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*Published in:*  
European Journal of Endocrinology

*DOI:*  
[10.1530/EJE-20-0237](https://doi.org/10.1530/EJE-20-0237)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

van Santen, H. M., Alexander, E. K., Rivkees, S. A., Frey, E., Clement, S. C., Dierselhuis, M. P., Lebbink, C. A., Links, T. P., Lorenz, K., Peeters, R. P., Reiners, C., Vriens, M. R., Nathan, P., Schneider, A. B., & Verburg, F. (2020). Clinical considerations for the treatment of secondary differentiated thyroid carcinoma in childhood cancer survivors. *European Journal of Endocrinology*, 183(3), P1-P10.  
<https://doi.org/10.1530/EJE-20-0237>

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# Clinical considerations for the treatment of secondary differentiated thyroid carcinoma in childhood cancer survivors

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## Abstract

The incidence of differentiated thyroid carcinoma (DTC) has increased rapidly over the past several years. Thus far, the only conclusively established risk factor for developing DTC is exposure to ionizing radiation, especially when the exposure occurs in childhood. Since the number of childhood cancer survivors (CCS) is increasing due to improvements in treatment and supportive care, the number of patients who will develop DTC after surviving childhood cancer (secondary thyroid cancer) is also expected to rise. Currently, there are no recommendations for management of thyroid cancer specifically for patients who develop DTC as a consequence of cancer therapy during childhood. Since complications or late effects from prior cancer treatment may elevate the risk of toxicity from DTC therapy, the medical history of CCS should be considered carefully in choosing DTC treatment. In this paper, we emphasize how the occurrence and treatment of the initial childhood malignancy affects the medical and psychosocial factors that will play a role in the diagnosis and treatment of a secondary DTC. We present considerations for clinicians to use in the management of patients with secondary DTC, based on the available evidence combined with experience-based opinions of the authors.

*European Journal of  
Endocrinology*  
(2020) **183**, P1–P10

## Introduction

The incidence of differentiated thyroid carcinoma (DTC) has increased substantially over the past several years due to increased patient and clinician awareness as well as increased use and sensitivity of neck ultrasound (1). Thus far, the only conclusively established risk factor

for developing DTC is exposure to ionizing radiation, especially when the exposure occurs in childhood (2, 3).

The consequences of exposure to radioactive iodine have been described extensively after the Chernobyl disaster, where no adequate measures were taken to limit

I-131 exposure and, consequently, a clear increase in the incidence of papillary thyroid carcinoma was observed (4, 5). In contrast, as a consequence of a smaller radiation release and immediate exposure limiting actions, no such increase was seen after the Fukushima meltdown (6).

Children who have been exposed to external radiation to a field including the thyroid gland are at increased risk for DTC. The relative risk for developing DTC increases linearly through 2–4 Gy, levels off between 10 and 30 Gy, and declines thereafter. The latency between radiation exposure and the development of DTC can be very long: the risk remains elevated for as long as 50 years or more after radiation exposure. In childhood cancer survivors (CCS), a non-synergistic (additive) association of chemotherapy with radiation has been observed for DTC (3). Compared to the general population, the risk for DTC has been reported to be increased in CCS treated solely with chemotherapy. Among 1344 survivors treated with chemotherapy alone, a standardized incidence ratio for thyroid cancer of 3.8 (95% CI, 2.7 to 5.1 was observed) (7). DTC has also been described to occur after radionuclide therapy with <sup>131</sup>I-MIBG in children with neuroblastoma (NBL) (8, 9).

Since the number of CCS is increasing due to improvements in treatment and supportive care (10, 11), it is expected that the number of patients who will develop DTC after surviving childhood cancer (secondary thyroid cancer) will rise in parallel. When DTC is diagnosed in a patient after radiation exposure for the treatment of a previous childhood malignancy, treatment for DTC will usually follow established guidelines for pediatric or adult DTC, depending on the age at DTC diagnosis (12, 13, 14). Unfortunately, these guidelines do not take into account the unique circumstances of CCS. Certainly, these guidelines offer no specific distinction for patients who develop DTC as a consequence of cancer therapy during childhood, including recommendations for the diagnostic testing, staging and treatment of patients with a history of childhood cancer or radiation exposure. However, it is stipulated in both the adult and pediatric guidelines of the American Thyroid Association (ATA) that the risk profile of patients with DTC as a secondary malignancy may be different than when compared to patients with sporadic DTC. Furthermore, the histologic type, molecular etiology, and overall prognosis must be reflected in the diagnostic and therapeutic measures. As such, both ATA documents state that decisions regarding the extent of surgery for indeterminate thyroid nodules are influenced by several factors, including the estimated pre-surgical likelihood of malignancy based upon clinical risk factors of which a

history of radiation is explicitly named as one. However, a history of radiation exposure is not included in the risk stratification system used to guide treatment in the ATA guidelines because there is insufficient evidence on which to base such an inclusion on.

There are several medical and psychosocial considerations which need to be considered and which may affect the diagnosis and treatment of secondary DTC. As a consequence, this process could or perhaps should differ from the approach in sporadic DTC patients. For example, the treatment of any prior primary malignancy may result in side effects which limit DTC treatment. Also, the additional psychological consequences of being faced with a second malignancy while still young, such as fear of an unfavorable prognosis, can affect management (Table 1). Furthermore, differences in genetic characteristics of secondary DTC may be important, although these have not yet been shown to affect clinical behavior (15, 16, 17). Another uncertain factor is the patients' prognosis – even though DTC in most patients, especially in younger individuals, is associated with a normal life expectancy (18), data do not exist specifically for CCS. Even though DTC alone is unlikely to reduce life expectancy, the cumulative impact of the primary malignancy and its therapy and the treatment and potential late effects of DTC treatment (such as further subsequent malignancies) may be associated with a reduction in life expectancy.

