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PENTEC ORGAN SYSTEM REVIEW

Primary Hypothyroidism in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: From the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative, a systematic review and meta-analysis of publications reporting on radiation dose-volume effects for risk of primary hypothyroidism after radiation therapy for pediatric malignancies was performed.

Methods and Materials: All studies included childhood cancer survivors, diagnosed at age <21 years, whose radiation therapy fields exposed the thyroid gland and who were followed for primary hypothyroidism. Children who received pituitary-hypothalamic or total-body irradiation were excluded. PubMed and the Cochrane Library were searched for studies published from 1970 to 2017. Data on age at treatment, patient sex, radiation dose to neck or thyroid gland, specific endpoints for hypothyroidism that were used in the studies, and reported risks of hypothyroidism were collected. Radiation dose-volume effects were modeled using logistic dose response. Relative excess risk of hypothyroidism as a function of age at treatment and sex was assessed by meta-analysis of reported relative risks (RR) and odds ratios.

Results: Fifteen publications (of 1709 identified) were included for systematic review. Eight studies reported data amenable for dose-response analysis. At mean thyroid doses of 10, 20, and 30 Gy, predicted rates of uncompensated (clinical) hypothyroidism were 4%, 7%, and 13%, respectively. Predicted rates of compensated (subclinical) hypothyroidism were 12%, 25%, and

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44% after thyroid doses of 10, 20, and 30 Gy, respectively. Female sex (RR = 1.7, $P < .0001$) and age >15 years at radiation therapy (RR = 1.3, $P = .005$) were associated with higher risks of hypothyroidism. After a mean thyroid dose of 20 Gy, predicted risks of hypothyroidism were 13% for males <14 years of age, increasing to 29% for females >15 years of age.
Conclusion: A radiation dose response for risk of hypothyroidism is evident; a threshold radiation dose associated with no risk is not observed. Thyroid dose exposure should be minimized when feasible. Data on hypothyroidism after radiation therapy should be better reported to facilitate pooled analyses.

1. Clinical Significance

Radiation therapy is critical in the management of several pediatric malignancies in which direct or incidental exposure of the thyroid gland can occur. Therefore, some survivors are at risk for late-onset injury to the thyroid, resulting in hypothyroidism, hyperthyroidism, benign thyroid nodularity, and/or malignancy.[1-9] Hypothyroidism is the most common late effect after therapeutic radiation exposure of the thyroid gland.[1-3,8,10,11] This systematic review from Pediatric Normal Tissue Effects in the Clinic (PENTEC) aims to describe the risk of hypothyroidism in cancer survivors who, during childhood, were treated with radiation therapy that resulted in incidental exposure of the thyroid gland to radiation.

The thyroid gland, via release of endogenous thyroid hormones, acts on all tissues and organs, affecting metabolism, cellular differentiation, growth, and development. Hypothyroidism may manifest with classic symptoms, including weight gain, growth retardation, cold intolerance, dry skin, brittle hair, constipation, menstrual irregularities, muscle cramping, and slower mentation; classic clinical signs include periorbital and peripheral edema, hypotension, bradycardia, pericardial effusions, pleural effusions, and prolonged relaxation of deep tendon reflexes. In the general adult population, the baseline risk of hypothyroidism is on the order of 0.1% to 2% for uncompensated hypothyroidism (described in "Endpoints and Toxicity Scoring") and 4% to 10% for compensated hypothyroidism, not requiring hormone replacement (discussed in "Endpoints and Toxicity Scoring").[12] Baseline risks increase with age.[13] The most common etiology of hypothyroidism is autoimmunity (ie, Hashimoto thyroiditis) caused by antithyroid peroxidase (anti-TPO) antibodies. Anti-TPO antibodies may be present before development of thyroid dysfunction,[14] and adults with anti-TPO antibodies may be at increased risk of developing hypothyroidism after exposure to irradiation.[15,16] Persistently elevated thyroid-stimulating hormone (TSH) after exposure to irradiation is a risk factor for the development of thyroid nodules.[1]

Figure 1 depicts the hypothalamic–pituitary–thyroid gland axis. The hypothalamus, with input from the brain and circulating hormones, controls pituitary function via secretion of releasing hormones. For thyroid function, thyrotropin-releasing hormone stimulates secretion of TSH from the anterior pituitary; TSH stimulates the thyroid gland to produce and secrete thyroid hormones, triiodothyronine (T3) and thyroxine (T4). The pituitary gland and hypothalamus are "upstream" drivers of the thyroid gland, and hence radiation-associated injury to these structures can also manifest as hypothyroidism. This "secondary" or central hypothyroidism, causing a low free T4 in conjunction with low to normal TSH, is not specifically reviewed here.

In a Childhood Cancer Survivor Study (CCSS) report of 14,290 five-year survivors,[8] a mean thyroid dose of >20 Gy from radiation therapy, dosimetrically reconstructed as described in a recent review,[17] was associated with a 6.6-fold (95% confidence interval, 5.6-7.8) risk of patient-reported primary hypothyroidism. A large range in incidence of hypothyroidism has been reported (<5% to >75%)[18] owing to interstudy differences in relevant parameters, such as age and sex composition of the studied cohort, follow-up time, radiation therapy dose, technique, and the frequency and type of follow-up testing. We address suggested data collection and reporting in future studies in "Toxicity Scoring Recommendations."

