

## REVIEW

# The effect of surveillance for differentiated thyroid carcinoma in childhood cancer survivors on survival rates: a decision-tree-based analysis

Alexander Heinzel<sup>1</sup>, Dirk Müller<sup>2</sup>, Hanneke M van Santen<sup>3,4</sup>, Sarah C Clement<sup>3,5</sup>, Arthur B Schneider<sup>6</sup> and Frederik A Verburg<sup>7,8</sup>

<sup>1</sup>RWTH University Hospital Aachen, Department of Nuclear Medicine, Aachen, Germany

<sup>2</sup>Institute for Health Economics and Clinical Epidemiology, University of Cologne, Cologne, Germany

<sup>3</sup>Wilhelmina Children's Hospital, University Medical Center Utrecht, Department of Pediatric Endocrinology, Utrecht, The Netherlands

<sup>4</sup>Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

<sup>5</sup>Emma Children's Hospital, Amsterdam UMC, Department of Pediatrics, Amsterdam, The Netherlands

<sup>6</sup>University of Illinois at Chicago, Department of Medicine, Chicago, IL, USA

<sup>7</sup>Erasmus MC Rotterdam, Department of Radiology & Nuclear Medicine, Rotterdam, The Netherlands

<sup>8</sup>University Hospital Würzburg, Department of Nuclear Medicine, Würzburg, Germany

Correspondence should be addressed to F A Verburg: [f.verburg@erasmusmc.nl](mailto:f.verburg@erasmusmc.nl)

This paper forms part of a collection on the Late Effects of Cancer Treatment. The guest editors for this collection were Claire E Higham and Judith Gebauer.

## Abstract

**Background:** Childhood cancer survivors (CCS) who received radiation therapy exposing the thyroid gland are at increased risk of developing differentiated thyroid cancer (DTC). Therefore, the International Guideline Harmonization Group (IGHG) on late effects of childhood cancer therefore recommends surveillance. It is unclear whether surveillance reduces mortality.

**Aim:** The aim of this study was to compare four strategies for DTC surveillance in CCS with the aim of reducing mortality: Strategy-1, no surveillance; Strategy-2, ultrasound alone; Strategy-3, ultrasound followed by fine-needle biopsy (FNB); Strategy-4, palpation followed by ultrasound and FNB.

**Materials and methods:** A decision tree was formulated with 10-year thyroid cancer-specific survival as the endpoint, based on data extracted from literature.

**Results:** It was calculated that 12.6% of CCS will develop DTC. Using Strategy-1, all CCS with DTC would erroneously not be operated upon, but no CCS would have unnecessary surgery. With Strategy-2, all CCS with and 55.6% of CCS without DTC would be operated. Using Strategy-3, 11.1% of CCS with DTC would be correctly operated upon, 11.2% without DTC would be operated upon and 1.5% with DTC would not be operated upon. With Strategy-4, these percentages would be 6.8, 3.9 and 5.8%, respectively. Median 10-year survival rates would be equal across strategies (0.997).

**Conclusion:** Different surveillance strategies for DTC in CCS all result in the same high DTC survival. Therefore, the indication for surveillance may lie in a reduction of surgery-related morbidity rather than DTC-related mortality. In accordance with the IGHG guidelines, the precise strategy should be decided upon in a process of shared decision-making.

## Key Words

- ▶ childhood cancer survivors
- ▶ differentiated thyroid cancer
- ▶ screening strategies

Endocrine Connections  
(2022) 11, e220092

## Introduction

Childhood cancer survivors (CCS) who received radiation therapy to the cervical region (cranial/ cranio-spinal or chest) are at increased risk of developing differentiated thyroid cancer (DTC) among other malignancies. Long-term survivors of childhood malignancy have an increased incidence of second primary thyroid cancer after radiotherapy that is curvilinear with dose, such that risk steadily increases up to approximately 20 Gy, above which there is a downturn in the dose-response (1, 2).

In general, DTC has a good prognosis, especially when diagnosed at a young age, and life expectancy in most patients is normal. There is no evidence in literature to confirm a worse prognosis for patients with radiation-induced DTC (3). However, some studies report that a younger age at the time of exposure had an inversely proportional correlation with the extra-thyroidal extension of tumor and lymph node involvement and a greater probability of distant metastasis (4, 5).

Since a systematic review of the literature previously showed that earlier detection of DTC appears to be associated with better outcomes (3), a case could be made for employing routine thyroid surveillance in order to detect DTC in CCS as early as possible. In 2018, the International Guideline Harmonization Group (IGHG) on guidelines for late effects of childhood cancer, therefore, released recommendations on surveillance for DTC in at-risk CCS (6). These guidelines stated that surveillance for DTC may be reasonable as mortality and morbidity may be reduced if DTC is detected at an early stage. The decision about which surveillance modality (i.e. neck palpation or thyroid ultrasonography) to use to detect a thyroid nodule, possibly indicating DTC, should be made by the healthcare provider in consultation with the survivor after careful consideration of the advantages and disadvantages of the two modalities.

