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Complications of Treatment

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

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ABSTRACT

Radiation exposure to the thyroid gland during treatment of childhood, adolescent and young adult cancer (CAYAC) may cause differentiated thyroid cancer (DTC). Surveillance recommendations for DTC vary considerably, causing uncertainty about optimum screening practices. The International Late Effects of Childhood Cancer Guideline Harmonization Group, in collaboration with the PanCareSurFup Consortium, developed consensus recommendations for thyroid cancer surveillance in CAYAC survivors. These recommendations were developed by an international multidisciplinary panel that included 33 experts in relevant medical specialties who used a consistent and transparent process. Recommendations were graded according to the strength of underlying evidence and potential benefit gained by early detection and appropriate management. Of the two available surveillance strategies, thyroid ultrasound and neck palpation, neither was shown to be superior. Consequently, a decision aid was formulated to guide the health care provider in counseling the survivor. The recommendations highlight the need for shared decision making regarding whether to undergo surveillance for DTC and in the choice of surveillance modality.

Introduction

Childhood, adolescent and young adult (CAYAC) survivors are at risk for developing subsequent malignancies [1–7], of which approximately 10% involve the thyroid gland [7]. The occurrence of differentiated thyroid carcinoma (DTC) is predominantly attributable to radiation therapy that directly or incidentally involves the thyroid gland [8–10]. Among CAYAC survivors who received radiation exposure to the thyroid gland, standard incidence ratios of DTC range from 5- to 69-fold depending on radiation dose [8]. Consequently, periodic surveillance of CAYAC survivors at increased risk of developing DTC has been advocated [11–13]. However, since most DTC have a favourable prognosis [14], there is debate regarding both the necessity of routine surveillance and the optimal modality for screening. Surveillance for late effects can expose survivors to unnecessary harms if it results in overdiagnosis or false positive test results, both of which can result in avoidable distress. For this reason, some deem that recommending health screening is unethical unless all possible harms as documented by the best available evidence are considered in the context of potential benefits [15]. To guide the clinical care of CAYAC survivors at increased risk for DTC, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) appointed an expert panel to examine and summarize all available evidence regarding the risk factors for DTC and the benefits, risks, and harms of different strategies for screening for occult DTC. Herein, we present recommendations for surveillance of CAYAC survivors at risk for DTC that were formulated following evaluation of this evidence.

Methods

The development of this guideline adheres to the IGHG methods as previously described [16]. The expert panel comprised representatives from the North American Children's Oncology Group (COG) [11], the Dutch Childhood Oncology Group (DCOG) [12], and the UK Children's Cancer and Leukaemia Group (UKCCLG) [13], as well as experts in thyroid nodule/cancer management from a range of medical specialties (pediatric/adult endocrinology, radiology, thyroid surgery, and nuclear medicine) and geographic regions. The core leadership group identified key topics and appointed four working groups, each composed of five to eight experts.

Evidence-based guideline development involved several stages. First, the concordance and discordance between the COG, DCOG and UKCCLG recommendations for DTC surveillance in CAYAC survivors was evaluated. Subsequently, focused clinical questions were developed to address areas of discordance in existing DTC surveillance guidelines as well as areas of concordance that were controversial in the literature with the intent to develop recommendations based on these questions (Appendix A). To identify all relevant literature, an English language PubMed search was performed. Keywords and medical subject heading terms were used to identify all potentially relevant titles and abstracts. Search terms and dates varied by topic (Appendix B). Manual cross-referencing was used to identify additional articles, and experts suggested relevant papers that may have been missed in the search. Two independent reviewers selected the studies and abstracted data using standardized data-abstraction forms. Survivors of CAYAC were defined as individuals treated for cancer up to 21 years of age and at least two years post-treatment, irrespective of current age. When evidence was lacking for CAYAC survivors, we extrapolated evidence from other populations such as patients who had received radiation therapy for benign thyroid lesions, individuals exposed to radiation as a consequence of nuclear fallout or atomic bombs, and patients with sporadic DTC. The quality of the evidence and the strength of the recommendations were graded according to evidence-based medicine methods developed by experts within the Cochrane Childhood Cancer Group [17] and the IGHG [16] using existing methods including the Applying Classification of Recommendations and Level of Evidence criteria of the American Heart Association (Data Supplement), and the Grading of Recommendations, Assessment, Development and Evaluations Working Group (GRADE; Appendix C) [18,19]. Expert panel members discussed the evidence and formulated recommendations for surveillance based upon evidence and expert opinion. Final recommendations, the strength of each recommendation, and the quality of the evidence informing each recommendation, were arrived at by consensus of the panel members. The final document was critically appraised by two independent external experts and three patient representatives.

Results

Table 1 summarizes the areas of discordance and concordance between the published long-term follow-up guidelines for DTC surveillance in CAYAC survivors. Evidence summaries for the clinical questions covering the areas of discordance are provided in Appendix D. Summaries of the available evidence and assessment of the strength of evidence addressing each clinical question are shown in Table 2. The final recommendations as well as the

Table 1
Concordances and discordances in DTC surveillance recommendations.