Older age at radiation exposure is associated with greater risks of radiation-induced hypothyroidism. In most studies, subclinical or compensated hypothyroidism is roughly 3-fold more common than clinical or overt hypothyroidism.

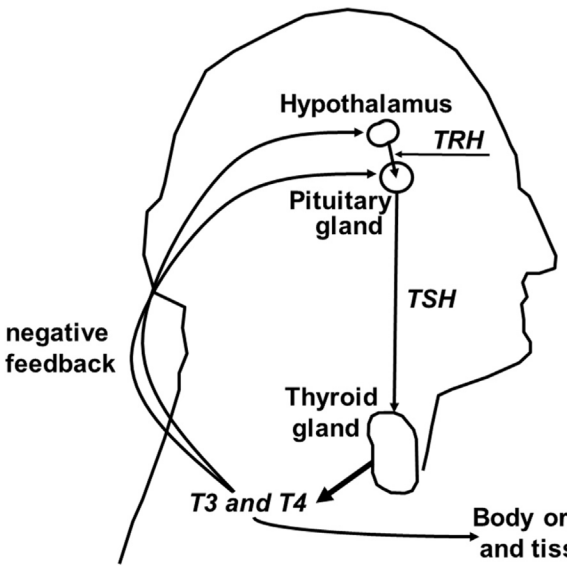

Fig. 1. Hypothalamic–pituitary–thyroid axis. The hypothalamus, with central nervous system and hormonal inputs, releases thyrotropin-releasing (TRH) hormone that stimulates secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH stimulates secretion of triiodothyronine (T3) and thyroxine (T4) from the thyroid gland, and these hormones affect multiple organ systems as described in the text.

The time interval to onset of compensated or clinical hypothyroidism is generally within the first 5 years after radiation therapy, with a peak seen between 2 and 4 years. Rarely, after higher (>40 Gy) radiation doses, clinical onset occurs within the first year after radiation therapy.[1,3,19] Conversely, some patients are not diagnosed until after 5 to 10 years.[1,3,19,20] Spontaneous recovery of thyroid function has also been reported.[21]

2. Endpoints and Toxicity Scoring

Hypothyroidism may be asymptomatic (occult), detected only by an isolated elevated TSH,[22] and often referred to as *subclinical or covert hypothyroidism.* This is opposed to *clinical or overt hypothyroidism* in which the thyroxine (T4) levels are low and clinical symptoms are present.

In this document, we will use the following nomenclature for primary hypothyroidism:

1. *Compensated hypothyroidism* occurs when the pituitary gland releases increased amounts of TSH to hyperstimulate a dysfunctional thyroid gland, thus successfully maintaining adequate levels of circulating thyroid hormones.
2. *Uncompensated hypothyroidism* occurs when T4 remains low despite elevated TSH (ie, the thyroid gland cannot adequately function despite hyperstimulation).

Radiation-induced hypothyroidism resulting from thyroid gland exposure can be either *compensated or uncompensated.* Radiation-induced compensated hypothyroidism often progresses, usually over months to years, to uncompensated, clinical hypothyroidism.[2]

Because these descriptive endpoints are binary, meaning that they are either present or not, a formal grading system is generally not used in published studies. The Common Terminology Criteria for Adverse Events (CTCAE) version 3, 4, and 5 grading scales for hypothyroidism[23,24] are shown in Table 1. Grade 1 CTCAE version 4 to 5 toxicity ("Asymptomatic; clinical or diagnostic observations only") is considered compensated hypothyroidism. Patients with grade 2 CTCAE version 4 to 5 toxicity require thyroid hormone replacement and are considered to have uncompensated hypothyroidism. CTCAE grade 3 (severe symptoms) or higher (life-threatening or fatal) thyroid toxicity is highly unusual for late radiation injury. A more-detailed toxicity grading system for hypothyroidism, which has not been widely adopted, delineated symptomatic, objective, management, and analytic (SOMA) criteria.[25,26] The analytic ("A" of SOMA) criteria for grade 2 and 3 toxicity were 0% to 50% and >50% decreases in T4, respectively.

3. Anatomy and Developmental Dynamics

The developed thyroid gland is a bilobed, butterfly-shaped endocrine gland in the low anterior neck, partially encircling the larynx and trachea anteriorly, extending superiorly from the thyroid cartilage and inferiorly to the tracheal rings.[2] The right and left lobes are connected by a narrow isthmus. The gland consists of follicles, lined with a single layer of epithelial cells that actively transport iodine into the follicle and generate and secrete thyroid hormones.