As all surveillance strategies will result in some false-positive results, attention must be paid to the morbidity from instances of unnecessary surgical procedures. Therefore, the benefits of surveillance for those with DTC need to be weighed against the potential harms to CCS not affected by DTC.

Various surveillance strategies can be employed using palpation, ultrasound (US) and, if necessary, fine-needle biopsy (FNB), or a combination of these modalities in succession. In clinical practice, this usually means surveillance by either US or palpation followed by US, often, but not always, followed by FNB of suspicious nodules.

Although some evidence suggests that earlier detection of DTC has a favorable effect on prognosis (3), there is no direct evidence that surveillance of CCS for DTC in fact results in a reduction of DTC-related mortality. Therefore, the aim of the present study was to perform a comparative analysis of the different clinically used surveillance strategies mentioned above for their effect on DTC-related survival.

## Materials and methods

### Literature search

For the purpose of modeling the decision tree analysis, data on the prevalence of DTC as well as data on the sensitivity and specificity of palpation, thyroid US and FNB were extracted from relevant studies in the literature through January 1, 2017. The data used for the present study were taken from the structured literature search performed for the recommendations on thyroid cancer surveillance among CCS in accordance to the IGHG methods as previously described (6).

This literature search identified one study comparing US to palpation in CCS which reported all data which we required for constructing the model (Table 1); for modeling purposes, sensitivity and specificity for these modalities were taken from this study (7). No studies were found specifically examining the diagnostic value of FNB in CCS. Therefore, we extracted the necessary data from studies of FNB in children and adults with sporadic DTCs; we derived data on sensitivity and specificity from the largest study which had histological verification of all examined patients (8).

Additionally, we searched for reported DTC mortality rates after thyroid surgery. For the purpose of this study, we employed data from the largest study available before our literature cut-off date (9).

### Assumptions for modeling

For modeling, we assume different surveillance strategies are associated with different median tumor diameters. For the present analysis, we assumed that any nodule with a diameter exceeding 1 cm (i.e. median longest axis diameter of 1.1 cm) would be detected by US and selected for FNB. We assume that palpation, which is less sensitive, would detect tumors with a median long-axis diameter of 2.6 cm (10). We furthermore assumed that patients in whom no surveillance took place or in whom a tumor was falsely

**Table 1** Values used for the decision tree including distributions for the Monte Carlo simulations. The variables D1–D19 refer to Figure 1 A–D. The beta distributions are characterized by mean and s.d., and the triangular distributions are characterized by likeliest value as well as minimum and maximum. The s.d. for the beta distributions is derived from the Würzburg thyroid cancer database based on data analysis. For the beta distributions derived from literature where no s.d. was available, a conservative assumption of an s.d. of 50% was employed.

Probability of	Variable	Mean/Likeliest	SD/Range	Source	Distribution
Differentiated thyroid cancer	D1	0.126	0.063	Somerville <i>et al.</i> 2002	Beta
Lethal complications in thyroidectomy	D2	0.00065	0.000325	Gomez-Ramirez <i>et al.</i> 2015	Beta
No distant metastases without follow-up	D3	0.869	0.025	Würzburg thyroid cancer database	Beta
Survival with distant metastases	D4	0.895	0.038	Würzburg thyroid cancer database	Beta
Survival without distant metastases	D5	0.984	0.005	Würzburg thyroid cancer database	Beta
Pathological US	D6	0.692	0.346	Somerville <i>et al.</i> 2002	Beta
No distant metastases with follow-up US	D7	0.989	0.004	Würzburg thyroid cancer data base	Beta
True-negative US	D8	0.990	0.98–1	Somerville <i>et al.</i> 2002	Triangular
Positive FNB if US positive	D9	0.336	0.168	Mikosch <i>et al.</i> 2000	Beta
True-positive FNB	D10	0.476	0.238	Mikosch <i>et al.</i> 2000	Beta
True-negative FNB	D11	0.967	0.934–1	Mikosch <i>et al.</i> 2000	Triangular
Pathological palpation	D12	0.287	0.1435	Somerville <i>et al.</i> 2002	Beta
Pathological US if palpation positive	D13	0.902	0.804–1	Somerville <i>et al.</i> 2002	Triangular
Positive FNB if US positive + palpation positive	D14	0.412	0.206	Mikosch <i>et al.</i> 2000	Beta
True-positive FNB if US + palpation positive	D15	0.633	0.3165	Mikosch <i>et al.</i> 2000	Beta
No distant metastases with follow-up palpation	D16	0.952	0.011	Würzburg thyroid cancer database	Beta
True-negative FNB if US + palpation positive	D17	0.938	0.876–1	Mikosch <i>et al.</i> 2000	Triangular
True-negative palpation	D18	0.931	0.862–1	Somerville <i>et al.</i> 2002	Triangular
True-positive US	D19	0.182	0.091	Somerville <i>et al.</i> 2002	Beta

FNB, fine-needle biopsy; SD, standard deviation; US, ultrasound.

not identified by a surveillance strategy would become clinically evident due to local symptoms at a median diameter >4 cm (i.e. pT3 according to the TNM system) – for the purpose of this analysis, we assumed 4.1 cm.