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Concordant/ discordant
Who needs DTC surveillance?				
Treatment that increases risk				
RT that includes the thyroid gland	Yes	Yes	Yes	Concordant
RT specified	Cranial Nasopharyngeal Oropharyngeal Waldeyer's ring Cervical (neck) Supraclavicular Spine (cervical, whole) STLI Extended Mantle Mantle Mediastinal Mini-Mantle TBI TLI	Cervical (neck) TBI	Radiotherapy to a field including thyroid; including: Neck Spine Mantle Mediastinum TBI	Concordant
^{131}I-MIBG	No	Yes	Yes	Discordant
Chemotherapy	No	No	Busulphan based condition for BMT	Discordant
Risk factors	Younger age at treatment Female sex Thyroid gland directly in radiation field TBI Radiation dose (risk increased up to 30 Gy with a downturn of risk after 30 Gy	Not stated	Not stated	Discordant
What surveillance modality should be used to detect a thyroid nodule that might represent DTC?				
Surveillance for thyroid cancer	Thyroid palpation	Thyroid palpation	Thyroid palpation	Concordant
At what frequency and for how long should DTC surveillance be performed?				
Surveillance begins	Not stated	>5 years after diagnosis	Not stated	Discordant
Surveillance frequency	Yearly	Every outpatient clinic visit	Yearly	
Duration of surveillance	Not stated	Not stated	Not stated	
What should be done when abnormalities are identified?				
Refer to thyroid specialist	Yes	Yes	Yes	Concordant

Abbreviations: DTC: differentiated thyroid carcinoma; RT: radiotherapy; STLI: subtotal lymphoid irradiation; TBI: total body irradiation; TLI: total lymphoid irradiation; MIBG: meta-iodobenzylguanidine; BMT: bone-marrow transplantation; Gy: gray.

strength of the recommendations and the quality of the evidence informing each recommendation are provided in Table 3. To inform the final recommendations, we summarized the available evidence for the following questions.

Does earlier detection of DTC by surveillance impact morbidity and mortality?

Evidence

No randomized trials have been performed to evaluate if earlier detection of DTC by surveillance impacts morbidity and mortality. Available evidence limited to non-cancer populations was evaluated to assess the impact of DTC stage at diagnosis on outcome [20]. Evidence from studies of children suggests that detection of DTC at an early stage is associated with lower rates of recurrence and mortality (level C) [20]. Evidence from studies of adults indicates that advanced staged DTC is a risk factor for recurrence (level B) and mortality (level A) [20]. Additionally, data demonstrates that more extensive surgery increases the risk of developing transient hypoparathyroidism (RR 6.45 (0.329–3.456)) (level A) and that higher doses of radioiodine increase the risk for developing second primary malignancies (OR for leukemia after exposure to 3.7–18.4 Giga Becquerel (GBq): relative risk (RR) 3.1 (1.0–10.3)) (level B), for solid cancers after exposure to 7.4–14.7 GBq (RR 1.5 (1.0–2.0)) [20]. When DTC is detected at an early stage, patients may require less extensive surgery and potentially no or lower doses of radioactive iodine therapy [21,22]. In conclusion, indirect evidence suggests that early detection of DTC by surveillance may be beneficial for CAYAC survivors.

Which CAYAC survivors are at risk for developing DTC and who should be counseled about possible DTC surveillance?

Evidence

CAYAC survivors treated with radiation therapy that includes the thyroid gland are at an increased risk of developing DTC (level A) [8,10,23–26]. Furthermore, the incidence of DTC in neuroblastoma survivors who received therapeutic ^{131}I-MIBG may be increased (level C) [27,28]. Administration of chemotherapy alone has not been linked unequivocally to an elevated risk of DTC (level B) [10,26]. However, in a pooled analysis of four studies that synthesized all international evidence available to date from studies with radiation dosimetry, the RR for DTC following treatment with anthracyclines was 4.5 (95% confidence interval (CI) 1.4–17.8) in non-irradiated patients (level B) [10].

The dose-response curve describing the relationship between the cumulative dose of external radiation and the risk for DTC is linear up to approximately 10 Gy, plateaus between 10 and 30 Gy, and declines at higher radiation doses (level A) [10]. However, no safe radiation dose could be identified since DTC has been reported in survivors who received thyroid radiation doses of less than 1 Gy and the risk remains increased in individuals

Table 2
Conclusions of evidence for DTC surveillance in CAYAC survivors.