The thyroid gland develops from the foregut endoderm,[27,28] which terminally differentiates and becomes functional in utero at ~12 weeks. After this, the number of follicles remains unchanged, but they continue to increase in size. The thyroid gland grows in size from ~5 mL at 6 years to ~16 mL at 15 years.[29] The thyroid follicles represent functional subunits that can be considered arranged in parallel. This would lead to the expectation of mean thyroid dose as a reasonable predictor of radiation-related toxicity, but with a note of caution that serial versus parallel organ structure may be an oversimplification is some scenarios.[30,31]

There is a clear age dependence of the thyroid gland to susceptibility to radiation-induced injury (described in more detail in "Review of Dose Volume Response Data and Risk Factors"), with older children exhibiting greater susceptibility to hypothyroidism in adulthood than younger children. This may reflect the greater sensitivity of the thyroid gland in growing pubertal children, compared with preadolescents. Biologic underpinnings for this age dependence are unclear but may relate to differences in glandular growth inhibition, sensitivity

Table 1 CTCAE grading scale for hypothyroidism

Grade	Criteria for CTCAE version 3	Criteria for CTCAE versions 4 and 5
1	Asymptomatic, intervention not indicated	Asymptomatic; clinical or diagnostic observations only
2	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL
3	Symptoms interfering with ADL; hospitalization indicated	Severe symptoms; limiting self-care ADL; hospitalization indicated
4	Life-threatening myxedema coma	Life-threatening consequences; urgent intervention indicated
5	Death	Death

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

of the thyroid follicular epithelium,[32] and induction of radiation-induced reciprocal translocations in normal thyroid cells.[33] There are no known genetic factors for predisposition or susceptibility to radiation-induced thyroid injury.

4. Defining Volumes: Pediatric Imaging Issues

Although the thyroid gland is well visualized on planar computed tomography (CT) and magnetic resonance imaging, many studies, particularly those in the pre−3-dimensional radiation therapy era, used the neck dose as a surrogate for thyroid dose. Given its relatively small size, uniform dose within the thyroid gland was assumed. A recent CT-based atlas (not for any specific age group), sponsored by 9 major cooperative groups,[34] provides no specific guidelines in contouring the thyroid gland and notes that the thyroid gland "has considerable contrast compared to its surrounding tissues." Intra-/interfractional movement will depend on the immobilization devices used. A several-millimeter setup uncertainty of the bony and cartilaginous structures in the head and neck, including the thyroid gland, likely occurs when using an immobilization mask. This small setup uncertainty would not be clinically significant for thyroid exposure in scenarios in which the entire thyroid gland is encompassed within the radiation field, which is less common in current practice that uses more conformal radiation delivery with intensity modulated radiation therapy and/or proton therapy. In modern practice, partial thyroid radiation exposure could occur in pediatric patients treated with radiation therapy for some lymphomas or head and neck malignancies (including sarcomas).

5. Review of Dose Volume Response Data and Risk Factors

The PENTEC systematic review of radiation-induced hypothyroidism was undertaken to ascertain the dose response of the thyroid in childhood cancer survivors.

Search methodology for identification of studies

The PENTEC systematic review of radiation-induced hypothyroidism was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[35] Search criteria were developed (by C.R. and L.K.) to identify studies that evaluated radiation dose effects on the risk of hypothyroidism among survivors of childhood cancer. PubMed and the Cochrane Library were searched (by C.R. and L.K.) for studies published, or available online in press, from 1970 to 2017. Appendix E1 provides further details of the search strategy. Two investigators (M.T.M. and J.A.V.) independently reviewed titles and abstracts; subsequently, these same investigators independently reviewed full texts of any article that either reviewer considered potentially eligible.

Inclusion criteria

After the literature search, studies were evaluated for inclusion or exclusion. All study designs except case reports were eligible for inclusion. To be evaluated for this report, studies must have included only, or analyzed separately, survivors of childhood cancer (diagnosed before age ≤21 years) treated for cancer with radiation therapy in the thyroid region. The outcome of interest, primary hypothyroidism, had to be described. Patients who developed hypothyroidism after pituitary−hypothalamic or cranial−spinal radiation therapy or total body irradiation were excluded.

Data extraction

Age at treatment, risk of hypothyroidism relative to dose to the thyroid or neck, and hypothyroidism as an endpoint definition were extracted. For eligible studies, 2 authors (M.T.M. and J.A.V.) independently extracted the information on patient and treatment characteristics as well as outcomes of interests.

Search results

The literature search identified 1709 unique references. Based on our prespecified inclusion criteria, we excluded 1622 studies based on review of title and abstract. Thereafter, all but 15 were excluded after review of the full text. Tables 2 and 3 and Table E1 summarize these 15 studies.[1,3,7,21,36-46] Eight studies,[3,21,36-38,43-45] all retrospective, reported data amenable for assessment of the association between radiation dose to thyroid and risk of subclinical or clinical hypothyroidism. From these 8 studies, 2682 patients were included in the dose-response analyses (performed by I.R.V. and S.M.B.). Of 6 of those 8 studies that reported follow-up time after treatment,[36-38,43-45] the range of median or mean follow-up was 6 to 19 years; minimum follow-up was 5 years in another study.[3]

