of developing a malignant thyroid nodule.

Optimal treatment approach for pediatric DTC

Our findings confirm that DTC in children is a rare disease, with an incidence of 5.3 per million person-years (2010–2019; 0-24 years) (chapter 2). Choosing the optimal treatment approach may be complex and cannot be generalized due to variations in the individual presentation, risk factors, and prognosis. For this reason, treatment for pediatric DTC should be individualized and requires a multidisciplinary approach in a pediatric thyroid cancer expertise center.

The overall goal of treatment for pediatric DTC is to tailor therapy to treat the tumor sufficiently and limit overtreatment, considering both the possible medical adverse effects of treatment and the psychological impact of undergoing treatment. Children with DTC should be stratified into those who may benefit from higher-intensity treatment versus those in whom lower-intensity treatment will suffice, regardless of whether they have high or low-risk disease. For example, in children with advanced disease, total thyroidectomy with central and/or lateral lymph node dissection and radioactive iodine treatment may be beneficial, however, for those with a small low-invasive tumor and no metastases, a total thyroidectomy alone or even only a lobectomy might be sufficient.

Evaluation of the ATA recommendation sparing adjuvant RAI therapy in low-risk patients showed that withholding RAI therapy might not have a negative impact on remission rates (32). It must be taken into consideration, however, that all children underwent prophylactic CLND. The evidence on how to use stratification of DTC, in terms of clinical, pathological, and molecular characteristics, in personalized treatment is scarce. A large multicenter prospective study is needed to compare outcome of pediatric DTC between patients with low-invasive DTC treated with or without prophylactic CLND and with or without RAI therapy. Outcome parameters of such a study should include remission rates as well as adverse effects after different treatment modalities. Late recurrences of DTC might occur, therefore long-term follow-up is needed.

The definition of low-invasive DTC is still an issue of debate and needs to be clarified before such a multicenter prospective study is launched. The ATA defined low-risk patients as patients with ‘disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)’. However, next to these pathological characteristics also genetic alterations and imaging findings might be predictive for low-invasive disease and should be part of the stratifying approach. Future studies must therefore aim to develop a dynamic prediction model for tumor behavior based on pathological as well as molecular characteristics and imaging findings.

Future directions for research on the thyroid nodule in childhood

Preoperative setting:

To determine the predictive value of suspicious neck ultrasound findings in a lymph node for presence of a DTC metastasis.

To determine whether other imaging modalities than neck ultrasound contribute to evaluating the presence of lymph node and or distant metastases preoperatively.

Postoperative setting:

To determine which histopathological criteria are related to distant/any metastases in childhood DTC.

To determine which genetic alterations are associated with aggressive tumor behavior.

To determine the sensitivity, specificity, positive and negative predictive value of cervical ultrasound, RAI WBS and FDG PET/CT for the presence of lymph node and distant metastases postoperatively.

General:

To obtain insight in DTC in the age group 16-25 years to guide age-appropriate management of DTC.

II) Regarding thyroid function during childhood cancer treatment

Our unique large prospective study performed in 284 children with newly diagnosed cancer showed significant changing thyroid parameters after three months. FT4 concentrations declined ≥20% in 28% of the children. The clinical relevance of these declining FT4 concentrations is unclear and needs to be investigated in further research. The potential effects of having prolonged lowered thyroid hormones, on final height, weight, dyslipidemia, fatigue, and early frailty in childhood cancer survivors should be studied. The final results of the THYRO-dynamics study including thyroid function parameters at the end of treatment and three months after end of treatment will help to answer these questions.

The increase in rT3 concentrations we found reflect the changes in the activity of the deiodinases due to illness or administered drugs and thus may indicate presence of mild ESS. Future research must elucidate the longitudinal course of isolated rT3 elevation and the T3/rT3 ratio in children with cancer which may be associated to the severity of illness and recovery of disease. These questions may be (partly) answered in the final analyses of the THYRO-Dynamics study which are expected in 2024.