	Level of evidence
Does detection of DTC in an early phase by surveillance impact morbidity and mortality?	
Possible benefits of detection of DTC at an early stage	
Detection of DTC at an early stage is associated with a lower recurrence rate in *children*	Level C [20]
Detection of DTC at an early stage is associated with a lower recurrence rate in *adults*	Level B [20]
Detection of DTC at an early stage is associated with a lower mortality rate in *children*	Level C [20]
Detection of DTC at an early stage is associated with a lower mortality rate in *adults*	Level A [20]
If early identification of DTC results in less extensive surgery, does it contribute to a reduction of surgical complications?	
Decreased risk for surgical complications after detection of DTC at an early stage in *children*	Conflicting evidence
Decreased risk of temporary hypoparathyroidism after detection of DTC at an early stage in *adults*	Level A [20]
Does early identification DTC, possibly resulting in a reduction of the number and dosage of radioiodine treatment, contribute to a reduction of severe adverse effects (second primary malignancies (SPM) of radioiodine treatment)?	
Increased risk for SPM following radioiodine treatment after detection of DTC at an early stage in *children*	No evidence
Increased risk for SPM following radioiodine treatment after detection of DTC at an early stage in *adults*	Level B [20]
Who should be counseled about the risk of DTC and informed about possible DTC surveillance?	
Risk following radiation therapy that includes the thyroid gland	
Increased risk after radiation therapy >1 Gy	Level A [8,10,23–26]
Risk following therapeutic ^{131}I-MIBG	
Increased risk after therapeutic ^{131}I-MIBG	Level C [27,28]
Risk following chemotherapy only	
No increased risk after chemotherapy only	Level B [10,26]
Increased risk after anthracyclines	Level B [10]
Factors that alter the radiation risk	
Risk by radiation dose	Level A [10]
>0–1 Gy: RR 1.9 (95% CI 1.0–3.7)	
2–4 Gy: RR 7.4 (95% CI 3.3–16.4)	
5–9 Gy: RR 14.9 (95% CI 7.1–31.4)	
10–19 Gy: RR 14.8 (95% CI 7.1–31.4)	
20–29 Gy: RR 15.2 (95% CI 7.8–28.4)	
30–39 Gy: RR 9.3 (95% CI 4.3–20.3)	
>40 Gy: RR 5.1 (95% CI (2.2–11.9)	
Increased risk after high fraction size	No evidence
Increased risk after high dose-rate	No evidence
Increased risk in survivors of CAYAC who were young at primary cancer diagnosis	Level B [10,25]
Increased risk in female vs. male survivors of CAYAC	Conflicting evidence [23–26]
Increased risk after chemotherapy in addition to a radiation thyroid dose <20 Gy vs. radiotherapy alone <20 Gy	Conflicting evidence [9], [26]
Increased risk after persistent elevated thyrotrophin levels throughout follow-up	No evidence
If the decision to commence surveillance is made, what surveillance modality should be used to detect a thyroid nodule that may represent a DTC?	
Diagnostic value of thyroid neck palpation vs. ultrasonography to detect a thyroid nodule possibly indicating the presence of DTC	
Poor diagnostic value of neck palpation	Level A [24,29–34]
Sensitivity: 17–43%	
Specificity: 96–100%	
Diagnostic value of US vs neck palpation to detect a thyroid nodule	Level A [35–37]
Sensitivity: ~95 to 100%	
Specificity: ~95 to 100%	
Diagnostic value of sonographic features vs. cytological and histological confirmation to detect the presence of DTC	
Poor diagnostic value of *individual* sonographic features	Level A [38–41]
The diagnostic value of *combinations* of sonographic features is higher than *individual* sonographic features but varied considerably from study to study	Level A [42–51]
Sensitivity: 48–99%	
Specificity: 44–96%	
Which additional risk factors can be used to predict the presence of thyroid cancer in patients with a thyroid nodule?	
Risk factors that increase the risk of thyroid cancer in patients with a thyroid nodule	
Increased risk after prior head and neck irradiation	Level B [52]
Increased risk in male vs. female patients	Level B [52]
Increased risk in patients with a family history of thyroid cancer	Level B [52]
Which additional diagnostic tests can be used to predict the presence of DTC in patients with a thyroid nodule?	
Diagnostic value of fine needle aspiration cytology vs. histological confirmation to predict the presence of DTC	
Fair diagnostic value of fine needle aspiration cytology in *children*	Level A [53–59]
Sensitivity: 60–100%	
Specificity: 65–95%	
Inadequacy rate: 2–28%	
Good diagnostic value of ultrasound-guided fine needle aspiration cytology in *adults*	Level A [60–67]
Sensitivity: 82–96%	
Specificity: 71–99%	
Inadequacy rate: 5–12%	
Fine needle aspiration biopsy is in general a safe procedure	Level A [68]

(*continued on next page*)

Table 2 (*continued*)

	Level of evidence
If the decision to commence surveillance is made at what frequency should DTC surveillance be performed?	
There is a peak incidence of radiation induced thyroid cancer 10.0–20.0 years after primary cancer diagnosis (range 4.2–38.0 years)	Level B [8,23,26,29,69–79,95,96]
Risk factors that alter the latency time	No evidence
Average growth rate of thyroid nodules	No evidence
Course of DTC risk over time	No evidence

