Hypothyroidism after radiotherapy for nasopharyngeal carcinoma

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Abstract: Radiation-induced hypothyroidism (RIHT) is one of the most common late complications in nasopharyngeal carcinoma (NPC) patients who underwent definite radiotherapy (RT) with or without chemotherapy. RIHT is usually observed as late adverse effect with peak incidence of 2 years and affects long-term quality of life as well as increased risk of life-threatening conditions. As a result, it is recommended to perform lifelong measurement of thyroid-stimulating hormone (TSH) and thyroid hormones levels. Radiation damage to the thyroid gland can be due to damage of follicular epithelial cells, parenchymal cells and small blood vessels, capsular fibrosis, iodine insufficiency from malnutrition, and autoimmune reaction. Risk factors of RIHT include female gender, younger age, small thyroid volume, abnormal pretreatment TSH levels, and irradiated dose and volume of the thyroid gland. With no specific dose constraint during plan optimization, intensity-modulated radiotherapy (IMRT) results in unexpectedly higher dose and irradiated volume of thyroid gland, compared to conventional technique. It might contribute to higher RIHT incidence with shorter latency period. Therefore, this review summarizes the pathophysiologic changes of thyroid gland after radiation and recommendations of thyroid constraint from literatures as well as predictive tools for predicting RIHT in NPC.

Keywords: Radiation-induced hypothyroidism (RIHT); nasopharyngeal carcinoma (NPC); predictive model

Introduction

Nasopharyngeal carcinoma (NPC) is a unique type of head-and-neck cancers (HNC). Differences from other cancers in head and neck region include (I) definite radiotherapy (RT) and/or chemotherapy is the primary treatment, (II) intensity-modulated radiotherapy (IMRT) is considered standard treatment technique, (III) pituitary gland is partially included in the radiation field, (IV) surgical neck dissection involving thyroid gland is not performed, and (V) long survival outcome is expected. Despite advance RT techniques, treatment causes unavoidable irradiation to normal organs (e.g., thyroid gland, salivary glands, mandible, spinal cord) which leads to radiation-induced toxicities and affects long-term quality of life (QoL) in NPC survivors.

Radiation-induced hypothyroidism (RIHT) is the most common late effect of thyroid gland after RT to the neck. Incidence of RIHT ranged from 23–53% in HNC (1-4), and 14–54% in NPC (5-15). RIHT is observed as a late adverse event and usually occurs within 2 years after treatment. Without comprehensive follow-up, delayed diagnosis of RIHT results in diminished QoL and increases risk of life-threatening conditions like ischemic heart disease, myxedema, and birth defect (16-18).

Although evidences suggested a dose-response relationship between thyroid dosimetry and risk of RIHT (6,8,12,13), currently, there has been no consensus for dose constraint of thyroid gland, even in the latest Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)
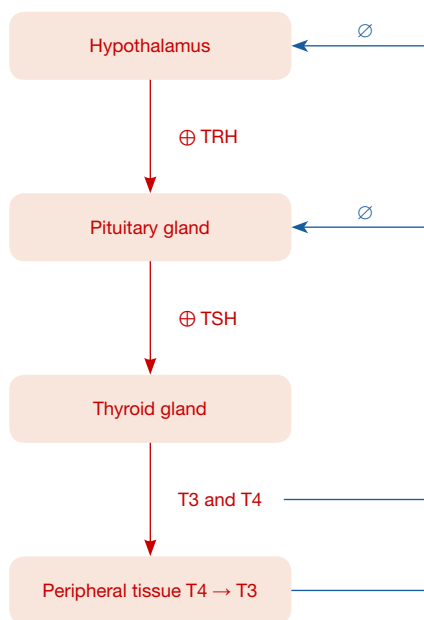
TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine. ⊕ = stimulating; ∅ = negative feedback

Figure 1 Hypothalamic–pituitary–thyroid axis and thyroid homeostasis.

guideline (19). This review summarizes the pathophysiologic changes of thyroid gland after radiation and recommendations of thyroid constraint from literatures as well as predictive tools for predicting RIHT in NPC.

