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

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Keywords

Differentiated thyroid carcinoma · PTEN hamartoma tumor syndrome, pediatric · Thyroid carcinoma surveillance program · Thyroid cancer genetics

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

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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 USA 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 (Fig. 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.

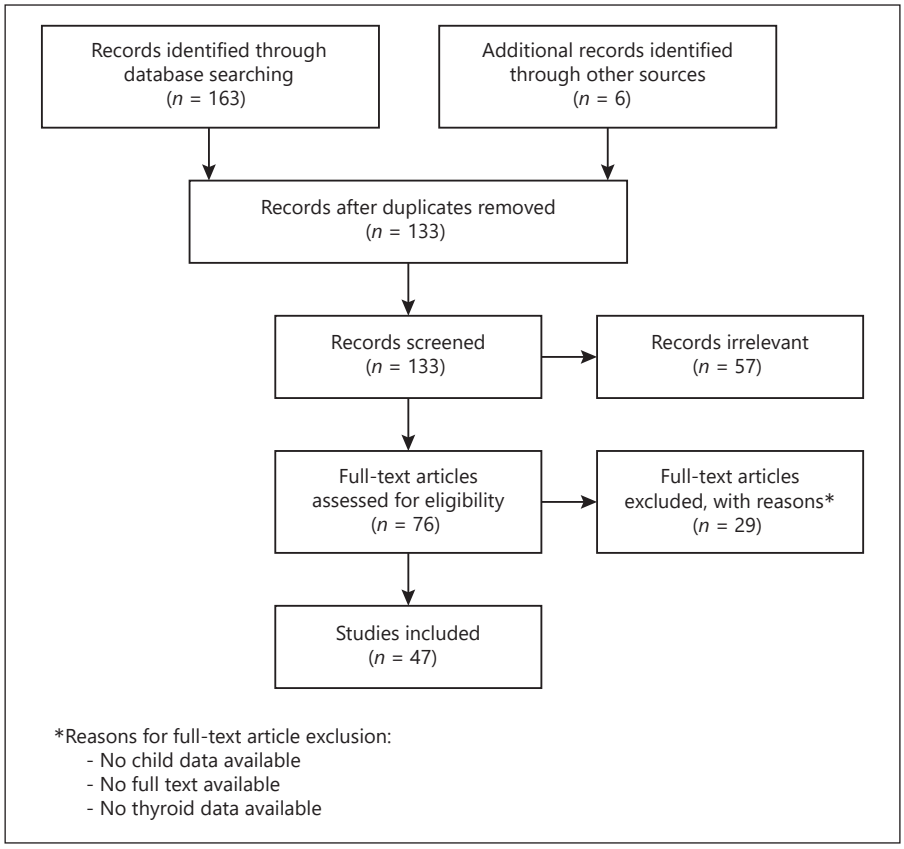

Fig. 1. Flow diagram of extensive literature results. Search strategy, Pubmed, search terms: (Cowden syndrome OR Cowden disease OR Bannayan Riley Ruvalcaba syndrome OR PTEN hamartoma syndrome) AND (thyroid cancer OR thyroid carcinoma OR thyroid nodule OR thyroid disease). To specify the search for childhood 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 is shown.

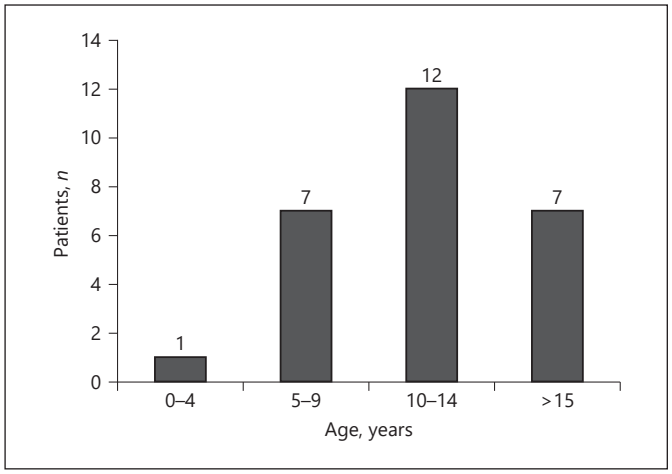

Fig. 2. Age distribution of pediatric patients with PHTS diagnosed with DTC. In total, 27 children (<18 years) with PHTS were identified with DTC. These patients were divided into 4 age categories: 0–4 years (n = 1), 5–9 years (n = 7), 10–14 years (n = 12), >15 years (n = 7).

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 www.karger.com/doi/10.1159/000508872 for all online suppl. material). 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), with most cases of DTC diagnosed between the ages of 10 and 14 years (Fig. 2).

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, follicular thyroid carcinoma (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 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 combina-

Table 2. Pros and cons of screening for DTC

Arguments for and against DTC surveillance of patients at risk (independently 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 noninvasive
High specificity (96–100%) for detecting a thyroid nodule that might represent DTC (many true-negative and few false-positive results for nodules)
Disadvantages
Low sensitivity (17–43%) for detecting a thyroid nodule that might represent DTC (few true-positive and many false-negative results 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
Noninvasive
High sensitivity (approx. 95–100%) for detecting a thyroid nodule that might represent DTC (many true-positive and few false-negative results for nodules)
High specificity (approx. 95–100%) for detecting a thyroid nodule that might represent DTC (many true-negative and few false-positive results 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].

tion 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 childhood cancer survivors 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 childhood cancer survivors (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.

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 re-

sults 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.

Statement of Ethics

Informed consent was obtained from both patients and their parents for publication.

Disclosure Statement

The authors have nothing to disclose.

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