Level A, high level of evidence (i.e. consistent evidence from well performed and high quality studies or systematic reviews with a low risk of bias, and direct, consistent and precise results); level B, moderate to low level of evidence (i.e. evidence from studies or systematic reviews with few important limitations); and level C, very low level of evidence (i.e. evidence from studies with serious flaws, only expert opinion or standards of care).
Abbreviations: DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adult cancer; MIBG: meta-iodobenzylguanidine; Gy: gray; RR: relative risk; CI: confidence interval; SPM: second primary malignancy.

who received radiation doses exceeding 40 Gy [10]. Data on the impact of dose rate and fraction size on DTC risk are not available. Some evidence indicated that survivors who are younger at primary cancer diagnosis/treatment are at increased risk of developing DTC (level B) [10,25]. Unfortunately, consistent data for risk by age at radiation exposure are lacking. Similar to the general population, an increased risk for DTC has been reported in female compared to male survivors with a RR of 2.0 (95% CI 1.5–2.8) in the pooled analysis described above [10]; however other studies have reported no association with gender (conflicting evidence) [23–26]. Another factor that has been proposed to alter the risk for DTC in CAYAC survivors treated with radiotherapy is the addition of chemotherapy. The largest study to date demonstrated that survivors who had been treated with a thyroid radiation dose <20 Gy plus chemotherapy were more likely to develop DTC than those who received radiation without chemotherapy (RR 4·0 95% (CI 1·4-16·5)) [9]. However, a study by Taylor and colleagues did not observe this association (conflicting evidence) [26]. No studies were identified that addressed whether an elevated thyrotropin concentration promotes the development of DTC.

Recommendations

1. CAYAC survivors treated with radiation therapy that includes the thyroid gland (level A evidence) or therapeutic ^{131}I-MIBG (level C evidence) should be counseled by their health care provider regarding their increased risk for developing DTC (strong recommendation).
2. CAYAC survivors should be advised to inform their health care provider if they detect a thyroid mass, independent of the presence or absence of associated symptoms (expert opinion; strong recommendation).
3. At-risk survivors (i.e., those treated with radiation therapy that includes the thyroid gland (level A evidence; strong recommendation), should be counseled about options for DTC surveillance. The decision to commence surveillance should be made by the health care provider in consultation with the survivor after careful consideration of the survivor's perspective about the advantages and disadvantages of DTC surveillance (Box 1, Fig. 1) (expert opinion; strong recommendation).
4. For neuroblastoma survivors who received therapeutic ^{131}I-MIBG (level C evidence; weak recommendation) it may be reasonable to counsel about DTC surveillance.. The decision to commence surveillance should be made by the health care provider in consultation with the survivor after careful consideration of the survivor's perspective about the advantages and disadvantages of DTC surveillance (Box 1, Fig. 1) (expert opinion; strong recommendation).

Box 1 Arguments for and against DTC surveillance in at-risk CAYAC survivors (independent of surveillance modality).

Advantages:

- CAYAC survivors undergoing surveillance are likely to have DTC detected at an earlier stage. This may reduce the extent of surgery and/or need for radioiodine therapy, which could decrease overall morbidity, recurrence as well as mortality.
- CAYAC survivors who do not have a DTC detected when they undergo surveillance may benefit by being reassured that they do not have a new 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 interventions may result in stress and anxiety, as well as inconvenience, costs, and complications of unnecessary biopsies or surgery.
- There is a risk that surveillance will detect an indolent DTC, which may never cause clinical problems and lead to overtreatment.
- False negative results of surveillance may lead to some survivors being falsely reassured that they do not have DTC, when in fact they do.

Abbreviations: DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adult cancer.

If the decision is made to commence surveillance, what surveillance modality should be used to detect a thyroid nodule that may represent a DTC?

Evidence regarding the diagnostic value of thyroid palpation and thyroid ultrasonography was evaluated by assessing the literature reporting sensitivity and specificity for detecting DTC using the specific procedures.