Also, we only considered patients <45 years at DTC diagnosis and >18 years at follow-up as most DTC cases will develop in a time frame from 5 to 25 years after radiation exposure. Later DTC cases cannot be distinguished with certainty from sporadic DTC cases since they occur more frequently with increasing age.

### Survival

For the present analysis, we queried the Würzburg Thyroid Cancer Database (described extensively by, for example, Verburg *et al.* (11, 12, 13, 14) using the methodology described before by Machens *et al.* (15) and Verburg *et al.* (16) to establish the risk of distant metastases associated with each of the assumed median tumor diameters. We

did not consider other prognostic factors as up to and including the seventh version of the TNM system (17) the presence of distant metastases is the only prognostic factor relevant to DTC-related mortality in patients >18 and <45 years. Although the latest edition of the TNM system has shifted this up to 55 years with some debate as a result (18, 19, 20, 21), most data in literature are still based on the cut-off at 45 years, which we therefore retained for the present analysis. We subsequently queried the Würzburg thyroid cancer database to establish the 10-year cause-specific survival rate for patients <45 years of age with and without distant metastases.

### Decision tree analysis

A decision tree was constructed using TreeAge Pro 2009 (TreeAge Inc., Williamstown, MA, USA). The outcome was defined as the DTC-related survival rate 10 years after surveillance. The starting point of the decision

tree model is a surveillance procedure, or, in case of Strategy-1, the absence thereof at the time point such a procedure would normally occur. Four different strategies for surveillance and consecutive further analysis and treatment were investigated, each with their own assumptions:

- Strategy-1: no surveillance with neck palpation or thyroid US. Patients would receive appropriate diagnostic procedures and adequate treatment upon incidentally noticing a cervical ‘lump’ or locally compressive symptoms as described in the Materials and methods section.
- Strategy-2: surveillance by US alone. Any nodule which in US is deemed suspicious (i.e. category 4 and higher by TIRADS (22) or similar scoring systems) is operated upon immediately without performing an FNB. It is furthermore assumed that cancer cases not found by surveillance will receive treatment upon noticing local symptoms as described for Strategy-1.
- Strategy-3: surveillance by US followed by FNB of any suspicious thyroid nodule. Only FNB positive (i.e. Bethesda IV–V findings) and those requiring histological clarification (i.e. Bethesda III) will receive surgery. It is furthermore assumed that cancer cases not found by surveillance will receive treatment upon noticing local symptoms as described for Strategy-1.
- Strategy-4: surveillance by palpation in positive cases followed by the procedure described in Strategy-3. It is assumed that cancer cases not found by surveillance will receive treatment upon noticing local symptoms as described in Strategy-1.

The decision tree for each of these four strategies is displayed in Fig. 1, panels A–D.

### Statistical analysis

Kaplan–Meier analysis was used for analysis of cause-specific survival using SPSS version 23 (IBM Corp.).

In order to test for the robustness of the results, we calculated probabilistic sensitivity analyses using a second-order Monte Carlo simulation with 10,000 samples assuming a s.d. of at least 40% for each decision node, again using TreeAge Pro 2009. For the attribution of probability distributions to variables affecting the results, triangular distributions were used. A statistically significant difference in survival rates between different surveillance strategies was considered to be present if

there was no overlap between the central 95% CIs of results of surveillance strategies.