To gauge the potential reproducibility of the modeled dosimetric data relative to modern treatment planning, the task force medical physicist (E.Y.) reviewed the dose accuracy for each study (Table E2). Based on the text within the publication, this evaluation included a categorization of the reported doses as well as an estimate, when possible, of the accuracy of those doses. In general, the planning and treated approaches used in these reports would not have yielded steep dose gradients. As opposed to specifying neck or thyroid dose, 1 investigation reported prescribed dose, 1 did not specify, and 2 did not provide sufficient information to determine whether calculations beyond prescribed dose were used. Seven[3,21,36,38,43-45] of the 8 modeled studies binned dose to the neck or thyroid. Our dose-response model used each study's reported dose as the thyroid dose and used the midpoint dose if dose-bins were reported. All these factors increase uncertainty in the shape of the modeled dose response. Although we did not quantitatively incorporate these potential uncertainties into the normal

Table 2 Selected studies in analyses of hypothyroidism after radiation therapy for pediatric malignancies: Study characteristics

Author, year (institution)	PMID	Treated disease	Years of treatment	Age at treatment, y	No. of patients	Sex M:F	Dose to thyroid* (Gy)	Dose to neck (Gy)	Chemotherapy regimens
Hancock, 1991 (Stanford)	1861693	HL	1961-1989	2-82 mean 28	1787	1047:740	NR	0-44	Several
				<17	272†	NR			
Hildreth, 1987 (NYU)	3588850	Enlarged thymus	1926-1957	Infancy	153	107:46	NR	0.05-4.2	None
					51	28:23		0	
Lange, 1983‡ (U Penn)	6402288	HL	1970-1980	3-18 median 12.5	66	40:26	NR	20-44	Several
Constine, 1984‡ (Stanford)	6692289	HL	1962-1979	4-16	119	63:56	Calculated for 4 patients and not corrected	15-60	Single agent or MOPP
Devney, 1984‡ (U Minnesota)	6747754	HL	1971-1978	4-16	28	11:17	0 (n = 4) max 28-51 mean: 44 (estimated)	Mean 43.8	Several
Kaplan, 1983‡ (JCRT)	6824006	Mostly HL§	NR	<19	92	NR	NR (estimated)	NR	Several
Green, 1980 (Roswell Park)	7421731	HL	1970-1978	"Pediatric"	27	NR	NR	34.0-40.3	None
Healy, 1996‖ (St Bartholomew's H)	8696697	HL	NR	4.6-16.6 median 12.5	46	30: 16	22.5-40 (median 35)	NR	NR
Bossi, 1998 (U Pavia)	9793265	HL	NR	2-14	25¶	15: 10	NR	0-42	Several
Atahan, 1998 (Hacettepe U)	9862158	HL	1975-1989	2-18 median 8.5	46	NR	<20 (n = 1) 20-25 (n = 15) 25-30 (n = 17) >30 (n = 13)	NR	Several
Sklar, 2000‡ (multi-inst.)	10999813	HL	1970-1986	2-20 median 14	1791	959: 832	<1-55 (estimated)	<1-55 (estimated)	Yes (regimens NR)
Metzger, 2006‡ (St. Jude)	16575001	HL	1980-2002	3.0-21.8 median 15.3	461	266: 195	0 to >21	NR	Several
Bolling, 2011‡,‖ (multi-inst., CCSS)	21167655	HL	2001-2009	0.8-21 median ~14.6	125	NR	15-50	NR	Several
Demirkaya, 2011‡ (Uludag U)	21750638	HL	1995-2008	2.8-17.0 mean 10.3	55	37:18	NR	25.2-36	Several
Rodriquez, 2014 (U Siena)	25198559	HL	1983-2012	3.2-17.3 median 11.8	13¶	7:6	NR	0-35 (median 20)	Several

(*Continued*)

Table 2 (*Continued*)

Author, year (institution)	PMID	Treated disease	Years of treatment	Age at treatment, y	No. of patients	Sex M:F	Dose to thyroid* (Gy)	Dose to neck (Gy)	Chemotherapy regimens
Inskip, 2018 (multi-inst., CCSS)	29763379	HL	1970-1986	12-17 median 15	1550	NR for HL	26.9-43.6 (median 38)	NR	Several

Studies arranged by PubMed identification number (PMID).

Abbreviations: ALL = acute lymphoblastic leukemia; CCSS = Childhood Cancer Survivor Study; HL = Hodgkin lymphoma; MOPP = mustargen, oncovin, procarbazine, prednisone; NHL = non-Hodgkin lymphoma; NR = not reported.

* Study specified "thyroid dose," though in some studies this may reflect neck dose. Dose subgroups are listed here unless the rate of toxicity was also grouped by dose (in which case that data are listed in Table 3).

† In the published paper, a table reports age <16 and the text reports age <17 years for same group of patients.

‡ Studies included in normal tissue complication probability (NTCP) model (Fig. 1), Table 3, and supplemental tables. Those 7 studies not included in the NTCP model did not provide risks of hypothyroidism relative to thyroid/neck dose exposure.

§ HL (n = 44), NHL (n = 9), Wilms (n = 18), neuroblastoma (n = 11), other (n = 13).

‖ Prospective study. All others were retrospective.