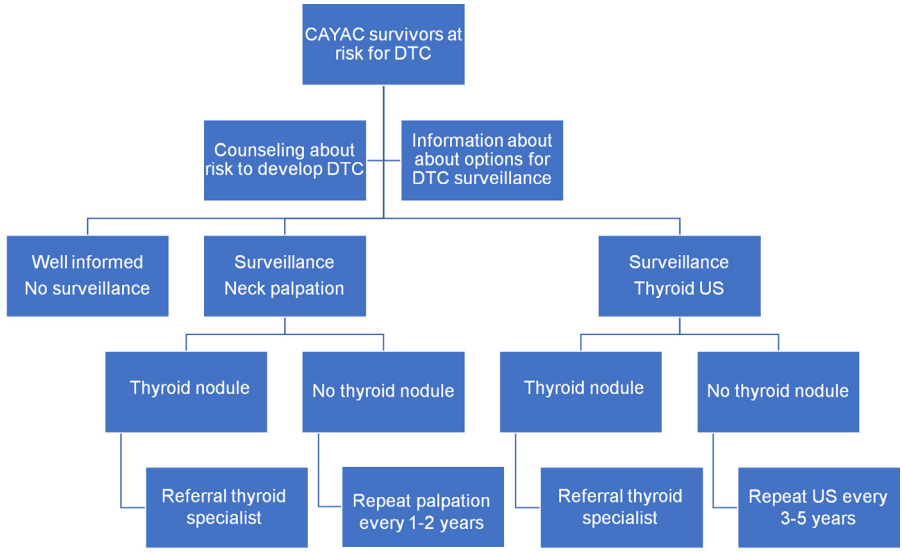
Evidence

What is the diagnostic value of neck palpation versus thyroid ultrasonography for detecting a thyroid nodule that might represent DTC?

Table 3
Harmonized recommendations for DTC surveillance in CAYAC survivors.

Who should be counseled about the risk of DTC?
1. It *is recommended* that CAYAC survivors treated with radiation therapy that includes the thyroid gland (level A evidence) or therapeutic ^{131}I-MIBG (level C evidence) should be counseled by their health care provider regarding their increased risk for developing DTC.
2. It *is recommended* that CAYAC survivors should be advised to inform their health care provider if they detect a thyroid mass, independent of the presence or absence of associated symptoms (expert opinion).
Who should be informed about DTC surveillance?
3. It *is recommended* that at-risk survivors (i.e., those treated with radiation therapy that includes the thyroid gland) (level A evidence) should be counseled about options for DTC surveillance. The decision to commence surveillance should be made by the health care provider in consultation with the survivor after careful consideration of the advantages and disadvantages of DTC surveillance (Box 1) in the context of the survivor's individual preferences.
4. It *may be reasonable* to inform neuroblastoma survivors who received therapeutic ^{131}I-MIBG (level C evidence) about options for DTC surveillance. The decision to commence surveillance should be made by the health care provider in consultation with the survivor after careful consideration of the advantages and disadvantages of DTC surveillance (Box 1) in the context of the survivor's individual preferences.
If the decision to commence surveillance is made, what surveillance modality should be used to detect a thyroid nodule that may represent a DTC?
5. It *is recommended* to use neck palpation or thyroid ultrasonography as a screening modality if surveillance for DTC is planned. Health care providers should be aware that both diagnostic tests have advantages and disadvantages and can identify benign as well as malignant nodules resulting in need for invasive procedures (Box 2, Figure 1) (level A evidence). The decision regarding which modality to use should be made by the health care provider in consultation with the survivor after careful consideration of the advantages and disadvantages of the two modalities in the context of the practice setting, the health care provider's experience, expertise of local diagnosticians (radiology), and the survivor's preferences.
6. Ultrasound and FNA and/or biopsy *is recommended* to be performed in centers where there is experience in assessment of thyroid cancers so that appropriate interpretation of radiographic features and clinical risk factors can minimize the number of unnecessary invasive and additional diagnostic procedures. When ultrasound is used for surveillance, the cervical lymph node stations should always be visualized (expert opinion).
If the decision to commence surveillance is made, at what frequency should DTC surveillance be performed?
7. It *is reasonable* to commence surveillance for DTC 5 years after radiation therapy that includes the thyroid gland or therapeutic ^{131}I-MIBG (level B evidence).
8. It *is recommended* that even when a CAYAC survivor does not opt for periodic surveillance with either ultrasonography or palpation, it is appropriate to include examination of the neck as part of a complete physical exam whenever a survivor is assessed by a health care provider (expert opinion).
9. If periodic thyroid palpation is chosen as the screening modality it *may be reasonable* to repeat surveillance for DTC every 1-2 years (expert opinion; weak recommendation). If thyroid ultrasonography is chosen as screening modality; it *may be reasonable* to repeat surveillance for DTC every 3-5 years if there are no abnormalities found initially (expert opinion).
What should be done when abnormalities are identified?
10. Consultation with a thyroid specialist *is recommended* for survivors with a thyroid nodule (detected either by palpation or thyroid ultrasonography, or incidentally noted on other imaging studies (such as CT or MRI)) (expert opinion).

Strong recommendation, with a low degree of uncertainty
Moderate recommendation
Weak recommendation



Abbreviations: DTC: differentiated thyroid carcinoma; US: ultrasonography

Fig. 1. Options for surveillance of DTC in CAYAC survivors at risk.