During the structured literature search that was performed for the International Guidelines Harmonization Group (IGHG) recommendations for screening CCS at risk for developing thyroid cancer (19), we identified a distinct lack of evidence about the optimal diagnostic procedures and treatment of radiation-induced DTC in CCS. During the process of defining the IGHG recommendations, topics related to DTC treatment after diagnosis were discussed, and here we summarize the content of these discussions. Therefore, the aim of the present document is to provide expert level recommendations for clinicians to use where high-level evidence is lacking. When future DTC guidelines provide specific evidence-based guidance for DTC in CCS, these should be given priority over the present document. Furthermore, wherever the present document refers to diagnostic or therapeutic procedures, these should be carried out in accordance with applicable guidelines.

## Methods

For the present paper, we refer to the very recent thorough literature search performed for the IGHG

**Table 1** 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 using CT-scanning or low-dose I-131 in the diagnostics of DTC
Previous exposure to toxic agents for the childhood cancer	Bleomycin increases the risk for pulmonary dysfunction Alkylating agents and abdominal irradiation increase the risk for gonadal dysfunction Total body irradiation or <sup>131</sup> I-MIBG treatment increases the risk for 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 already has 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 regards to the risk to develop a third malignancy
Risk for cardiotoxicity and prescribing levothyroxine therapy	Anthracycline chemotherapy agents or chest irradiation may increase the risk for cardiotoxicity	Consider keeping TSH concentrations in the lower normal but not suppressive range
Psychological aspects	Fear for unfavorable prognosis similar to the previous cancer	The psychological impact of being diagnosed with DTC as secondary malignancy may be higher than being diagnosed with sporadic DTC

recommendations (19). In short, the evidence-based guideline development for the IGHG group involved several stages. First, concordances and discordances between the Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG) and United Kingdom Childhood Cancer Study Group (UKCCSG) recommendations for DTC surveillance in children and young adolescent cancer (CAYAC) survivors were 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 of developing consensus recommendations based on these questions. 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. 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. CCS were defined as individuals treated for cancer initially diagnosed up to an age of 21 who were at least 2 years post-treatment, irrespective of current age. When evidence was lacking for CCS, evidence was extrapolated 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 and the IGHG 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). Panel members discussed the evidence and formulated recommendations for surveillance based on 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 among the panel members.

The considerations presented here (Table 2) were produced by participants in the group involved in the IGHG guideline document, supplemented with relevant external specialists with specific expertise and experience in the treatment of DTC. This effort was chaired by a board-certified pediatric endocrinologist (HvS) and a board-certified nuclear medicine physician (FAV), both of whom have extensive experience in the care of pediatric DTC. Discussions on controversial points were held via electronic communication. All of the authors agreed with the considerations as formulated in the final version of this document.

## Screening

**Consideration 1:** *In CCS at risk for thyroid carcinoma, the decision to undergo periodic surveillance should be made by the healthcare provider in consultation with the CCS after careful consideration of the advantages and disadvantages of DTC surveillance.*

The most common clinical presentation of DTC in the non-irradiated patient is a growing nodule in the neck, detected by the patient, the patient's family or the patient's peers. When compared to adults with DTC, children with DTC may present more frequently with a persistently enlarged cervical lymph node. In CCS, however, a malignant thyroid nodule will frequently be found on screening, either by palpation or thyroid ultrasound, because most CCS will be seen regularly and screened for DTC in an out-patient survivor clinic. Due to their prior experience with malignant disease and increased awareness, most CCS are more likely to seek swift medical attention when a lump or lymph node in the neck is noticed. This may result in diagnosis of DTC at a smaller tumor size and/or a less advanced stage (20), which may be favorable as early detection of DTC has been shown to have positive effect on recurrence rate, morbidity and mortality (21).

The question of whether CCS at risk for DTC should be screened for this disease has been dealt with in depth by the IGHG thyroid cancer group (19). While it was found that no direct evidence exists as to whether intensified thyroid cancer surveillance positively impacts DTC-related survival or decreases DTC-related morbidity, it was nonetheless concluded that surveillance for DTC is reasonable in survivors whose thyroid gland was exposed to external radiation and neuroblastoma survivors who received therapeutic <sup>131</sup>I-MIBG. It was further recommended that the decision to undergo periodic surveillance should be made by the healthcare provider in consultation with the CCS after careful consideration of the advantages and disadvantages of DTC surveillance.

Screening for DTC may be performed by palpating the thyroid gland or by thyroid ultrasound. Neck palpation is recommended as routine part of the physical examination for all CCS when visiting the physician who cares for them during survivorship, as specificity for the detection of thyroid nodules is high (22). As screening all CCS at risk with thyroid ultrasound may result in a considerable number of false-positive results, followed by unnecessary diagnostic and surgical procedures and psychological stress, it is currently not advised to screen all CCS at risk with thyroid ultrasound. Instead, it is recommended that

the decision to screen with palpation or neck ultrasound be made together with the survivor and should include considerations on the presence of the specific expertise with, for example, thyroid ultrasound in the local team as well as the needs and wishes of the survivor (19). If thyroid ultrasound is chosen as screening modality, this should be done in a center with expertise in thyroid cancer by an experienced thyroid radiologist, to minimize unnecessary additional diagnostics or surgical procedures.