¶ This paper provided a table of individual patient characteristics and hypothyroidism endpoints.

tissue complication probability (NTCP) models, we concluded that the dosimetric uncertainties were acceptable and within the models' mathematical uncertainties. However, we recognize that lack of uniformity in dose calculation across studies is a limitation in these analyses. More consistent reporting standards (discussed later) can reduce these uncertainties. Table E3 summarizes the assessment of bias in the 8 studies used for NTCP modeling.

Dose effect relationship

After assessment of competing modeling strategies (performed by I.R.V. and S.M.B.; see Appendix E2), the most robust model was achieved by pooling all dose-response pairs with confidence intervals in a single data set. Given the different sample sizes, and potential of 1 study[3] to dominate the results, we analyzed the sensitivity to leaving out single studies. The inclusion or exclusion of a single study had limited effect on the dose-response relationship with conventional pooling of data (Fig. E2 in Appendix E2).

We performed a logistic dose response fit according to the equation:

$$P(D) = \frac{1}{1 + exp\left(4\gamma_{50}\left(1 - \frac{D}{D_{50}}\right)\right.}$$

where γ_{50} and D_{50} denote the normalized slope and dose at 50% risk of complications,[47] and $P(D)$ is the risk of any hypothyroidism associated with the dose D. Observations are weighted by inverse variance and the fit was performed using the *glm* function in Matlab with a logit link function. In brief, this model was chosen because it was less sensitive to individual studies in a leave-one-out fashion than a previously proposed meta-analysis method.[48] Figure 2 shows the fitted model of any (compensated or uncompensated) hypothyroidism risk as a function of dose. Best-fit parameters are γ_{50} = 0.7 (95% CI, 0.6-0.9) and D_{50} = 33 Gy (95% CI, 27-39 Gy).

Risk factors for hypothyroidism

For thyroid doses of 10, 20, and 30 Gy, the predicted average risk of compensated (subclinical) hypothyroidism was 12%, 25%, and 44% respectively. Five studies allowed extraction of both compensated and uncompensated hypothyroidism.[21,36,37,44,45] The synthesized relative risk (RR) of compensated hypothyroidism versus uncompensated hypothyroidism was 3.5, although the accuracy of this is affected by how hypothyroidism was defined in the report and possible variation in clinical practice with respect to initiation of hormone replacement. Accepting these limitations, our analyses predict expected rates of uncompensated hypothyroidism at 10, 20, and 30 Gy of 4%, 7%, and 13% respectively (Table 4).

We observed good evidence of risk modulation by sex and age, as indicated by the inverse variance weighted synthesis of the relative risk of these factors performed using review manager v.5.3[49] and depicted in Table 5. Age

Table 3 Studies included in analyses of hypothyroidism after radiation therapy for pediatric malignancies: Specific endpoints that were evaluated, time to event, thyroid/neck dose, and prognostic factors

Author	Reported endpoint (s)[†] (no. of events/no. at risk)	FU time, y	Time post-RT to toxicity	Dose[*] to thyroid/neck: no. of events/ no. at risk	HR for hypothyroidism *P* value	Nondosimetric factors (adverse)
Lange	Any hypothyroidism: 18/66 Compensated hypothyroidism: 12/66	Median 6.3	NR	20 Gy: 5/20 36 Gy: 13/44	NR	NR
Constine	Elevated TSH: 75/119	NR	≤26 Gy: mean 1.5 y >26 Gy: mean 2.6 y	≤26 Gy: 4/24 >26 Gy: 71/95	*P* <.001	• NS: sex, median age, chemo • For peak TSH, younger age (*P* = .04) weakly correlated
Devney	Any hypothyroidism: 21/28 Compensated hypothyroidism: 16/28	5.9-11.9 median 7.8	median 1.7 y	0 Gy: 0/4 28-51 Gy: 21/24	RT dose: NS	• NS: pre-RT lymphangiogram, age
Kaplan	Low thyroxine: 7/92 High TSH: 35/92	5-34 y mean 19	5-21 y	<30 Gy: 6/41 ≥30 Gy: 34/50	RT dose: *P* <.007	• Pre-RT lymphangiogram (*P* = .01) • NS: chemotherapy, sex, age, time intervals between RT, and evaluation
Sklar	Any hypothyroidism: 456/1791 Requiring THR: 380/1494	Minimum 5 Range NR age at FU: 12-47 median 30	0-27 y (mean 7)	0 Gy: 7/92 <35 Gy: NR[‡] 35-44.99 Gy: NR[‡] ≥45 Gy: NR[‡]	1.0 HR = 3.8, *P* = .004 HR 5.5, *P* = .0002 HR = 10.7, *P* <.0001	• Female (HR 1.7, *P* <.0001) • Age >15 y (HR = 1.5, *P* = .0001) • <5 y from diagnosis (HR 2.1, *P* <.0001) • NS: chemotherapy
Metzger	Any hypothyroidism: 196/461 Requiring THR: 173/461	1.8-24.9 median 11.3	NR	0 Gy: 1/30 ≤21 Gy: 40/137 >21 Gy:155/294	HR = 1.0 HR = 16.7, *P* = .005	• White race (HR 2.5, *P* <.001) • Female (HR 1.4, *P* = .03) • NS: age >14, B symptoms, HL histology, HL stage, chemotherapy