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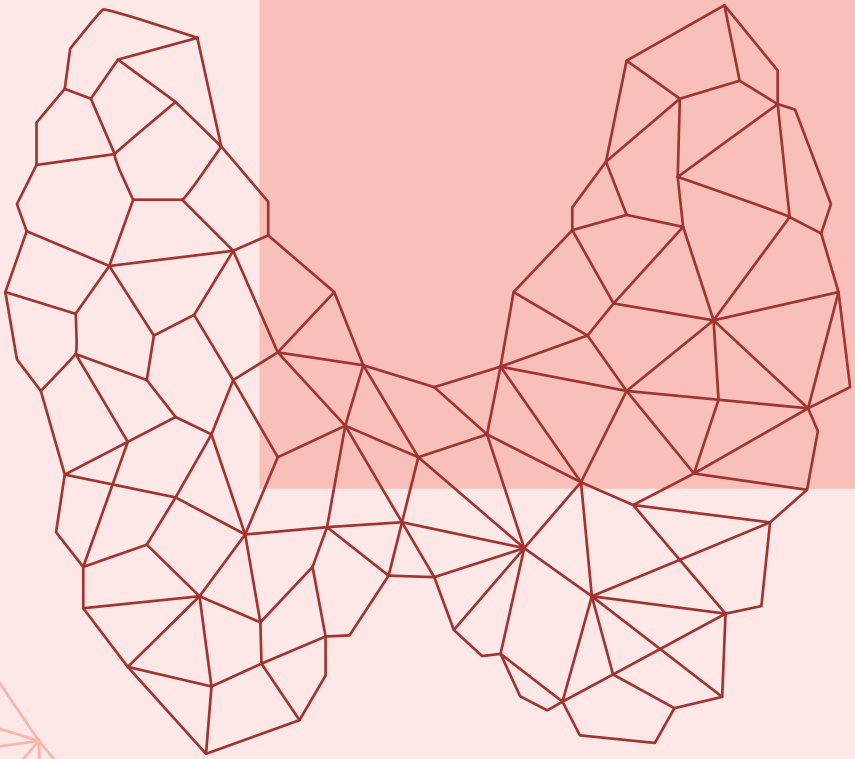

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Appendices

Nederlandse samenvatting

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Nederlandse samenvatting

Gedifferentieerd schildkliercarcinoom bij kinderen

Schildkliercarcinoom bij kinderen komt zelden voor. Bij de meeste kinderen is er sprake van een zogenaamd gedifferentieerd schildkliercarcinoom (differentiated thyroid carcinoma, DTC), dat ontstaat uit de zogenaamde follikelcellen van de schildklier. DTC wordt onderverdeeld in een papillaire (PTC) en een folliculaire variant (FTC). De wereldwijde incidentie van DTC neemt toe. Mogelijk oorzaken hiervoor zijn: verbeterde beeldvormingstechnieken, overdiagnostiek, een toenemende prevalentie van obesitas en blootstelling aan radiatie (1–3). Een risicofactor voor DTC is het vrouwelijk geslacht. Andere risicofactoren voor DTC zijn blootstelling aan halsbestraling, behandeling met ^{131}I gelabeld meta-iodobenzylguanidine (MIBG), een familiegeschiedenis met schildkliercarcinoom en een schildkliercarcinoom predispositie syndroom (bijvoorbeeld PTEN hamartoom tumorsyndroom (PHTS)).

Kinderen met DTC presenteren zich vaak met een palpabele nodus in de schildklier. Een echo van de schildklier is geïndiceerd om het risico op een maligniteit vast te stellen. Het weefsel in de nodus of massa kan worden onderzocht door middel van een dunne naald biopt. De kans dat het weefsel van maligne origine is, wordt ingeschat aan de hand van het Bethesda-classificatiesysteem (4). Alleen als er sprake is van bewezen DTC wordt een totale thyreoidectomie geadviseerd. Een centrale en/of laterale halsklierdissectie wordt uitgevoerd als er pre- of perioperatief bewijs is voor lymfekliermetastasen. In principe krijgen alle kinderen met DTC een nabehandeling met radioactief jodium ($^{131}I^-$). De rol van postoperatieve behandeling met radioactief $^{131}I^-$ is een onderwerp van discussie. $^{131}I^-$ vernietigt schildklierweefsel, waardoor resterend schildklier(tumor)weefsel en eventuele micrometastasen of afstandsmetastasen, worden behandeld (5).