**Table 2** Considerations for the treatment of differentiated thyroid cancer in childhood cancer survivors.

### Screening

1. In CCS at risk for thyroid carcinoma, the decision to undergo periodic surveillance should be made by the healthcare provider in consultation with the CCS after careful consideration of the advantages and disadvantages of DTC surveillance

### Diagnostics

2. If a suspicious thyroid nodule is detected in a patient who has been exposed to neck radiation, fine-needle aspiration cytology of this lesions is recommended
3. In case of a suspicious or unclear biopsy or cytology result, diagnostic hemi-thyroidectomy should be strongly considered
4. In CCS with a strong suspicion or diagnosis of DTC, further preoperative diagnostics should be kept to a minimum. Should anatomical medical imaging nonetheless be necessary, MRI is the preferred imaging modality

### Clinical behavior

5. There is insufficient genetic or clinical evidence to support a more aggressive treatment strategy for secondary DTC in CCS

### Patient characteristics and background that may affect treatment

6. The medical history of CCS should be considered carefully in choosing DTC treatment, since complications or late effects from prior treatment may elevate the risk of some therapeutic modalities
7. Since CCS are likely to be at increased risk of complications during and after anesthesia, a careful evaluation of this possibility should be performed before thyroid surgery in CCS
8. As CCS who develop a secondary DTC may be at increased risk for developing other (tertiary) cancers, restrictive use of I-131 therapy is advocated in this population. In general, I-131 therapy should be given either as adjuvant treatment or for treatment of advanced disease, but not only for the purpose of thyroid remnant ablation

### Psychosocial aspects

9. For CCS who develop a secondary DTC, the psychological impact will be substantial and special attention should be paid to providing psychological support

### Organization of care

10. Treatment for DTC in CCS should occur in an experienced thyroid center and the multidisciplinary team should include a (pediatric) oncologist to enable the addressing of previously named considerations

## Diagnostics

**Consideration 2:** *If a suspicious thyroid nodule is detected in a patient who has been exposed to neck radiation, fine-needle aspiration cytology of this lesions is recommended.*

**Consideration 3:** *In case of a suspicious or unclear biopsy or cytology result, diagnostic hemithyroidectomy should be strongly considered.*

**Consideration 4:** *In CCS with a strong suspicion or diagnosis of DTC, further preoperative diagnostics should be kept to a minimum. Should anatomical medical imaging nonetheless be necessary, MRI is the preferred imaging modality.*

If a thyroid nodule is palpated in a CCS, an ultrasound of the neck, including the thyroid gland and the cervical lymph nodes, is advised. In case of sonographic suspicion for thyroid malignancy (>1 cm and/or suspicious ultrasound features and/or concurrent suspicious lymph node enlargement), cytological evaluation by fine-needle with or without aspiration (FNAC) is recommended, preferably under ultrasound guidance (13). If thyroid function tests show thyrotoxicosis, thyroid scintigraphy should be performed in order to rule out the presence of autonomous nodules, which on ultrasound may show characteristics suspicious of malignancy. There is no evidence that, in case of comparatively small thyroid nodules with an indeterminate FNAC result (Bethesda classification 3, 4 or 5), additional diagnostic testing should be different in CCS cancers compared to sporadic DTC. Since the fact that the pre-test risk of malignancy for a nodule to be malignant may be different in CCS, molecular testing may be less reliable as a rule-out test. For subjects with Bethesda 3 and 4 lesions, with no suspicious features on ultrasound, following the nodule with sonography may be advised. In Bethesda 5 lesions, given the *a priori* increased risk for DTC in irradiated individuals, diagnostic hemithyroidectomy is preferred.

Despite a history of irradiation, we do not recommend FNAC in lesions < 1.0 cm in children or adult CCS, unless ultrasound investigation is highly suspicious for malignancy (i.e. showing features such as irregular margins, missing halo sign, microcalcifications, suspicious lymph nodes, or signs of extracapsular invasion). In case of an indeterminate FNAC result, depending on the needs and wishes of the individual CCS, it may be preferable to perform a diagnostic hemithyroidectomy in order to obtain certainty in the form of histological analysis of the nodule. This is consistent with the current ATA recommendation stating that, for indeterminate FNAC of thyroid nodules, several factors, including history of radiation, could cause one to opt for surgical intervention. Alternatively, more

frequent follow-up with 6–12 monthly ultrasound can be considered instead of diagnostic hemithyroidectomy. This decision should be discussed with the patient as part of shared decision-making. Some CCS will have a strong desire for the greatest possible degree of certainty that they do not have a new malignancy, while others would rather avoid surgery if possible.

For those who desire the greatest possible degree of certainty, additional diagnostic tests may be considered; however, these tests have not been studied specifically in the CCS setting. Additional diagnostics may be done with genetic testing on the FNAC specimen with a gene expression or gene sequencing classifier (where available). Molecular testing may be of additional value in the case of finding a BRAF mutation in Bethesda 5 cases, but for other results, evidence is lacking that it has direct consequences for the next diagnostic step. Molecular imaging such as Tc-99m-methoxy-isobutyl-nitril (MIBI) scintigraphy has an excellent negative predictive value and a very high sensitivity; however, it has a limited positive predictive value (meaning that a negative test result is very unlikely to have overlooked a DTC case) (23, 24). Which of these tests can be performed depends on local availability.

In case disseminated disease is suspected, caution is advised in choosing the modality for preoperative imaging. We recommend against the acquisition of additional CT scanning in CCS for preoperative staging of DTC. CCS may already have been exposed to high doses of chest radiation at time of treatment for their previous cancer. In cases where there are known or suspicions of locoregional lymph nodes, ultrasound investigation will usually be sufficient imaging. When additional imaging is required, MRI is preferred. For detection of lung metastases, low-dose chest CT scanning may be considered.