(*Continued*)

Table 3 (*Continued*)

Author	Reported endpoint (s)[†] (no. of events/no. at risk)	FU time, y	Time post-RT to toxicity	Dose[*] to thyroid/neck: no. of events/ no. at risk	HR for hypothyroidism *P* value	Nondosimetric factors (adverse)
Bolling	Pathologic thyroid value: 30/95	Median 3.3 y for entire cohort. NR for subgroup	7-74 mo	15-25 Gy: 24/74 >25 Gy: 6/21	HR = 3.07, *P* = .002[§] HR = 3.77, *P* = .009[§]	NR
	Requiring THR: 6/95		1-83 mo	15-25 Gy: 4/74 >25 Gy: 2/21	NR	
Demirkaya	Abnormal thyroid function: 14/55 Subclinical hypothyroidism: 11/55 Overt hypothyroidism: 3/55	0.9-16.3 mean 5.6	1-2 y: 3 2-3 y: 2 3-4 y: 3 4-5 y: 4 >5 y: 2	0 Gy: 2/13 25.2 Gy: 6/22 30.6 Gy: 1/14 36 Gy: 5/6	NR	• Histopathologic subgroups: NS • 3 vs 6 cycles of chemotherapy: NS

Abbreviations: FU = follow-up; HL = Hodgkin lymphoma; HR = hazard ratio; NR = not reported; NS = not significant (ie, factors were not significant for greater risks of toxicity); THR = thyroid replacement hormone.

[*] Table E2 describes the dosimetry calculations used in these studies.

[†] Endpoints as described in the paper. Table E1 summarizes the endpoints analyzed in each study as well as the type and frequency of assessment for hypothyroidism

[‡] This paper provided a histogram, with the percent of patients within each bin of thyroid dose exposure, allowing accurate estimation of the number of patients in each dose bin. Actuarial risks of hypothyroidism (Kaplan-Meier plots out to 20+ years), as opposed to absolute number of events, were reported. For modeling, the risks at 10 years were used.

[§] Compared to another group that received prophylactic cranial radiation.

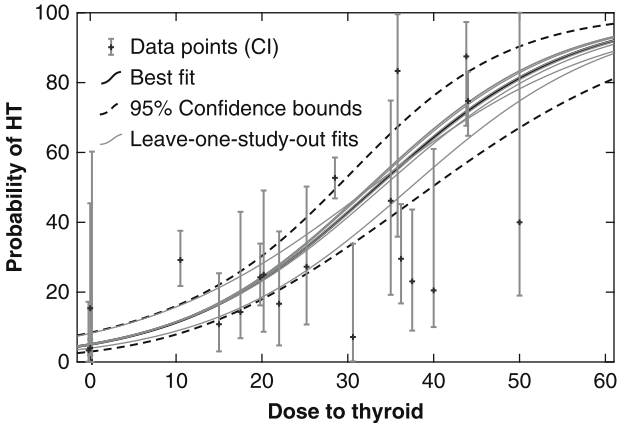

Fig. 2. Normal tissue complication probability model of any (compensated or uncompensated) hypothyroidism risk as a function of dose. Best-fit parameters for the PENTEC model (see text for equation) are $\gamma 50 = 0.7$ (95% CI, 0.6-0.9) and D50 = 33 Gy (95% CI, 27-39 Gy). This model represents fit to all available data from 8 studies. Fit with confidence bounds is shown, together with a leave-one-study out analysis, in which data from each of the 8 studies are omitted and a fit is performed on the remaining 7 studies. These leave-one-study-out fits are depicted as the 8 thin gray lines and serve as sensitivity analyses (ie, showing that the model is not overly sensitive to a single data set). *Abbreviations:* CI = confidence interval; HT = hypothyroidism.

Table 4 Data from normal tissue complication probability model: Dose response for compensated and uncompensated hypothyroidism after radiation therapy for pediatric malignancies

	Mean dose to thyroid (Gy)		
Endpoint	**10**	**20**	**30**
Risk of compensated (subclinical) hypothyroidism	12%	25%	44%
Risk of uncompensated (clinical) hypothyroidism*	4%	7%	13%

* Based on a risk ratio of 3.5 for compensated vs uncompensated.

>15 years at time of radiation therapy[3,43] (RR 1.3 [95% CI, 1.1-1.6]; $P = .005$) and female sex[3,21,43,44] (RR 1.7 [95% CI, 1.4-2.0]; $P \leq .0001$) were associated with increased risks of hypothyroidism. Observed heterogeneity measured by I^2 in these analyses were $I^2 = 39\%$ and $I^2 = 57\%$, respectively, indicating some heterogeneity. I^2 can be interpreted as the proportion of variation exceeding the expected level from sampling alone.[50]

Patient-related risk factors were included in the dose response to yield age-specific and sex-specific dose-response curves by using the assumed prevalence of each risk factor in the 8 studies underlying the overall dose-response curve and the observed RR of hypothyroidism for that risk factor. The prevalence of male versus female patients was reported in 6 of these 8 studies (1376:1144 patients). Median age in the 2 largest studies in the dose-response analysis is 14 and 15 years, and the remaining studies report slightly lower median age at diagnosis. We assumed a 50% prevalence of patients aged <14 years in the estimation of the dose-response analysis accounting for age.