De follow-up van kinderen behandeld voor DTC, bestaat uit een klinische evaluatie, nek palpatie, het meten van de tumor marker thyreoglobuline (Tg), anti-thyreoglobuline antistoffen (TgAbs) en een echo van de hals. Als er een verdenking is op een recidief kan eventueel een dunne naald biopsie worden gedaan, dan wel aanvullende beeldvorming worden verricht in de vorm van een MRI, een diagnostische ^{123}I scan of een [18F] fluorodeoxyglucose positron emissie tomografie (FDG PET)/computer tomografie (CT).

Schildklierdysfunctie tijdens kinderoncologische behandeling

Schildklierhormoon is extreem belangrijk voor kinderen. Schildklierhormoon is nodig voor zowel de stofwisseling van alle cellen in het lichaam als voor (lengte) groei, hersenontwikkeling, spiermassa en botontwikkeling. Bij een tekort aan schildklierhormoon groeien kinderen niet goed, voelen kinderen zich moe, kunnen zij obstipatie ontwikkelen, kan er spier- en gewrichtspijn optreden, een toename in gewicht worden bemerkt en een trage hartactie ontstaan. Desondanks is er niet veel bekend over de dynamiek van schildklierhormoon tijdens de behandeling van kanker op de kinderleeftijd.

De schildklierfunctie kan beïnvloed worden door chemotherapie, bestraling of andere (ondersteunende) medicatie die gebruikt wordt tijdens de behandeling van kanker. Ook kan het ziek-zijn zelf een verlaging van schildklierhormoon geven. Dit wordt euthyroid sick syndrome (ESS) genoemd. ESS wordt beschouwd als een beschermend mechanisme tijdens ziekte.

Dit proefschrift

In dit proefschrift hebben wij ons gericht op het verbeteren van de uitkomsten van kinderen met DTC door de kennis te vergroten over DTC bij kinderen en daarnaast de zorg, zowel nationaal als internationaal te harmoniseren (**deel I**). In **deel II** van dit proefschrift hebben wij ons gericht op het voorkomen van schildklierdysfunctie tijdens kinderoncologische behandeling te onderzoeken.

Deel I. Gedifferentieerd schildkliercarcinoom bij kinderen

In hoofdstuk 2 hebben wij de incidentie en overlevingscijfers beschreven van DTC en medullair schildkliercarcinoom (MTC) bij Nederlandse kinderen, adolescenten en jongvolwassenen (0-24 jaar) over een periode van 30 jaar. In totaal werden er in Nederland tussen 1990 en 2019 839 patiënten tussen de 0-24 jaar gediagnosticeerd met schildkliercarcinoom. Wij vonden een toename van de incidentie van PTC, een stabiele incidentie van FTC en een dalende incidentie van MTC. Lymfekliermetastasen werden in een substantieel deel van de patiënten (40%) gevonden, afstandsmetastasen in een relatief klein deel van de patiënten (3%). Ondanks dat kinderen zich vaak presenteren met uitgebreide ziekte waren de overlevingscijfers zeer goed, namelijk >98.5% na 10 jaar.

In hoofdstuk 3 beschrijven we dat de incidentie van DTC in kinderen met PHTS varieert tussen de 4-12%. De mediane leeftijd dat DTC wordt gediagnosticeerd bij deze patiënten is 12 jaar. De jongste patiënt was vier jaar. We vonden geen verschil in gedrag van de tumor bij kinderen met PHTS vergeleken met kinderen met een sporadisch vorm van DTC. Gebaseerd op onze bevindingen adviseren we surveillance voor DTC bij alle kinderen met PHTS. Surveillance dient te bestaan uit jaarlijkse nek-palpatie en een driejaarlijkse echo van de nek vanaf de leeftijd van 10 jaar. Er zijn echter individuele overwegingen van belang en er dient (er) gedeelde besluitvorming plaats te vinden met het kind en de ouders om te starten met surveillance voor DTC.

Nationale en internationale harmonisatie van zorg voor kinderen met zeldzame ziektes is belangrijk om de uitkomsten te verbeteren. Tot voor kort waren er geen Nederlandse of Europese aanbevelingen voor de behandeling van schildkliernoduli en DTC bij kinderen. In hoofdstuk 4 wordt de eerste Nederlandse leidraad voor de behandeling van DTC bij kinderen weergegeven. Deze leidraad was de eerste stap naar een geharmoniseerde Europese richtlijn. Deze eerste Europese richtlijn wordt in hoofdstuk 5 gepresenteerd. De aanbevelingen in dit proefschrift bieden handvatten voor zorgverleners om weloverwogen keuzes te maken voor de behandeling van kinderen met een schildkliernodus of DTC.