## Results

### Parameters in literature

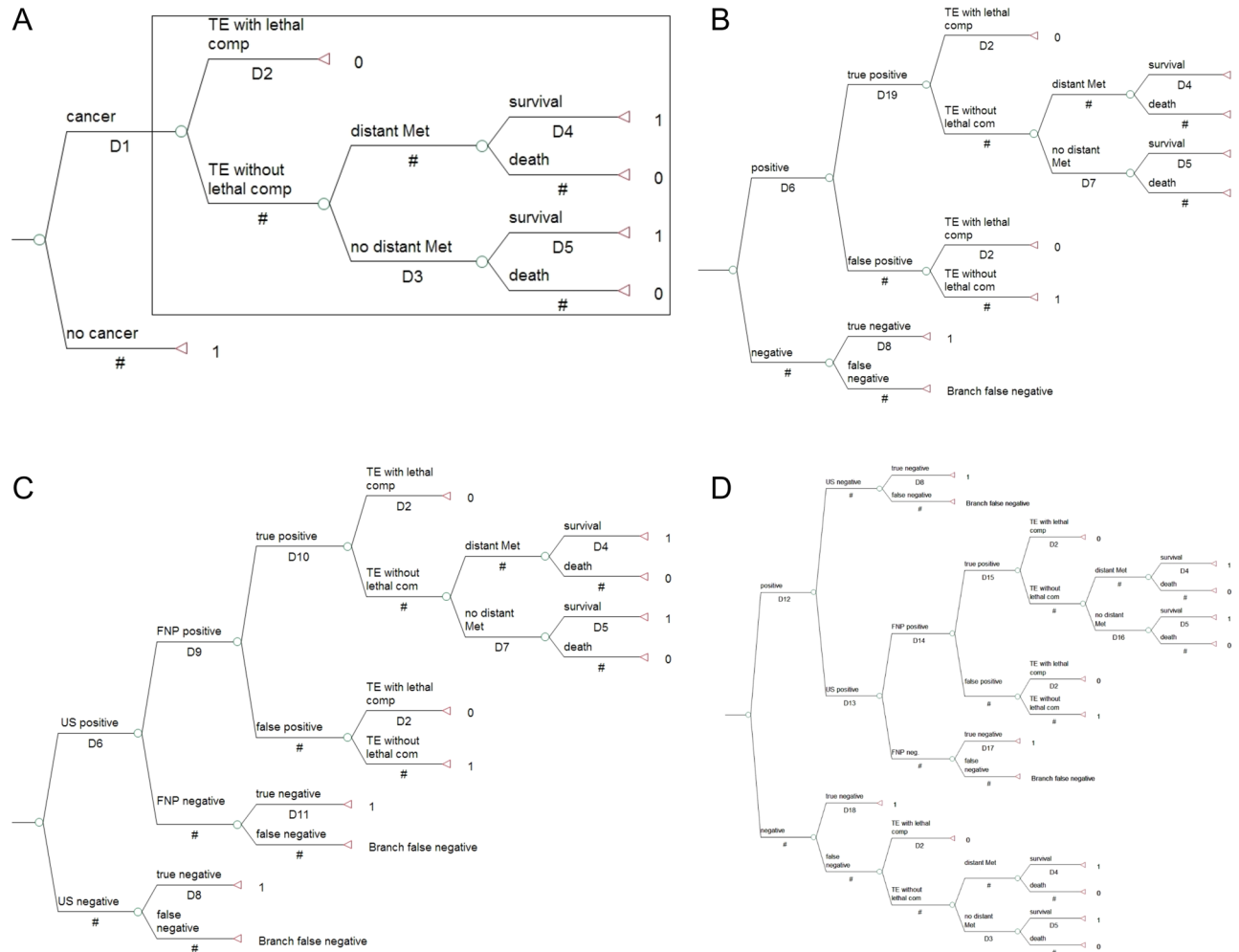
The precise parameters entered into the decision model as well as the source from which these were derived for each decision node are given in Table 1.

### Database query

The cumulative risk for the presence of distant metastases in patients >18 and <45 years at diagnosis in the Würzburg Thyroid Cancer Database (data 1980–2015) was  $1.1 \pm 0.4\%$  at a tumor diameter of 1.1 cm,  $4.8 \pm 1.1\%$  at 2.5 cm and  $13.1 \pm 2.5\%$  at 4.1 cm. For patients without distant metastases and >18 and <45 years of age at diagnosis, 10-year survival was  $98.4 \pm 0.5\%$ . For patients <45 years of age with distant metastases at diagnosis 10-year survival was  $89.5 \pm 3.8\%$ . These parameters are also summarized in Table 1.

### Results of surveillance

The decision trees for the four strategies are shown in Fig. 1, panels A–D. The results of decision tree analyses in terms of the fraction of patients with a correct diagnosis of DTC, incorrect DTC diagnosis in patients without cancer, missed DTC diagnosis or correct identification of a patient without DTC at the end of each surveillance procedure are given in Table 2. In summary, of a hypothetical 1000 CCS's, with Strategy-1, no patient would be operated on as a result of surveillance and 126 patients with DTC would incorrectly not be operated on due to not performing surveillance or, as assumed in the present model, diagnosed at a much later stage of disease. With Strategy-2, 126 DTC patients would correctly be operated on as a result of surveillance and no patient would incorrectly not be operated on. With Strategy-3, 111 DTC patients would correctly be operated on after surveillance and 15 DTC patients would incorrectly not be operated on. When using Strategy-4, 68 DTC patients would correctly be operated on and 58 DTC patients would incorrectly not be operated on. In contrast, unnecessary thyroid surgery due to false positive results of surveillance would occur in no patient with Strategy-1, in 556 patients with Strategy-2, 112 patients with Strategy-3 and in 39 patients with Strategy-4.