The mathematical details are provided in Appendix E3. A web application performing the calculation steps is available online (https://dcccrt.shinyapps.io/pentecthyroid2/). This application generates NTCP models for hypothyroidism based on patient age, sex, and thyroid dose.

We caution that an important assumption behind the analysis is independence of relative risk between age, sex, and dose, with no effect modification or interaction among these risk factors. For example, the RR associated with being <14 years old is assumed to be the same at all thyroid dose levels. We could not adequately challenge the assumptions of independence owing to the lack of access to individual patient data (see "Data Reporting Standards Specific to This Organ"). For thyroid cancer, such a large-scale individual patient data analysis was conducted recently.[51]

We recommend exercising caution in interpreting the absolute risk estimates from the apps and figures. The depicted confidence intervals are statistical measures of variability of the fit given the observed data with weighting as described but do not take into account that binning of data has been used in individual studies and that there is a variation in case mix in the included studies. The confidence

Table 5 Risk factors for hypothyroidism after radiation therapy for pediatric malignancies

Risk factor	Risk ratio (95% CI), *P* value	No. of patients	No. of studies
Age (older vs younger)	1.3 (1.1-1.7); $P = .005$	2252	2
Sex (female vs male)	1.7 (1.4-2.0), $P < .0001$	2426	4

Data relating to age and sex were extracted as relative risks or odds ratios where modeled (by I. Vogelius) in the original publications or as crude rates in the absence of such modeling. Extracted data were combined using inverse variance weighting in the review manager software.

Two studies allowed analysis of age at exposure (cut-point of 14-15 years) on hypothyroidism risk. Four studies allowed analysis of sex on hypothyroidism risk; female sex was associated with greater risk. In both analyses we observed moderate heterogeneity between studies. Eight studies reported data amenable for dose-response assessment; 2682 patients were included in dose-response analysis. The risk ratio of subclinical vs clinical (ie, need for thyroid hormone replacement) was 3.5 (95% CI, 2.5-5.0).

Abbreviation: CI = confidence interval.

intervals may therefore be an underestimation of the full model uncertainty in some clinical scenarios. Independent testing of the proposed model with individual patient data to challenge the model is therefore recommended.

In addition, almost all data were from patients treated for Hodgkin lymphoma. As such, the study population is not fully representative of all childhood patients at risk of hypothyroidism after radiation exposure to the thyroid gland. Furthermore, comparatively few patients in this analysis were treated in the first decade of life. Therefore, the current models do not provide sufficient heterogeneity in age at exposure to fully explore potential heterogeneity in dose response. Finally, the potential effect of concurrent chemotherapy exposures is not accounted for owing to the lack of data.

6. Recommendations for Nominal Dose-Volume Goals

We found ample evidence of the presence of a thyroid gland dose response for risk of hypothyroidism. Differences in radiation therapy techniques across studies, and applicability of the NTCP data to more modern radiation therapy techniques, is a limitation. Notably, we found no data on hypothyroidism risk as a function of absolute or relative thyroid volume (ie, partial volume) radiation exposure in children. Partial thyroid exposure is potentially relevant in the era of more conformal radiation therapy dose delivery, particularly in a classically arranged parallel organ, with the caveat that parallel versus serial classification is imperfect, as discussed earlier.

Conceding that there are limitations to modeling toxicity risks from pooled binned data, the PENTEC model did not demonstrate a lower threshold dose to the thyroid gland to prevent the development of hypothyroidism. We cannot rule out that such a threshold exists, particularly with appreciable baseline risks of hypothyroidism in the general population (see "Clinical Significance"), but we do not have data to conclude with any confidence that sufficiently low doses would lead to no excess risk. Another factor to consider is the risk of thyroid malignancy after low-dose radiation. Hypothyroidism may be considered an acceptable risk in some patients (particularly given its common presentation in the general population as discussed in "Anatomy and Developmental Dynamics"), as opposed to underdosing the target volume or perhaps overdosing another normal tissue. Individualized risk estimation tools are given, and we recommend keeping the dose to the thyroid as low as reasonably achievable, with consideration of the remaining aspects of the radiation dose plan. To this end, the thyroid should be delineated and considered in plan optimization. To inform treatment planning decisions, Table 6 shows the risks of hypothyroidism for specific thyroid dose, patient age at time of radiation, and sex.

A CCSS study[46] of 11,503 patients with average follow-up >16 years modeled risks of hypothyroidism >5 years after radiation therapy (ascertained by questionnaires) as a function of pituitary and thyroid dose exposures. Thyroid radiation dose dependence on hypothyroidism was diminished at high pituitary doses. These data were not included in our NTCP models because the 246 patients with Hodgkin lymphoma were not analyzed separately from patients with central nervous system cancers or leukemias (who would have potentially undergone brain radiation therapy). From their modeled data, with 0 Gy pituitary exposure, the 5-year prevalence of hypothyroidism (compensated or uncompensated) was ~5% and ~7% at 10 Gy and 30 Gy thyroid dose exposure, respectively. These rates are lower than those from our modeled data (Table 4), likely due in part to the CCSS study excluding 416 patients who received a diagnosis of hypothyroidism <5 years from cancer diagnosis, as well as possible underreporting of hypothyroidism in questionnaires and omitting patients with missing age at diagnosis of hypothyroidism.