In hoofdstuk 6 hebben wij de toegevoegde waarde van het routinematig uitvoeren van een echo van de hals tijdens de follow-up van kinderen met DTC geëvalueerd. Wij hebben gekeken naar de bijdrage van deze echo in het opsporen van resterend schildkliertumorweefsel of een recidief vergeleken met andere surveillance opties. Gebaseerd op onze bevindingen stellen wij voor om de huidige aanpak, het maken echo van de hals na een totale thyreoidectomie bij alle kinderen, te continueren. Als er op deze eerste postoperatieve echo van de hals geen verontrustende bevindingen worden gedaan, dan stellen wij voor om bij alle kinderen zonder TgAbs en met een niet- detecteerbaar Tg of een laag detecteerbaar Tg gedurende de verdere follow-up de zogenaamde 'Eerst Tg'-aanpak toe te passen (hoofdstuk 6). Dit houdt in dat er alleen een echo van de hals wordt gemaakt, als er sprake is van een stijgend Tg. Bij een klein aantal patiënten met verhoogde TgAbs vonden wij resterend schildkliertumorweefsel of een recidief. Daarom denken we dat het vervolgen van de TgAbs trend niet voldoende is in deze situatie. In deze specifieke gevallen raden wij aan om in de follow-up zowel TgAbs te bepalen als een echo van de hals te maken.

In hoofdstuk 7 hebben we de resultaten van FDG PET/CT als eerstelijns nucleaire beeldvormingsmethode retrospectief geëvalueerd zonder dat deze patiënten eerst een diagnostische ^{123}I scan hadden ondergaan. In deze studie hebben wij gekeken naar volwassen patiënten die werden verdacht van resterend schildkliertumorweefsel of een recidief, doordat zij een (laag) aantoonbaar Tg hadden. Wij vonden in meer dan de helft van de patiënten FDG positieve laesies, waarbij in 93% van deze patiënten DTC werd bevestigd. Echter, we zagen ook dat bij 70% van de patiënten zonder FDG positieve laesies, DTC werd bevestigd binnen drie maanden na de FDG PET/CT.

Samenvattend lieten wij met deze casussen zien dat FDG PET/CT van toegevoegde waarden kunnen zijn om resterend schildkliertumorweefsel of een recidief op te sporen bij patiënten met (laag) aantoonbaar Tg. Dit sluit DTC echter niet uit wanneer er geen FDG positieve laesies worden gevonden.

Overlevenden van kinderkanker hebben een groter risico om een tweede type kanker te ontwikkelen (6). In hoofdstuk 8 hebben wij de klinische presentatie, behandeling en uitkomsten onderzocht van DTC als tweede of volgende kanker bij overlevenden van kinderkanker in Nederland.

Zoals eerdere studies ook hebben laten zien, vonden wij dat DTC als tweede of volgende kanker zich vaker presenteert met een kleinere tumor en zich vaker bilateraal bevindt (7,8). We vonden geen verschillen in gedrag van de tumor en uitkomsten tussen kinderen met DTC als tweede of volgende kanker en kinderen met een sporadische vorm van DTC.

Radiotherapie wordt gezien als grootste risico factor voor de ontwikkeling van DTC als tweede of volgende kanker. Wij vonden echter in ons cohort dat een derde van de patiënten alleen chemotherapie heeft ontvangen voor de behandeling van hun kinderkanker. Grote

gecombineerde analyses hebben laten zien dat alkylerende chemotherapie ook een verhoogd risico kan vormen voor het ontwikkelen van DTC als tweede of volgende kanker (9).

Deel II. Schildklierdysfunctie tijdens kinderoncologische behandeling

Schildklierdysfunctie kan optreden tijdens kinderoncologische behandeling. Hier is echter maar weinig onderzoek naar gedaan. In hoofdstuk 9 hebben wij systematisch gezocht naar alle beschikbare literatuur met betrekking tot schildklierdysfunctie tijdens antineoplastische therapie voor kinderkanker. Een primaire hypothyreoidie werd beschreven in 18% van de kinderen die werden behandeld met een hoge dosis interferon-α (HDI-α) of tyrosine kinase inhibitoren (TKIs). Wij vonden ook dat ESS tussen de 42% en 100% voorkomt bij kinderen die behandeld worden met een combinatie van systemische antineoplastische middelen.