## Clinical behavior

**Consideration 5:** *There is insufficient genetic or clinical evidence to support a more aggressive treatment strategy for secondary DTC in CCS.*

While radiation-induced DTC has been shown to have a different genetic profile than sporadic DTC (more RET/PTC rearrangements), there is insufficient evidence to suggest that radiation-induced DTC behaves differently to sporadic cases. Subtle, yet significant, differences in gene expression have been reported in DTC in children and young adults following the Chernobyl accident, which were associated with their previous low-dose radiation exposure (25). The radiation exposure of CCS at risk for DTC will, in most cases, be higher than the exposure of

the thyroid in the population in Chernobyl, and it can be questioned whether this will lead to further differences in the genetic pattern of DTC. In a recent study of 3006 cancer survivors, the contribution of pathogenic/likely pathogenic (P/LP) mutations in cancer predisposition genes to their second neoplasm risk was evaluated using whole-genome sequencing. In this cohort, thyroid cancer developed in *SUFU*, *PTCH1*, *TP53*, *BRCA2*, and *RB1* mutation carriers, although the overall cumulative incidence of developing any secondary neoplasm was similar between survivors with and without P/LP mutations who were treated with radiotherapy (26). The significance and implications of these findings will have to be determined in future cohorts. Although there are some studies suggesting that behavior of radiation-induced DTC is more aggressive than sporadic DTC, to date there is insufficient evidence to substantiate this and there is no evidence that its prognosis is worse (27, 28, 29).

In our opinion, current evidence is insufficient to recommend more aggressive treatment for DTC in CCS based on genetic characteristics or clinical behavior of the tumor.

In the coming years, the genetic landscape of radiation-induced DTC in CCS must be unraveled further and correlated with clinical behavior. In this light, it would be of interest to compare the differences in genetics between radiation-induced DTC in children and adult CCS.

### Patient characteristics and background that may affect treatment

**Consideration 6:** *The medical history of CCS should be considered carefully in choosing DTC treatment, since complications or late effects from prior treatment may elevate the risk for toxicity of some therapeutic modalities.*

**Consideration 7:** *Since CCS are likely to be at increased risk of complications during and after anesthesia, a careful evaluation of this possibility should be performed before thyroid surgery in CCS.*

**Consideration 8:** *As CCS who develop a secondary DTC may be at increased risk for developing other (tertiary) cancers; restrictive use of I-131 therapy is advocated in this population. In general, I-131 therapy should be given either as adjuvant treatment or for treatment of advanced disease, but not for the purpose of thyroid remnant ablation.*

Children, young adolescents and adults who survived childhood cancer usually have an extensive medical history. Depending on the nature of their primary malignancy, previous treatment may include cytotoxic chemotherapy, cranial, cervical and/or

thoracic radiation therapy, or total body irradiation. These former therapies may influence decision-making in the treatment of DTC (Table 1). For example, their potential to cause cardiac or pulmonary adverse effects later in life must be taken into account when planning anesthesia as these patients are likely to be at increased risk of complications during and after anesthesia (30). For this reason, in all CCS, a careful anesthesia evaluation should be performed, with reference to the actual functional organ status, before performing surgery.

### Cardiac effects

Treatment with anthracycline chemotherapeutic agents or radiation to the chest during childhood may induce cardiac problems, such as decreased left ventricular function and even cardiac failure later in life (31, 32). These potential cardiac risk factors must be taken into account when deciding on treatment for DTC with TSH suppressive levothyroxine therapy. TSH suppressive therapy, which is indicated for high and some intermediate risk DTC until a disease free status has been established, has been shown to have cardiac effects such as diastolic dysfunction and atrial tachycardia (33). This may be unfavorable in patients already at increased risk for cardiac problems due to previous childhood cancer treatment. For this reason, we advise evaluation of cardiac function in all CCS with DTC who have received cardiotoxic treatment before introduction of TSH suppressive levothyroxine therapy. Should suppressive therapy not be advisable, the comparatively indolent nature of DTC allows a dosing of levothyroxine therapy to keep TSH levels in the lower normal range, with a long-term median TSH level below 2 mU/L (34). While perhaps suboptimal from a DTC perspective, this will nonetheless strike a reasonable balance between minimizing DTC growth and minimizing cardiac risk.

### Pulmonary effects

Pulmonary late effects in CCS may occur, for example, in Hodgkin lymphoma survivors after treatment with bleomycin or thoracic radiation therapy (35, 36). Although infrequent, one of the most serious and potential lethal adverse effects of radioiodine therapy in DTC patients with extensive miliary pulmonary metastases is pulmonary fibrosis, especially if it is given in combination with previous bleomycin treatment (37). For this reason, pulmonary function should always be evaluated in CCS

who develop metastatic miliary pulmonary disease. Furthermore, it is advisable to perform pre-therapeutic dosimetry to ascertain that safety limits for pulmonary radioiodine uptake are not exceeded while maximizing the administered I-131 activity (38). Before deciding on additional courses of I-131 therapy, evaluating pulmonary function should be mandatory.

#### *Gonadal damage*

CCS may be at risk for premature ovarian insufficiency or testicular failure due to treatment with gonadotoxic agents, such as alkylating agents and abdominal/pelvic radiation (39, 40). Radioiodine has been associated with transient male and female gonadal dysfunction (41). While there is suggestion in the literature that I-131 therapy may decrease ovarian reserve, a recent study of a Dutch cohort DTC survivors showed no abnormalities in serum AMH concentrations or in pregnancy rate (42). Depending on age, we recommend that gonadal function be assessed before radioiodine is administered and all patients and/or parents should be counseled regarding the possibility of such effects occurring. In post-pubertal males, we recommend considering sperm banking before the administration of radioiodine therapy.