Table 6 Risks of any hypothyroidism after radiation therapy for pediatric malignancies, grouped by mean thyroid dose, age, and sex

	Risk of hypothyroidism*			
	Age <14 y		Age >15 y	
Mean thyroid dose	Female	Male	Female	Male
10 Gy	10%	6%	14%	8%
20 Gy	22%	13%	29%	17%
30 Gy	39%	23%	53%	31%
40 Gy	59%	35%	79%	47%

Age 14 to 15 y was used as a cutoff because the 2 studies that analyzed age used different cut-points. Presumably, the risks of hypothyroidism in patients irradiated at ages 14 to 15 y would be intermediate to those shown for ages <14 y and >15 y.

* Any hypothyroidism (ie, compensated or uncompensated).

7. Toxicity Scoring Recommendations

Patients at risk for radiation-induced hypothyroidism should undergo regular monitoring with thyroid function tests to assess function and physical examination to assess the presence of nodules. For reporting data on hypothyroidism in childhood cancer survivors, the consensus recommendation from the PENTEC thyroid group was to use the most recent CTCAE toxicity scoring system (Table 1) as it is commonly applied in clinical practice. The CTCAE grading system conveniently groups patients into those not requiring thyroid replacement (grade 1) and those for whom hormone replacement is necessary (grade ≥2).

8. Data Reporting Standards Specific to Thyroid Gland

To facilitate pooled analyses on risks of hypothyroidism, we recommend reporting data on patient demographics, cancer

diagnosis, and dosimetry as listed here. It would be necessary to separately subgroup these data for patients who have and those who have not developed thyroid dysfunction. Deidentified individual data, including dosimetric data, should be included in an online appendix.

Suggested specific data elements to include are as follows:

- Patient sex
- Patient race
- Family history of thyroid disease
- Personal history of autoimmune disease
- Age when treated with radiation therapy
- Clinical indication for radiation therapy (ie, cancer diagnosis)
- Prescribed radiation therapy dose to target
- Fractionation schedule
- Radiation therapy technique (ie, photon-based 2D, 3D, intensity modulated radiation therapy, volumetric modulated arc therapy; proton therapy—passive scatter, spot scanning, intensity modulated proton therapy)
- Thyroid gland: volume
- Thyroid radiation exposure
  - Mean dose
  - Relative volume receiving >1, 5, 10, 20, 30, 40, 50, and 60 Gy
- Consider providing full dose-volume histogram in supplemental online materials
- Chemotherapy use
  - If "yes," timing with respect to radiation therapy
  - Patient age or date of treatment
  - Systemic agents and doses used
- Timing of clinical/laboratory (ie, TSH, T3, T4) follow-up evaluations for late complications
- Whether patient was subject to screening for thyroid dysfunction
  - If "yes," intervals of and number of screens
- Attained age at last follow-up
- Vital status at last follow-up
  - In case of death, date/age at, and cause of, death
- Outcome
  - Diagnosis of hypothyroidism (yes/no)
  - Age of diagnosis of subclinical hypothyroidism not requiring intervention (grade 1 toxicity)
  - Age of diagnosis of clinical hypothyroidism, defined as hypothyroidism for which thyroid hormone replacement is indicated (if applicable; grade 2+ toxicity)
  - Time interval between exposure and event of hypothyroidism or last follow-up
  - Diagnosis of other thyroid condition(s), including thyroid cancer (age and type of condition)
- Thyroidectomy (if yes, age at surgery)
- Other exposures to ionizing radiation (if feasible)
  - Cumulative radiation exposure to the thyroid gland from diagnostic imaging and nuclear medicine procedures can contribute to risks of thyroid injury. In children and adults, these exposures have declined from those of the early 2000s.[52] Identifying all medical procedures in a given patient and quantifying radiation exposures from these procedures is challenging and perhaps not feasible. Exposure is dependent on institution- and patient-specific protocols, and nonuniform units of measurements (ie, Gy, Sv, and Ci) are used across different imaging and treatment modalities.

9. Future Investigations

The current analysis succeeded in providing a dose-response relationship and adjusting for the clinical risk factors of age and sex. However, strong assumptions are inherent in the modeling, such as binning of doses in the source papers and assumptions of independence between age, sex, and dose-related risks, in addition to counting crude incidences rather than a more appropriate survival statistics analysis. There is a need to externally test the model predictions (eg, by mapping the observed risk of hypothyroidism versus the predicted risk by the PENTEC model as function of age). To that end, we provide an online tool where the PENTEC prediction can be read out directly (https://dcccrt.shinyapps.io/pentecthyroid2/). We strongly encourage groups with available pediatric data for thyroid function to compare the observation with the predictions in this report and to challenge the observed dependence of dose, age, and sex.

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