**Figure 1** Decision trees used for each of the four strategies analyzed in this study. Panel A: no surveillance. Panel B: surveillance by ultrasound alone. Panel C: surveillance by ultrasound followed by fine needle biopsy (FNB) if ultrasound is pathologic. Panel D: surveillance by neck palpation, when pathologic followed by ultrasound and followed by FNB if ultrasound is pathologic. Outcome is defined as survival: 0 = death, 1 = survival of at least 10 years. O = Chance node, open triangle = termination (or 'outcome') node, the variables D1 till D19 represent the likelihoods (see Table 1), # refers to the corresponding likelihood 1 - n. The 'branch false negative' is identical to the strategy of no diagnosis starting from the decision node related to D2 indicated by the rectangle in Panel 1A. TE, thyroidectomy; comp, complications; Met, metastases; US, ultrasound.

**Table 2** The results of decision tree analysis in terms of the fraction of patients with a correct diagnosis of DTC (true positive), incorrect DTC diagnosis in patients without cancer (false positive), missed DTC diagnosis (false negative) or correct identification of a patient without DTC (true negative). The results are given as fractions of 1.

	True positive	True negative	False positive	False negative
No surveillance	0	0.874	0	0.126
US only	0.126	0.318	0.556	0
US + FNB	0.111	0.762	0.112	0.015
Palpation + US + FNB	0.068	0.835	0.039	0.058

FNB, fine-needle biopsy; US, ultrasound.

**Survival analysis**

Using the Monte Carlo simulation, calculated median 10-year survival rates were 0.997 (2.5–97.5% CI: 0.991–0.999) for Strategy-1, 0.997 (0.992–0.999) for Strategy-2, 0.997 (0.991–0.999) for Strategy-3 and 0.997 (0.993–0.999) for Strategy-4, meaning that there was no significant difference in survival between the four strategies.

**Discussion**

The presented analysis shows that even in a population at high risk for developing DTC a structured surveillance program will not have an effect on 10-year DTC-specific



survival rates. There is no difference in survival of DTC between patients who undergo surveillance and those who do not, nor is there a difference in survival of DTC between different surveillance strategies, one of which was to perform no surveillance at all.

The presented analysis clearly illustrates the possible adverse impact of surveillance and diagnostic tests. In this analysis, it was demonstrated that if surveillance were to be done by US alone, this would in fact lead to > 50% of the screened population undergoing unnecessary thyroid surgery with its associated complications. Furthermore, both surveillance by US alone and surveillance by US followed by FNB would lead to more CCS being operated on unnecessarily than for an actual DTC case. The latter is also seen in screening cohorts after for example, the Fukushima disaster (23, 24, 25).

The present results about survival, on the other hand, may not be surprising and can even be considered in line with the literature. Thyroid cancer surveillance in CCS will at least currently mostly affect younger (<45 years of age) patients. Although there is no data in literature that shows whether secondary DTC in CCS has a similar course of disease as sporadic DTC, there is no data to the contrary either – hence for lack of better the data gained in the sporadic DTC variant needs to be considered for further hypotheses. The natural course of sporadic DTC in patients aged <45 is slow and comparatively (at least to other cancer entities) benign. It has already been shown that the presence of sporadic DTC in such patients does not affect life expectancy when treated adequately – in young patients, this is regardless of stage at diagnosis (26, 27). Similarly, as DTC will at some point start causing clinical symptoms which will in the end lead to treatment of the disease, life expectancy in unscreened CCS despite larger and more extensive disease at diagnosis can be expected to be as good as those followed with regular surveillance. This is reflected in the identical survival rates resulting from all four follow-up strategies. Of note and to be considered in any young patient with DTC, inversely speaking a study by Goldfarb and Freyer showed that adolescent and young adult patients who develop thyroid cancer as a secondary malignancy have a significantly decreased overall survival compared to adolescent and young adults with primary thyroid cancer (28). In spite of a lack of difference in cancer-specific survival, another argument for surveillance may be a reduction in disease-related morbidity and an associated increase in quality-adjusted life years. There is some evidence in the literature to support that an earlier detection of

DTC will lead to lower disease-related morbidity (28). For instance, smaller, less extensive tumors are associated with lower rates of recurrent laryngeal nerve damage or permanent hypoparathyroidism due to surgery (29, 30). Nonetheless, as the present study illustrates, the benefits of surveillance aiming at a lower complication rate in DTC cases (decreased morbidity) must be balanced against the increase in complications in patients operated on unnecessarily due to false positive surveillance. In cancer survivors especially, other arguments may be present to aim at detecting DTC at an early stage such as genetic predisposition to developing DTC, previous toxic effects of treatment or psychological considerations (31).

We have refrained from modeling the morbidity for several reasons. First, complication rates are very dependent on the surgeon performing the procedure: high-volume surgeons will have a much lower complication rate than low-volume ones (32). Second, the effect on QALYs cannot be modeled as we have not been able to find adequate data in literature on the impact of complications of thyroid surgery on QALYs; however, it is not inconceivable that this effect is highly variable among individuals and therefore hard, if not impossible, to summarize effectively in a model like the one used in the present study. Furthermore, the level of detail about the relation between DTC stage and complication rates required to perform the decision tree analyses used here is not available in literature. Also, the results of studies relating to morbidity and mortality from surgery are prone to selection bias: it is at least conceivable that those who have worse results are more likely to report these in a survey-based study.