It is currently advised that pregnancy be delayed for at least 6 months after radioiodine therapy in order to allow for a sufficient decay of any remaining radioiodine after therapy and in case a second treatment with radioiodine may be necessary. As female CCS may be at risk for premature ovarian insufficiency due to treatment for their primary cancer, the desire for future pregnancies may be a reason to consider postponing or abstaining from adjuvant postoperative radioiodine treatment in the case of a low- or intermediate-risk DTC without evidence of remaining disease.

#### *Risk of tertiary malignancies*

In sporadic DTC patients, the occurrence of subsequent primary malignancies after radioiodine therapy has been described with an increased incidence of 2.7–8.7% (43, 44). For acute myeloid leukemia, there is a proven relationship between the cumulative administered I-131 activity and incidence of disease; however, this is not the case for many other malignancies (stomach, bladder, colon, salivary gland and breast) where there is some evidence of an increased incidence in post-radioiodine DTC patients (42). The fact that an individual already has had cancer during childhood and subsequently

develops thyroid cancer may implicate a germline genetic susceptibility or predisposition syndrome to develop cancer. In fact, it has been shown that the incidence of non-DTC primary tumors is not only elevated after, but also before DTC diagnosis, suggesting a common etiologic or genetic mechanism instead of a causal relation (45). This possible increased genetic susceptibility must be taken into account when deciding on adjuvant treatment with the ionizing radiation generating agent, radioiodine. Furthermore, CCS with DTC may have an increased risk of developing a third subsequent malignancy after radioiodine exposure due to extra vulnerability from previous treatments, such as previous exposure to total body irradiation or <sup>131</sup>I-MIBG (the second hit-model). For instance, CCS with a history of chest irradiation may already be at increased risk to develop breast cancer (46, 47).

Hence we propose an abundance of caution regarding the administration of postoperative radioiodine therapy in CCS. It can likely be avoided in many low-risk patients, but for patients with residual inoperable disease after surgery, I-131 treatment is essential. Possible methods, although expensive, to safely select patients for postoperative radioiodine therapy or to determine whether any metastatic disease is present outside of the thyroid bed include a diagnostic whole body scan with I-123 combined with integrated single PET (SPECT) and CT (together called SPECT/CT) or I-124 with FDG/PET. If no metastatic disease is found and serum Tg is stable or decreasing, the patient can be followed by monitoring Tg levels and regular assessment of the thyroid bed by means of neck ultrasound.

#### *Myelotoxicity*

Immediate bone-marrow problems after radioiodine therapy are very rare, even after high activity therapy (48) and are hardly ever of a clinically relevant magnitude. Most commonly, the effects occur within the first 4–6 weeks after therapy and are reversible within 3 months. Most common are mild leucopenia and thrombocytopenia; however, even these are rare and usually clinically insignificant. Radioiodine treatment has also been shown to result in a transient decrease of platelets (49). In CCS, the bone marrow may be particularly vulnerable, especially in survivors of childhood leukemia, after total body irradiation or after treatment with other bone-marrow suppressive agents. This may also be the case for neuroblastoma survivors who were treated with high cumulative activities (radiation dose) of I-131-MIBG,



as MIBG has also been described to cause bone-marrow suppression.

Especially in patients who are at increased risk of having less than optimal bone-marrow reserve, caution should be applied in the choice of I-131 activity. In patients with metastatic disease, lesion dosimetry prior to radioiodine therapy may help to determine the minimum effective activity which will still lead to a radiation absorbed dose of 300 Gy to the thyroid bed and at least 80 Gy to metastases (50, 51). Another approach could be to administer the activity corresponding to the dose in the blood not higher than the maximum tolerable activity (38).

### Psychosocial aspects

**Consideration 9:** For CCS who develop a secondary DTC, the psychological impact will be substantial and special attention should be paid to providing psychological support.

The diagnosis of a second malignancy as a child, adolescent or adult will have a substantial impact on the patient and his/her family. These patients and their closest relatives have already experienced one malignant disease, its diagnosis, hospitalization for its treatment, and the associated uncertainties and worries. The diagnosis of DTC in such a patient can be particularly traumatic given this prior history. It is for this reason that screening for DTC must be done in agreement with the survivor. Screening may give false-positive results which can lead to anxiety and worries unnecessarily. It is for this reason that special attention should be paid to psycho-oncological counseling of the patient with DTC where indicated and to their parents, care-givers and partners as appropriate. Fortunately, secondary thyroid cancer has an excellent prognosis, which enables positive counseling in most cases. It can be stressed that, especially in patients under 45 years of age at diagnosis, life expectancy is not impaired in DTC patients compared to a population of the same age and gender (18).

### Treatment of DTC in CCS

**Consideration 10:** Treatment for DTC in CCS should occur in an experienced thyroid center, and the multidisciplinary team should include a (pediatric) oncologist to enable the addressing of previously named considerations.

In the treatment of DTC in CCS, attention must be paid to the issues presented previously. It is crucial that the survivor understands that secondary thyroid cancer is (in most cases) different in terms of behavior,

treatment toxicity and prognosis than other forms of childhood cancer. The treating physician should be aware of the possible toxicity of previous administered drugs or radiation therapy in addition to the treatment modalities required for the treatment of DTC. Lastly, special attention should be paid to the psychological impact of having a secondary malignancy. For all of the previously named reasons, treatment for DTC in CCS is recommended in an experienced thyroid center. Due to the fact that expertise is needed in the modalities used for the previous cancer treatment and on thyroid cancer, the multidisciplinary team should include both (pediatric) endocrinologists and (pediatric) oncologist, as well as a thyroid expert radiologist, an endocrine surgeon, a nuclear medicine physician, a pathologist, a geneticist, a late effects physician and ideally a psychologist with a specialization in psycho-oncology.