In hoofdstuk 10 en 11 presenteren wij de eerste resultaten van een prospectieve studie in het grootste Europese centrum voor kinderkanker: de THYRO-Dynamics studie. In hoofdstuk 10 hebben wij gekeken naar de prevalentie en risicofactoren voor schildklierdysfunctie tijdens kinderoncologische behandeling bij kinderen met een nieuwe diagnose kinderkanker. Wij vonden een lage prevalentie van zowel hypo- als hyperthyreoïdie drie maanden na diagnose. ESS werd geconstateerd bij 1.5% van de kinderen drie maanden na de diagnose. Daarnaast werden geïsoleerde verhoogde reverse T3 (rT3) waarden gevonden bij 33% van de kinderen bij diagnose en bij 50% van de kinderen drie maanden na de diagnose. Deze verhoogde rT3 waarden werden voornamelijk waargenomen bij kinderen met een hersentumor. Daarnaast vonden wij ook dat schildklierhormoonparameters na drie maanden significant waren gedaald. Wij vonden een individuele daling van 20% in vrij T4 bij 28% van de kinderen. Vervolgstudies dienen zich te focussen op de mogelijke klinische gevolgen van deze daling in vrij T4 op bijvoorbeeld eindlengte, gewicht, dyslipidemie, vermoeidheid en vroegtijdige veroudering in overlevenden van kinderkanker.

In hoofdstuk 11 hebben we de schildklierhormoon parameters geëvalueerd bij kinderen die autologe of allogene stamceltransplantatie (SCT) ondergaan, zowel voor als drie maanden na SCT. Wij hebben ook gekeken naar de dynamiek en risicofactoren voor veranderingen over tijd. Wij vonden afwijkende schildklier stimulerend hormoon (TSH) en vrij T4 waarden bij 16% voor SCT en bij 10% drie maanden na SCT. Er werd geen hypo- en hyperthyreoïdie gevonden in de eerste drie maanden na SCT. Bij ESS passende verhoogde rT3 waarden, passend werden gevonden bij 9.3% voor SCT en 37% drie maanden na SCT. Deze verhoogde rT3 waarden konden wij relateren aan de mate van ziek- zijn. Gebaseerd op deze bevindingen kunnen wij concluderen dat surveillance voor hypo- en hyperthyreoïdie niet nodig is in de eerste drie maanden na SCT (10).

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Curriculum vitae

Chantal Anne Lebbink was born on May 4th, 1992, in Leiderdorp, the Netherlands. She grew up in Roelofarendsveen, together with her parents and brother. In 2010 she graduated from secondary school (Visser 't Hooft Lyceum, Leiden). That same year, she started a study Biomedical Sciences at the Catholic University Leuven. After one year, she moved to Amsterdam to study Psychobiology at the University of Amsterdam. In 2012, she started medical school at the University of Amsterdam. During her medical studies, she developed an interest in pediatric endocrinology and started as research student under supervision of dr. S.C. Clement and dr. H.M. van Santen.

After graduating from medical school in 2018, Chantal started as PhD candidate, resulting in this thesis, at the department of Pediatric Endocrinology at the Wilhelmina Children's Hospital and Princess Máxima Center for pediatric oncology in Utrecht. She was supervised by dr. H.M. van Santen, prof. dr. E.E.S. Nieuwenhuis and prof. dr. W.J.E. Tissing.

She coordinated the national and European guidelines for treatment of pediatric thyroid nodules and differentiated thyroid carcinoma. She also coordinated a prospective study, including >350 patients, on the dynamics of thyroid hormones during childhood oncology treatment.

During the last year of her PhD trajectory, she did research at The Hospital for Sick Children, Toronto, Canada on de value of ultrasound in the follow-up of differentiated thyroid carcinoma in children, supervised by dr. J.D. Wasserman. In January 2023, Chantal started working as pediatric resident (ANIOS) at Alrijne Ziekenhuis in Leiderdorp.