As with any model-based study, the present one suffers from several limitations, the most important one being the use of data from single studies. The model requires the input of data on sensitivity, specificity as well as disease prevalence, etc. However, due to different inclusion criteria used in applicable studies, it is impossible to produce a reliable aggregate value for these parameters. Therefore, we used the estimates reported by the largest, most complete study for derivation of data for each decision node. To compensate for differences in reported sensitivity, specificity, prevalence, etc. the Monte Carlo-based sensitivity analysis was performed using a high standard deviation of at least 40% for each of these values, thereby more than encompassing the entire width of values reported for different parameters in similar, but smaller studies.

A further weakness concerns the very specific patient group which was subject of the present analysis.

As thyroid nodules and DTC in CCS have only been a subject of very few studies, not all data required for the present model could be derived from literature. Therefore, we expanded our study definition to include a broader patient population, for example, where the accuracy of FNB is concerned, or even derive novel data from a well-published and validated DTC patient database available to us. In theory, this might bias the study, but there is thus far scant evidence in literature to support that DTC in CCS shows a different clinical behavior than sporadic DTC diagnosed at the same stage with similar treatment, although a recent study by Sapuppo *et al.*, who evaluated the frequency and type of thyroid disorders in patients treated with chemotherapy and radiotherapy or chemotherapy alone for childhood/adolescence malignancies, found that patients who developed thyroid nodules and thyroid cancer were treated for childhood cancer at a younger age than patients who developed hypothyroidism (33). In light of this at most scan evidence to the contrary, we therefore believe that based on what is known thus far, it is reasonable to assume a similar if not identical clinical behavior, justifying the use of data derived from non-CCS thyroid nodule and DTC patients.

In the future, the present model-based study should be confirmed by long-term prospective studies. However, considering the very long survival times in DTC and the very low absolute number of CCS developing DTC during their lives and the difficulties involved in the comparison of multiple surveillance strategies, no results of such study are likely to be forthcoming in decades.

For the present study, we chose to limit ourselves to use proven methodology for which large patient series and long-term follow-up were available. In the future, however, the balance between the current alternative surveillance strategies may shift, as new developments in genetic analysis of FNB aspirates as well as molecular imaging of thyroid nodules are now increasingly starting to contribute to a further reduction in the number of unnecessary thyroid cancer cases. However, as far as we know, such techniques have not yet been tested in CCS and were therefore not considered in the present study

Nonetheless, the results of the present study can be used to further steer clinical practice. As there is no difference in long-term survival between different surveillance strategies, other subordinate outcome factors will play a role. The fraction of cancer cases correctly identified as well as the number of false positive surveillance results will play a role in the choice of surveillance strategy. While the balance of each of these factors will be different for each physician and for each

patient when considering the individual psychological factors, the present model clearly shows that the number of false positive cases (over half of patients in a US-only based surveillance) is unacceptably high. The other surveillance strategies have a more acceptable balance between correctly operated, correctly not operated and incorrectly operated on patients. In the end, the surveillance strategy employed will also depend on the health care system a CCS is treated in. Where structured CCS follow-up programs exist, thyroid palpation will be part of routine physical examinations, whereas if such programs do not exist no surveillance will not adversely affect DTC-specific survival. The choice to screen with US with the aim of detecting DTC at an earlier stage will have to be made by the physician together with the CCS after counseling about the advantages and the disadvantages of different surveillance strategies.

## Conclusion

We have shown that there is no difference among four different surveillance strategies for DTC in CCS with regard to disease-specific mortality rates. Even 'no structured surveillance' does not seem to significantly affect disease-specific survival. These results demonstrate that the benefit of surveillance for DTC in CCS seems to lie rather in a potential reduction of treatment-related morbidity than in a potential reduction of thyroid cancer-related mortality.

Considering the potential additional morbidity resulting from unnecessary surgical procedures in patients with false-positive surveillance results, the possible benefits from routine surveillance for DTC in CCS need to be balanced carefully against the potential harms.

## Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Funding

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

## References

- 1 Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, Berkow RL, Hammond S, Neglia JP, Meadows AT, *et al.* Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet* 2005 **365** 2014–2023. ([https://doi.org/10.1016/S0140-6736\(05\)66695-0](https://doi.org/10.1016/S0140-6736(05)66695-0))