Appendix E summarizes seven studies in radiation-exposed individuals that compared the diagnostic value of thyroid nodule surveillance in asymptomatic individuals with neck palpation and thyroid ultrasound [24,29–34]. The diagnostic value of neck palpation was reported in three studies of CAYAC survivors [24,29,30], one study of children exposed to radiation for treatment of benign conditions [31], and three studies of individuals exposed to environmental radiation [32–34]. In the studies that used thyroid ultrasonography as the gold standard for determining the presence of a nodule, the sensitivity of neck palpation for detecting a thyroid nodule ranged from 17 to 43% and the specificity varied between 96 and 100% (level A). These results demonstrate that neck palpation has poor diagnostic value for detecting the presence of a thyroid nodule that might represent DTC in CAYAC survivors. The false negative rate of neck palpation for detecting a thyroid nodule is high, however the false positive rate is low.

What is the diagnostic value of thyroid ultrasonography versus neck palpation for detecting a thyroid nodule that might represent DTC?

Thyroid ultrasonography is considered the gold standard for detecting a thyroid nodule in a clinical setting with a sensitivity and specificity of 95–100% (level A) [35–37].

What is the diagnostic value of thyroid ultrasonography versus cytological and histological confirmation for diagnosing a DTC in an individual with a thyroid nodule?

Although thyroid ultrasonography has good diagnostic values for detecting thyroid nodules, its ability to discriminate between a benign or indolent nodule and DTC is poor (level A) [38–41]. Many clinically occult, non-palpable thyroid nodules may be identified due to the high sensitivity of ultrasonography (overdiagnosis). Several radiographic features have been reported to increase the likelihood that a thyroid nodule is malignant, including microcalcifications, irregular margins, hypoechogenicity, predominantly solid pattern, intranodular vascularity, taller than wide shape and absence of the halo sign [38,39]. However, no single radiographic feature is sufficiently sensitive or specific to differentiate DTC from a benign nodule (level A) [38–41]. Appendix F summarizes 10 studies that examined combinations of radiographic features to predict whether a thyroid nodule detected with ultrasound is malignant [42–51]. The sensitivity and specificity of combinations of radiographic features is higher than individual radiographic features. However, the diagnostic accuracy of different combinations varied considerably from study to study (level A) [42–51]. None of the studies exclusively included patients with a history of radiation exposure – all focused primarily on patients with sporadic DTC.

What are the clinical risk factors suggesting an increased likelihood of DTC in individuals diagnosed with a thyroid nodule identified by thyroid ultrasonography?

A meta-analysis performed by Campanella et al. indicated that when a thyroid nodule is found, the chance of it being malignant is increased in patients with a family history of thyroid carcinoma, those who have had head and neck irradiation and males (level B) [52]. All experts agreed that co-existence of suspicious enlarged regional cervical lymph nodes increases the likelihood that a thyroid nodule is malignant (expert opinion). However, the size of the nodule is not a risk factor for a nodule being malignant (level C).

What is the diagnostic value of FNA cytology versus biopsy to detect DTC in a thyroid nodule?

FNA cytology in children has a fair diagnostic value (level A) [53–59]. In seven included studies, the sensitivity of FNA cytology ranged from 60 to 100%, and the specificity varied between 65 and 99% (Appendix G). The inadequacy rate (i.e., unsatisfactory or insufficient for diagnosis or indeterminate cytology results) varied between 2 and 28%, reflecting the operator dependency of this modality. In adults, ultrasound-guided FNA cytology was found to have good diagnostic value (level A) [60–67].

What is the complication rate of FNA biopsy?

FNA biopsy of a thyroid nodule in adults and children is, in general, a safe procedure (level A). Pain and/or discomfort are the most common complications. Most complications following FNA biopsy have low morbidity and are self-limited; serious complications are extremely rare (level A) [68].

Recommendations

5. Neck palpation or thyroid ultrasonography can be used as a screening modality if surveillance for DTC is planned. Health care providers should be aware that both diagnostic tests have advantages and disadvantages and can identify benign as well as malignant nodules resulting in need for invasive procedures (Box 2, Fig. 1) (level A evidence; strong recommendation).

The decision regarding which modality to use should be made by the health care provider in consultation with the survivor after careful consideration of the advantages and disadvantages of the two modalities in the context of the practice setting, the health care provider's experience, expertise of local diagnosticians (radiology), and the survivor's preferences.

6. Ultrasound and FNA and/or biopsy should be performed in centers where there is experience in assessment of thyroid cancers so that appropriate interpretation of radiographic features and clinical risk factors can minimize the number of unnecessary invasive and additional diagnostic procedures. When ultrasound is used for surveillance, the cervical lymph node stations should always be visualized (expert opinion; strong recommendation).

Box 2 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 dependent on experience of the physician (high-interobserver variation).

Arguments for and against DTC surveillance with thyroid ultrasonography.

Advantages:

- Non-invasive.
- High sensitivity (~95 to 100%) for detecting a thyroid nodule that might represent DTC (many true positives and few false negatives for nodules).
- High specificity (~95 to 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 an identified 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 dependent on experience of the ultrasonographer (high-interobserver variation).

Abbreviations: DTC: differentiated thyroid carcinoma.

At what frequency and for how long should surveillance be performed?