### Conclusions

It may be questioned whether diagnostics or treatment of DTC in CCS should be different compared to sporadic DTC patients. As DTC in CCS is relatively uncommon, there is little evidence upon which to base these considerations. We can, however, provide recommendations to guide the caregiver based on our clinical experience, the available literature on late effects in CCS and the published literature regarding DTC in CCS. As each case will have unique aspects, we recommend that the caregiver individually designs the most optimal plan for diagnostic and therapeutic procedures for the specific CCS and includes the CCS in decision-making (individualized care). The CCS should be provided, in a timely fashion, with the information that is relevant and that he or she can comprehend and use.

#### Declaration of interest

Frederik Verburg is Associate Editor of the *European Journal of Endocrinology*. He was not involved in the editorial or peer-review process of this paper, on which he is listed as an author. The other authors have nothing to disclose.

#### Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

#### Acknowledgements

The authors thank all members of the IGHG working group for thyroid cancer surveillance, namely Kremer L C M, Simmons J H, Goldfarb M, Bardi E, Brignardello E, Constine L S, Dinauer C A, Drozd V M, Felicetti F, Heinzel A, van den Heuvel-Eibrink M M, Huang S A, Mulder R L, Neggers S J, Nieveen van Dijkum E J M, Oeffinger K C, van Rijn R R, Ronckers C M, Skinner R, Wasserman J D, Wynn T, and Hudson M M.

## References

- Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M & Maso LD. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. *New England Journal of Medicine* 2016 **375** 614–617. (<https://doi.org/10.1056/NEJMp1604412>)
- Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA & Boice JD. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiation Research* 1995 **141** 259. (<https://doi.org/10.2307/3579003>)
- Veiga LHS, Holmberg E, Anderson H, Pottern L, Sadetzki S, Adams MJ, Sakata R, Schneider AB, Inskip P, Bhatti P *et al.* Thyroid cancer after childhood exposure to external radiation: an updated pooled analysis of 12 studies. *Radiation Research* 2016 **185** 473.
- Hatch M & Cardis E. Somatic health effects of Chernobyl: 30 years on. *European Journal of Epidemiology* 2017 **32** 1047–1054.
- Nikiforov YE. Radiation-induced thyroid cancer: what we have learned from Chernobyl. *Endocrine Pathology* 2006 **17** 307–317. (<https://doi.org/10.1007/s12022-006-0001-5>)
- Takano T. Overdiagnosis of thyroid cancer: the children in Fukushima are in danger. *Archives of Pathology and Laboratory Medicine* 2019 **143** 660–661. (<https://doi.org/10.5858/arpa.2018-0586-LE>)
- Turcotte LM, Liu Q, Yasui Y, Henderson TO, Gibson TM, Leisenring W, Arnold MA, Howell RM, Green DM, Armstrong GT *et al.* Chemotherapy and risk of subsequent malignant neoplasms in the childhood cancer survivor study cohort. *International Journal of Clinical Oncology* 2019 **37** 3310–3319. (<https://doi.org/10.1200/JCO.19.00129>)
- Van Santen HM, Tytgat GAM, Van De Wetering MD, Van Eck-Smit BLF, Hopman SMJ, Van Der Steeg AF, Nieveen Van Dijkum EJM & Van Trotsenburg ASP. Differentiated thyroid carcinoma after 131I-MIBG treatment for neuroblastoma during childhood: description of the first two cases. *Thyroid* 2012 **22** 643–646. (<https://doi.org/10.1089/thy.2011.0464>)
- Clement SC, van Rijn RR, van Eck-Smit BLF, van Trotsenburg ASP, Caron HN, Tytgat GAM & van Santen HM. Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during 131I-metaiodobenzylguanidine treatment in children with neuroblastoma. *European Journal of Nuclear Medicine and Molecular Imaging* 2015 **42** 706–715. (<https://doi.org/10.1007/s00259-014-2967-4>)
- Phillips SM, Padgett LS, Leisenring WM, Stratton KK, Bishop K, Krull KR, Alfano CM, Gibson TM, De Moor JS, Hartigan DB *et al.* Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiology, Biomarkers and Prevention* 2015 **24** 653–663. (<https://doi.org/10.1158/1055-9965.epi-14-1418>)
- Gatta G, Corazzari I, Magnani C, Peris-Bonet R, Roazzi P, Stiller C, Oberaigner W, Jechova M, Rousarova M, Storm HH *et al.* Childhood cancer survival in Europe. *Annals of Oncology* 2003 **14** (Supplement 5) v119–127. (<https://doi.org/10.1093/annonc/mdg755>)
- Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P, Balafouta ST *et al.* American association of Clinical Endocrinologists, American college of endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. *Endocrine Practice* 2016 **22** 622–639. (<https://doi.org/10.4158/ep161208.gl>)
- Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenega S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M *et al.* Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015 **25** 716–759. (<https://doi.org/10.1089/thy.2014.0460>)
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M *et al.* 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016 **26** 1–133. (<https://doi.org/10.1089/thy.2015.0020>)
- Yamashita S & Saenko V. Mechanisms of disease: molecular genetics of childhood thyroid cancers. *Nature Clinical Practice Endocrinology and Metabolism* 2007 **3** 422–429. (<https://doi.org/10.1038/ncpendmet0499>)
- Sassolas G, Hafdi-Nejjari Z, Ferraro A, Decaussin-Petrucci M, Rousset B, Borson-Chazot F, Borbone E, Berger N & Fusco A. Oncogenic alterations in papillary thyroid cancers of young patients. *Thyroid* 2012 **22** 17–26. (<https://doi.org/10.1089/thy.2011.0215>)
- Vanden Borre P, Schrock AB, Anderson PM, Morris JC, Heilmann AM, Holmes O, Wang K, Johnson A, Waguespack SG, Ou SI *et al.* Pediatric, adolescent, and young adult thyroid carcinoma harbors frequent and diverse targetable genomic alterations, including kinase fusions. *Oncologist* 2017 **22** 255–263. (<https://doi.org/10.1634/theoncologist.2016-0279>)
- Verburg FA, Mäder U, Tanase K, Thies ED, Diessl S, Buck AK, Luster M & Reiners C. Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 172–180. (<https://doi.org/10.1210/jc.2012-2458>)
- Clement SC, Kremer LCM, Verburg FA, Simmons JH, Goldfarb M, Peeters RP, Alexander EK, Bardi E, Brignardello E, Constone 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 Consort. *Cancer Treatment Reviews* 2018 **63** 28–39. (<https://doi.org/10.1016/j.ctrv.2017.11.005>)
- Brignardello E, Felicetti F, Castiglione A, Gallo M, Maletta F, Isolato G, Biasin E, Fagioli F, Corrias A & Palestini N. Ultrasound surveillance for radiation-induced thyroid carcinoma in adult survivors of childhood cancer. *European Journal of Cancer* 2016 **55** 74–80. (<https://doi.org/10.1016/j.ejca.2015.12.006>)
- Clement SC, Kremer LCM, Links TP, Mulder RL, Ronckers CM, van Eck-Smit BLF, van Rijn RR, van der Pal HJH, Tissing WJE, Janssens GO *et al.* Is outcome of differentiated thyroid carcinoma influenced by tumor stage at diagnosis? *Cancer Treatment Reviews* 2015 **41** 9–16. (<https://doi.org/10.1016/j.ctrv.2014.10.009>)
- Brignardello E, Corrias A, Isolato G, Palestini N, Di Montezemolo LC, Fagioli F & Boccuzzi G. Ultrasound screening for thyroid carcinoma in childhood cancer survivors: a case series. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4840–4843. (<https://doi.org/10.1210/jc.2008-1528>)
- Giovanella L, Campenni A, Treglia G, Verburg FA, Trimboli P, Ceriani L & Bongiovanni M. Molecular imaging with 99mTc-MIBI and molecular testing for mutations in differentiating benign from malignant follicular neoplasm: a prospective comparison. *European Journal of Nuclear Medicine and Molecular Imaging* 2016 **43** 1018–1026. (<https://doi.org/10.1007/s00259-015-3285-1>)
- Campenni A, Siracusa M, Ruggieri RM, Laudicella R, Pignata SA, Baldari S & Giovanella L. Differentiating malignant from benign thyroid nodules with indeterminate cytology by 99mTc-MIBI scan: a new quantitative method for improving diagnostic accuracy. *Scientific Reports* 2017 **7** 6147. (<https://doi.org/10.1038/s41598-017-06603-3>)
- Handkiewicz-Junak D, Swierniak M, Rusinek D, Oczko-Wojciechowska M, Dom G, Maenhaut C, Unger K, Detours V, Bogdanova T, Thomas G *et al.* Gene signature of the post-Chernobyl papillary thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2016 **43** 1267–1277. (<https://doi.org/10.1007/s00259-015-3303-3>)
- Wang Z, Wilson CL, Easton J, Thrasher A, Mulder H, Liu Q, Hedges DJ, Wang S, Rusch MC, Edmonson MN *et al.* Genetic risk for subsequent neoplasms among long-term survivors of childhood cancer. *International Journal of Clinical Oncology* 2018 **36** 2078–2087. (<https://doi.org/10.1200/JCO.2018.77.8589>)
- Naing S, Collins BJ & Schneider AB. Clinical behavior of radiation-induced thyroid cancer: factors related to recurrence. *Thyroid* 2009 **19** 479–485. (<https://doi.org/10.1089/thy.2008.0343>)