- 2 Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Mertens AC, Liu Y, Hammond S, Land CE, Neglia JP, Donaldson SS, *et al.* Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. *Radiation Research* 2006 **166** 618–628. (<https://doi.org/10.1667/RR3605.1>)
- 3 Clement SC, Lebbink CA, Klein Hesselink MS, Teepeen JC, Links TP, Ronckers CM & van Santen HM. Presentation and outcome of subsequent thyroid cancer among childhood cancer survivors compared to sporadic thyroid cancer: a matched national study. *European Journal of Endocrinology* 2020 **183** 169–180. (<https://doi.org/10.1530/EJE-20-0153>)
- 4 Farahati J, Demidchik EP, Biko J & Reiners C. Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. *Cancer* 2000 **88** 1470–1476. ([https://doi.org/10.1002/\(sici\)1097-0142\(20000315\)88:6<1470::aid-cnrc27>3.0.co;2-w](https://doi.org/10.1002/(sici)1097-0142(20000315)88:6<1470::aid-cnrc27>3.0.co;2-w))
- 5 Reiners C, Biko J, Demidchik EP, Demidchik YE & Drozd VM. Results of radioactive iodine treatment in children from Belarus with advanced stages of thyroid cancer after the Chernobyl accident. *International Congress Series* 2002 **1234** 205–214. ([https://doi.org/10.1016/S0531-5131\(01\)00610-0](https://doi.org/10.1016/S0531-5131(01)00610-0))
- 6 Clement SC, Kremer LCM, Verburg FA, Simmons JH, Goldfarb M, Peeters RP, Alexander EK, Bardi E, Brignardello E, Constine LS, *et al.* Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treatment Reviews* 2018 **63** 28–39. (<https://doi.org/10.1016/j.ctrv.2017.11.005>)
- 7 Somerville HM, Steinbeck KS, Stevens G, Delbridge LW, Lam AH & Stevens MM. Thyroid neoplasia following irradiation in adolescent and young adult survivors of childhood cancer. *Medical Journal of Australia* 2002 **176** 584–587. (<https://doi.org/10.5694/j.1326-5377.2002.tb04589.x>)
- 8 Mikosch P, Gallowitsch HJ, Kresnik E, Jester J, Wurtz FG, Kerschbaumer K, Unterweger O, Dinges HP & Lind P. Value of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in an endemic goitre area. *European Journal of Nuclear Medicine* 2000 **27** 62–69. (<https://doi.org/10.1007/pl00006664>)
- 9 Gomez-Ramirez J, Sitges-Serra A, Moreno-Llorente P, Zambudio AR, Ortega-Serrano J, Rodriguez MT & del Moral JV. Mortality after thyroid surgery, insignificant or still an issue? *Langenbeck's Archives of Surgery* 2015 **400** 517–522. (<https://doi.org/10.1007/s00423-015-1303-1>)
- 10 Wiest PW, Hartshorne MF, Inskip PD, Crooks LA, Vela BS, Tepeak RJ, Williamson MR, Blumhardt R, Bauman JM & Tekkel M. Thyroid palpation versus high-resolution thyroid ultrasonography in the detection of nodules. *Journal of Ultrasound in Medicine* 1998 **17** 487–496. (<https://doi.org/10.7863/jum.1998.17.8.487>)
- 11 Verburg FA, Mader U, Tanase K, Thies ED, Diessl S, Buck AK, Luster M & Reiners C. Life expectancy is reduced in differentiated thyroid cancer patients  $\geq$  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>)
- 12 Verburg FA, Mader U, Grelle I, Visser TJ, Peeters RP, Smit JW & Reiners C. The thyroid axis 'setpoints' are significantly altered after long-term suppressive LT4 therapy. *Hormone and Metabolic Research* 2014 **46** 794–799. (<https://doi.org/10.1055/s-0034-1375678>)
- 13 Thies ED, Tanase K, Maeder U, Luster M, Buck AK, Hanscheid H, Reiners C & Verburg FA. The number of 131I therapy courses needed to achieve complete remission is an indicator of prognosis in patients with differentiated thyroid carcinoma. *European Journal of Nuclear Medicine and Molecular Imaging* 2014 **41** 2281–2290. (<https://doi.org/10.1007/s00259-014-2851-2>)
- 14 Verburg FA, Mader U, Luster M, Hanscheid H & Reiners C. Determinants of successful ablation and complete remission after total thyroidectomy and  $^{131}\text{I}$  therapy of paediatric differentiated thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2015 **42** 1390–1398. (<https://doi.org/10.1007/s00259-015-3076-8>)
- 15 Machens A, Holzhusen HJ & Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. *Cancer* 2005 **103** 2269–2273. (<https://doi.org/10.1002/cncr.21055>)
- 16 Verburg FA, Mader U, Luster M & Reiners C. Primary tumour diameter as a risk factor for advanced disease features of differentiated thyroid carcinoma. *Clinical Endocrinology* 2009 **71** 291–297. (<https://doi.org/10.1111/j.1365-2265.2008.03482.x>)
- 17 Sobin LH, Gospodarowicz MK & Wittekind C. *TNM classification of malignant tumours*. New York, NY, USA: Wiley-Blackwell 2009.
- 18 van Velsen EFS, Visser WE, Stegenga MT, Mader U, Reiners C, van Kemenade FJ, van Ginhoven TM, Verburg FA & Peeters RP. Finding the optimal age cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer. *Thyroid* 2021 **31** 1041–1049. (<https://doi.org/10.1089/thy.2020.0615>)
- 19 van Velsen EFS, Peeters RP, Stegenga MT, Mader U, Reiners C, van Kemenade FJ, van Ginhoven TM, Visser WE & Verburg FA. Evaluating the use of a two-step age-based cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer. *European Journal of Endocrinology* 2022 **186** 389–397. (<https://doi.org/10.1530/EJE-21-1056>)
- 20 Kim M, Kim WG, Oh HS, Park S, Kwon H, Song DE, Kim TY, Shong YK, Kim WB, Sung TY, *et al.* Comparison of the Seventh and Eighth Editions of the American Joint Committee on Cancer/Union for International Cancer Control Tumor-node-metastasis staging system for differentiated thyroid cancer. *Thyroid* 2017 **27** 1149–1155. (<https://doi.org/10.1089/thy.2017.0050>)
- 21 Verburg FA, Mader U, Luster M & Reiners C. The effects of the Union for International Cancer Control/American Joint Committee on Cancer Tumour, Node, Metastasis system version 8 on staging of differentiated thyroid cancer: a comparison to version 7. *Clinical Endocrinology* 2018 **88** 950–956. (<https://doi.org/10.1111/cen.13597>)
- 22 Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A & Dominguez M. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1748–1751. (<https://doi.org/10.1210/jc.2008-1724>)
- 23 Midorikawa S, Tanigawa K, Suzuki S & Ohtsuru A. Psychosocial issues related to thyroid examination after a radiation disaster. *Asia-Pacific Journal of Public Health* 2017 **29** 63S–73S. (<https://doi.org/10.1177/1010539516686164>)
- 24 Takano T. Overdiagnosis of juvenile thyroid cancer. *European Thyroid Journal* 2020 **9** 124–131. (<https://doi.org/10.1159/000503323>)
- 25 Clero E, Ostroumova E, Demoury C, Grosche B, Kesminiene A, Liutsko L, Motreff Y, Oughton D, Pirard P, Rogel A, *et al.* Lessons learned from Chernobyl and Fukushima on thyroid cancer screening and recommendations in case of a future nuclear accident. *Environment International* 2021 **146** 106230. (<https://doi.org/10.1016/j.envint.2020.106230>)
- 26 Maier TM, Schober O, Gerss J, Gorlich D, Wenning C, Schaeffers M, Riemann B & Vrachimis A. Differentiated thyroid cancer patients more than 60 years old paradoxically show an increased life expectancy. *Journal of Nuclear Medicine* 2015 **56** 190–195. (<https://doi.org/10.2967/jnumed.114.150284>)
- 27 Goldfarb M & Freyer DR. Comparison of secondary and primary thyroid cancer in adolescents and young adults. *Cancer* 2014 **120** 1155–1161. (<https://doi.org/10.1002/cncr.28463>)
- 28 Clement SC, Kremer LC, Links TP, Mulder RL, Ronckers CM, van Eck-Smit BL, van Rijn RR, van der Pal HJ, Tissing WJ, 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>)
- 29 Karamanakos SN, Markou KB, Panagopoulos K, Karavias D, Vagianos CE, Scopa CD, Fotopoulou V, Liava A & Vagenas K. Complications and risk factors related to the extent of surgery in