Evidence

Appendix H summarizes 16 studies that reported on the latency period of radiation-induced DTC in CAYAC survivors [8,23,25,26,29,69–79], DTC was most frequently diagnosed 10–20 years after the primary cancer diagnosis. However, DTC was reported as early as 4.2 years and as late as 38 years after the primary cancer diagnosis in CAYAC survivors (level B) [8,23,25,26,29,69–79]. There is insufficient evidence to identify a plateau phase for the cumulative incidence of radiation-induced DTC. Furthermore, considering that survival of childhood cancer has increased dramatically in the last decades, there are no reliable data on DTC incidence in older CAYAC survivors due to limited numbers in this group. The incidence of sporadic and occult thyroid (micro) carcinoma increases with age [80]; therefore the frequency of false-positive test results related to thyroid cancer surveillance (i.e. benign nodules or small cancers with very little chance of progression) will likely increase with increasing follow-up time.

Recommendations

7. It is reasonable to commence DTC surveillance 5 years after radiation therapy that includes the thyroid gland or therapeutic ^{131}I-MIBG (level B; moderate recommendation).
8. Even when a CAYAC survivor does not opt for periodic surveillance with either ultrasonography or palpation, it is appropriate to include examination of the neck as part of a complete physical exam whenever a survivor is assessed by a health care provider (expert opinion; strong recommendation).
9. If periodic thyroid palpation is chosen as the screening modality, this should occur every 1–2 years (expert opinion; weak recommendation). If thyroid ultrasonography is chosen as modality for DTC surveillance, it may be reasonable to repeat thyroid ultrasonography every 3–5 years if there are no abnormalities found initially (expert opinion; weak recommendation). No recommendation is made for how long surveillance should be continued.

What should be done when abnormalities are identified?

The primary purpose of this guideline is to present an evidence-based framework for DTC surveillance in at-risk CAYAC survivors. Therefore, we do not address all the steps required for the diagnosis and appropriate management of DTC after the detection of a suspicious nodule. Since radiation-induced DTC does not appear to differ in clinical behavior from sporadic DTC [81–84], treatment of such a DTC can be performed based on established treatment algorithms [21,22,85,86].

Recommendation

10. Consultation with a thyroid specialist is recommended for survivors with a thyroid nodule (detected either by palpation or thyroid ultrasonography, or incidentally noted on other imaging studies (such as CT or MRI)) (expert opinion).

Discussion

An expert panel of the IGHG evaluated evidence for the benefits and harms related to surveillance for DTC, a relatively common late treatment complication among CAYAC survivors treated with neck radiation. Based on available data, the panel concurred that CAYAC survivors at risk for DTC should be counselled about

DTC risk and options for surveillance. Initiation of surveillance and the surveillance modality should be made by the health care provider in consultation with the survivor following careful consideration of the advantages and disadvantages of DTC surveillance and surveillance modality (Box 1,2). The evidence summarized in this manuscript provides data to guide such discussions as well as outlines critical areas for future research [11–14,21–24,29,87,88].

An argument in favour of DTC screening is the possible reduction in morbidity, recurrence and mortality. Evidence from lower quality studies, limited mainly by small patient numbers, suggests that treatment of DTC at an earlier stage is associated with lower recurrence and mortality rates. Due to lack of studies in children, no evidence was identified that evaluated the impact of early detection of DTC in children on morbidity, defined as hypoparathyroidism, recurrent nerve injury, or subsequent malignant neoplasms resulting from more extensive surgery or thyroid ablation. In adults, evidence indicates that less advanced DTC is a favorable prognostic factor for recurrence and mortality. Additionally, data demonstrates that more extensive surgery increases the risk for developing transient hypoparathyroidism and that higher doses of radioiodine increases the risk for developing subsequent malignant neoplasms [20].

The potential benefits of detection of early stage DTC should be considered in the context of possible negative aspects of surveillance. Neck palpation for DTC may result in survivors being falsely reassured (false negative results). The possible harms of ultrasound screening for DTC include overdiagnosis (i.e., finding indolent non-clinically relevant carcinoma) and false positive test results (finding benign nodules), leading to increased costs and anxiety associated with unnecessary diagnostic and surgical interventions [11–14,21–24,29,87,88]. The plan to initiate surveillance and the decision regarding which surveillance modality to use should result from shared decision-making between the clinician and survivor (Fig. 1). Shared decision-making has been recognized as essential, particularly in situations where controversy exists regarding the benefits and risks/harms of a given intervention for individual patients. There is increasing support for shared decision-making involving children and adults in healthcare for a variety of healthcare issues. For example, shared decision-making has been encouraged in screening programs for individuals genetically predisposed to multiple endocrine neoplasias and environmentally predisposed to DTC after radionuclide accidents [89,90]. The shared decision-making model for DTC surveillance in CAYAC survivors involves communication regarding the advantages and disadvantages of thyroid cancer surveillance in general and the specific surveillance modality. Discussions between the health care provider and the survivor should include an explanation of the uncertainty of the available evidence at a level commensurate with the survivor's developmental status, cognitive abilities, and experience. Decisions to initiate screening should balance the benefits and harms conferred by the procedure while respecting the values and concerns of the individual CAYAC survivor.