- 28 van Santen HM, Clement SC, Ronckers C, Lebbink C, Hesselink MK, Teepeen J, Kremer L & Links TP. Clinical characterization of secondary thyroid cancer among childhood cancer survivors compared to sporadic thyroid cancer, a matched analysis. *Abstract Endocrine Society* 2018
- 29 Reiners C, Biko J, Haenscheid H, Hebestreit H, Kirinjuk S, Baranowski O, Marlowe RJ, Demidchik E, Drozd V & Demidchik Y. Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3039–3048. (<https://doi.org/10.1210/jc.2013-1059>)
- 30 Henderson TO & Nathan PC. Childhood cancer survivors: considerations for surgeons in the transition from pediatric to adult care. *Seminars in Pediatric Surgery* 2015 **24** 93–99. (<https://doi.org/10.1053/j.sempedsurg.2015.01.007>)
- 31 Lipshultz SE, Franco VI, Miller TL, Colan SD & Sallan SE. Cardiovascular disease in adult survivors of childhood cancer. *Annual Review of Medicine* 2015 **66** 161–176. (<https://doi.org/10.1146/annurev-med-070213-054849>)
- 32 Haddy N, Diallo S, El-Fayech C, Schwartz B, Pein F, Hawkins M, Veres C, Oberlin O, Guibout C, Pacquement H *et al.* Cardiac diseases following childhood cancer treatment: cohort study. *Circulation* 2016 **133** 31–38. (<https://doi.org/10.1161/CIRCULATIONAHA.115.016686>)
- 33 Klein Hesselink MS, Bocca G, Hummel YM, Brouwers AH, Burgerhof JGM, Van Dam EWCM, Gietema JA, Havekes B, Van Den Heuvel-Eibrink MM, Corssmit EPM *et al.* Diastolic dysfunction is common in survivors of pediatric differentiated thyroid carcinoma. *Thyroid* 2017 **27** 1481–1489. (<https://doi.org/10.1089/thy.2017.0383>)
- 34 Hovens GC, Stokkel MP, Kievit J, Corssmit EP, Pereira AM, Romijn JA & Smit JWA. Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 2610–2615. (<https://doi.org/10.1210/jc.2006-2566>)
- 35 Dietz AC, Chen Y, Yasui Y, Ness KK, Hagood JS, Chow EJ, Stovall M, Neglia JP, Oeffinger KC, Mertens AC *et al.* Risk and impact of pulmonary complications in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2016 **122** 3687–3696. (<https://doi.org/10.1002/cncr.30200>)
- 36 Huang TT, Hudson MM, Stokes DC, Krasin MJ, Spunt SL & Ness KK. Pulmonary outcomes in survivors of childhood cancer: a systematic review. *Chest* 2011 **140** 881–901. (<https://doi.org/10.1378/chest.10-2133>)
- 37 Hebestreit H, Biko J, Drozd V, Demidchik Y, Burkhardt A, Trusen A, Beer M & Reiners C. Pulmonary fibrosis in youth treated with radioiodine for juvenile thyroid cancer and lung metastases after Chernobyl. *European Journal of Nuclear Medicine and Molecular Imaging* 2011 **38** 1683–1690.
- 38 Verburg FA, Reiners C & Hänscheid H. Approach to the patient: role of dosimetric RAI Rx in children with DTC. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3912–3919.
- 39 Van Dorp W, Mulder RL, Kremer LCM, Hudson MM, Van Den Heuvel-Eibrink MM, Van Den Berg MH, Levine JM, Van Dulmen-Den Broeder E, Di Iorgi N, Albanese A *et al.* Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Journal of Clinical Oncology* 2016 **34** 3440–3450.
- 40 Skinner R, Mulder RL, Kremer LC, Hudson MM, Constine LS, Bardi E, Boekhout A, Borgmann-Staudt A, Brown MC, Cohn R *et al.* Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncology* 2017 **18**:e75–18.e90.
- 41 Clement SC, van Eck-Smit BLF, van Trotsenburg ASP, Kremer LCM, Tytgat GAM & van Santen HM. Long-term follow-up of the thyroid gland after treatment with 131I-Metaiodobenzylguanidine in children with neuroblastoma: importance of continuous surveillance. *Pediatric Blood and Cancer* 2013 **60** 1833–1838. (<https://doi.org/10.1002/pbc.24681>)
- 42 Nies M, Cantineau AEP, Arts EGJM, van den Berg MH, van Leeuwen FE, Muller Kobold AC, Klein Hesselink MS, Burgerhof JGM, Brouwers AH, van Dam EWCM *et al.* Long-term effects of radioiodine treatment on female fertility in survivors of childhood differentiated thyroid carcinoma. *Thyroid* 2020 In press. (<https://doi.org/10.1089/thy.2019.0560>)
- 43 Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML & Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World Journal of Surgery* 2010 **34** 1192–1202.
- 44 Clement SC, Peeters RP, Ronckers CM, Links TP, Van Den Heuvel-Eibrink MM, Nieveen Van Dijkum EJM, Van Rijn RR, Van Der Pal HJH, Neggers SJ, Kremer LCM *et al.* Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma – a systematic review. *Cancer Treatment Reviews* 2015 **41** 925–934. (<https://doi.org/10.1016/j.ctrv.2015.09.001>)
- 45 Verkooijen RBT, Smit JWA, Romijn JA & Stokkel MPM. The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. *European Journal of Endocrinology* 2006 **155** 801–806. (<https://doi.org/10.1530/eje.1.02300>)
- 46 Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Friedman DN, Mubdi NZ, Leisenring WM, Stovall M, Hammond S *et al.* Breast cancer after chest radiation therapy for childhood cancer. *Journal of Clinical Oncology* 2014 **32** 2217–2223.
- 47 Mulder RL, Kremer LCM, Hudson MM, Bhatia S, Landier W, Levitt G, Constine LS, Wallace WH, Van Leeuwen FE, Ronckers CM *et al.* Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncology* 2013 **14** e621–e629. ([https://doi.org/10.1016/S1470-2045\(13\)70303-6](https://doi.org/10.1016/S1470-2045(13)70303-6))
- 48 Verburg FA, Hänscheid H, Biko J, Hategan MC, Lassmann M, Kreissl MC, Reiners C & Luster M. Dosimetry-guided high-activity 131I therapy in patients with advanced differentiated thyroid carcinoma: initial experience. *European Journal of Nuclear Medicine and Molecular Imaging* 2010 **37** 896–903. (<https://doi.org/10.1007/s00259-009-1303-x>)
- 49 Prinsen HT, Hesselink ENK, Brouwers AH, Plukker JTM, Sluiter WJ, Van Der Horst-Schrivers ANA, Van Imhoff GW & Links TP. Bone marrow function after 131I therapy in patients with differentiated thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 3911–3917.
- 50 Jentzen W, Moldovan AS, Ruhlmann M, Gorges R, Bockisch A & Rosenbaum-Krumme S. Lowest effective 131I activity for thyroid remnant ablation of differentiated thyroid cancer patients: dosimetry-based model for estimation. *Nuklearmedizin*. 2015 **54** 137–143. (<https://doi.org/10.3413/Nukmed-0711-14-12>)
- 51 Maxon HR, Englaro EE, Thomas SR, Hertzberg VS, Hinnefeld JD, Chen LS, Smith H, Cummings D & Aden MD. Radioiodine-131I therapy for well-differentiated thyroid cancer – a quantitative radiation dosimetric approach: outcome and validation in 85 patients. *Journal of Nuclear Medicine* 1992 **33** 1132–1136.

Received 16 March 2020

Revised version received 24 April 2020

Accepted 4 June 2020