- thyroidectomy. Results from 2,043 procedures. *Hormones* 2010 **9** 318–325. (<https://doi.org/10.14310/horm.2002.1283>)
- 30 Wu SY, Chiang YJ, Fisher SB, Sturgis EM, Zafereo ME, Nguyen S, Grubbs EG, Graham PH, Lee JE, Waguespack SG, *et al.* Risks of hypoparathyroidism After total thyroidectomy in children: A 21-year experience in a high-volume cancer center. *World Journal of Surgery* 2020 **44** 442–451. (<https://doi.org/10.1007/s00268-019-05231-4>)
- 31 van Santen HM, Alexander EK, Rivkees SA, Frey E, Clement SC, Dierselhuis MP, Lebbink CA, Links TP, Lorenz K, Peeters RP, *et al.* Clinical considerations for the treatment of secondary differentiated thyroid carcinoma in childhood cancer survivors. *European Journal of Endocrinology* 2020 **183** P1–P10. (<https://doi.org/10.1530/EJE-20-0237>)
- 32 Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I & Dralle H. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World Journal of Surgery* 2000 **24** 1335–1341. (<https://doi.org/10.1007/s002680010221>)
- 33 Sapuppo G, Tavarelli M, Cannata E, La Spina M, Russo M, Scollo C, Spadaro A, Masucci R, Lo Nigro L, Russo G, *et al.* Risk of benign and malignant thyroid disorders in subjects treated for paediatric/adolescent neoplasia: role of morphological and functional screening. *Children* 2021 **8**. (<https://doi.org/10.3390/children8090767>)

Received in final form 10 October 2022

Accepted 14 October 2022

Accepted Manuscript published online 14 October 2022