If the decision is made to forego thyroid cancer surveillance, the CAYAC should be advised to report a self-detected thyroid mass or cervical lymph node. The IGHG expert panel agreed that neck palpation, including palpation of the thyroid gland should always be part of a physical exam in long-term survivors who attend outpatient clinics, irrespective of prior cancer therapies.

Data to highlight in discussions related to DTC screening include the well-established risk for developing DTC in CAYAC survivors who have been exposed to radiation therapy in the cervical region. Using data from an international pooled study, Kovalchik et al (2013) proposed a statistically-derived prediction model for determining individual absolute risk of developing DTC in CAYAC survivors in the 10 or 20 years after a given clinic visit [91]. According to the model with the most favorable discriminative performance (Area Under the Curve, AUC = 0.8), the main predictors for cumulative absolute risk of DTC were birth after 1970, age younger than 15 years at childhood cancer diagnosis, female sex, life-time diagnosis of thyroid nodule, and three childhood cancer treatment characteristics (any radiotherapy, neck radiotherapy, and alkylating agent-based chemotherapy) [91].

Data is emerging regarding other treatment-related risk factors such as adjuvant chemotherapy [10]. For example, a recent pooled analysis performed by Veiga et al. suggested that treatment with anthracyclines might be a risk factor in non-radiated patients. Because the clinical implications of this finding are as yet unclear, the expert panel did not endorse chemotherapy without irradiation as a risk factor that supports active screening. If new evidence arises regarding the relationship between anthracyclines (or other chemotherapy classes) and risk for DTC, these recommendations will be revised accordingly.

Further study is required to elucidate the natural history of DTC and clinical features of thyroid nodules associated with malignant transformation. These data are needed to characterize high risk groups and define the optimal frequency of DTC surveillance. Presently, it is unclear whether all thyroid cancers, particularly small cancers, will progress and become clinically relevant. However, the likelihood that a nodule is malignant is not correlated linearly with the size of the nodule [92–94]. Furthermore, it is not known if DTC risk declines at some time after radiation exposure after which surveillance for DTC could be discontinued. Since the current study cohorts of long-term CAYAC survivors remain relatively young, extended follow-up studies are necessary to provide more data on this topic.

The strengths of the harmonization process used for the development of this guideline include the use of rigorous systematic review methods to retrieve and pool the relevant data from a large number of studies, the transparency in deriving and rating the levels of evidence, the multidisciplinary expert panel involved in the process, and a focus on clearly defining both adverse and positive effects of screening. The expert panel identified several significant gaps in current knowledge that require further research to improve surveillance and DTC outcomes in CAYAC survivors (Box 3).

Box 3 Research priorities.

- Prevalence and risk factors for DTC in a large cohort (pooled-analysis) of neuroblastoma survivors who received therapeutic ^{131}I-MIBG.
- Clarification of risk factors (e.g., dose rate, fraction size, age, gender, thyrotrophin elevation, concurrent chemotherapy) that may alter the radiation-related DTC risk.
- Impact of genetic susceptibility on DTC risk in CAYAC survivors.
- Diagnostic accuracy of neck palpation to predict the presence of DTC.

Box 3 *continued*

- Diagnostic accuracy of radiographic features to predict the presence of DTC.
- Clinical risk factors that may suggest an increased likelihood of DTC in CAYAC survivors diagnosed with a thyroid nodule.
- Change in DTC risk by changes in the clinical features of thyroid nodules over time.
- Diagnostic accuracy of ultrasound-guided FNA cytology for predicting the presence of DTC in CAYAC survivors diagnosed with a thyroid nodule.
- Diagnostic accuracy of elastography and genetic testing for identification of DTC in CAYAC survivors diagnosed with a thyroid nodule.
- Lifetime risk of DTC in very long (>30 years after treatment) CAYAC survivors treated with radiation that exposed the thyroid gland.
- Clarification of risk factors that may alter the latency time of radiation-induced DTC.
- Growth rate of thyroid nodules in CAYAC survivors.
- Efficacy of DTC surveillance with neck palpation vs. thyroid ultrasonography in terms of benefits and harms.
- Role of TSH suppression to reduce the occurrence of DTC in CAYAC survivors whose thyroid was exposed to radiation therapy.

Abbreviations: DTC: differentiated thyroid carcinoma; MIBG: meta-iodobenzylguanidine; CAYAC: childhood, adolescent and young adult and young adult cancer; FNA: fine-needle aspiration; TSH: thyroid-stimulating hormone.

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Declaration of interests

EKA discloses significant financial interests or other relationships with commercial interests in the following area: consultant Veracyte, Inc. All other authors declare no significant financial interest or other relationships with commercial interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctrv.2017.11.005.

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