Pathophysiology of thyroid gland

Thyroid gland is a vital endocrine organ that produces and releases thyroid hormones [triiodothyronine (T3) and thyroxine (T4)] which help regulate metabolism, growth and development of human body. Other important organs that maintain thyroid homeostasis are hypothalamus and pituitary gland, known as hypothalamic–pituitary–thyroid (HPT) axis. Hypothalamus secretes thyrotropin-releasing hormone (TRH) which stimulates pituitary gland to produce thyrotropin or thyroid-stimulating hormone (TSH). The TSH stimulates thyroid gland to produce and release thyroid hormones to reach normal level in blood circulation. In normal situation, thyroid gland releases small amounts of T3, an active form of thyroid hormone, and large amount of T4, prohormone, which is converted to T3 in peripheral tissues. Then T3 and T4, in turn, causes negative feedback control to hypothalamus and pituitary

gland. Consequently, this loop-feedback mechanism maintains equilibrium concentrations for TRH, TSH and thyroid hormones (*Figure 1*).

Thyroid gland is sensitive to RT. Many radiation-induced thyroid disorders have been reported including hypothyroidisms and hyperthyroidisms, Hashimoto thyroiditis, Graves' disease, and thyroid tumors (2,20). Primary hypothyroidism is the most common thyroid disorder after head-and-neck RT, but actual mechanism is still clearly unknown. Radiation causes damages to follicular epithelial cells, parenchymal cells and small blood vessels of thyroid gland, leading to reduction of thyroid mass (6,13). Other causations include capsular fibrosis and iodine insufficiency due to malnutrition. Also, it is speculated that immune-mediated reaction is one of the common processes (2,8). In NPC patients treated with RT, there was abnormal rise of thyroid antibodies, thyroperoxidase antibody (anti-TPO) and thyroglobulin antibody (anti-TG), which were indicators of thyroiditis from autoimmune response (8). Under normal circumstances, TPO and TG are enzyme and glycoprotein that involve in the synthesis of thyroid hormones (*Figure S1*).

Diagnosis of hypothyroidism

Diagnosis of hypothyroidism requires laboratory tests, i.e., TSH, (free) T3 and (free) T4, with or without clinical signs/symptoms. Clinical or overt hypothyroidism is generally defined as high serum TSH level with low T4 and presence of clinical presentations of hypothyroidism including generalized symptoms (fatigue, weakness, cold intolerance, weight gain, dry skin, edema, constipation, menorrhagia), neuromuscular symptoms (myalgia, paresthesia, arthralgia, cognitive dysfunction, impaired consciousness) and psychiatric symptoms (depression). Subclinical or biochemical hypothyroidism is usually defined as increased serum TSH level and low/normal T4 without symptoms. In normal population, clinical hypothyroidism is found about 1–2% and more common in older women (21). The prevalence of subclinical hypothyroidism is about 6% and associated with an increased risk of coronary heart disease and mortality in patients with high serum TSH concentration (≥10 mIU/L) (17,18). Therefore, early thyroid hormone replacement therapy, e.g., levothyroxine, is recommended in those individuals with subclinical hypothyroidism and serum TSH concentration ≥10 mIU/L. After radiation treatment, approximately 10% and 30% of

patients developed clinical and subclinical hypothyroidism, respectively, and about one-fourth in the latter group developed clinical symptoms later with a median time of 11 months (9). Noting that, given radiation dose to pituitary gland in NPC patients with T3 (base of skull involvement) and T4 (intracranial involvement), central hypothyroidism can also occur and is characterized as low TSH and T4 (7,14).

Radiation-induced hypothyroidism

Changes of thyroid glands after radiation

In NPC, cervical lymph nodes are usually involved, therefore, it is recommended to regularly include bilateral neck lymphatics in the clinical target volumes (22). As thyroid gland is a normal structure located in lower neck region, neck irradiation causes inevitable dose to the thyroid gland.

Several studies reported dose-response relationship between mean thyroid dose and glandular volume reduction (6,13) as well as hormonal changes (6,8,12,13). Longitudinal studies on the pattern of thyroid gland changes after RT in NPC patients found that most changes occurred in the first 2 years. With the mean pre-treatment thyroid volume of approximately 18 cm^3 in Lin studies, there was thyroid volume loss about 20%, 30% and 40% at 6, 12 and 30 months, respectively (6,13). There was a decrease of free T4 level starting at 6 months after RT, obvious drop at 12-month interval, reaching 20% reduction at 30-month interval, and became steady after 36 months. Similarly, serum free T3 level showed slightly decreased at 6 months but relatively remained steady throughout the study period. In contrast, the TSH level showed a rising trend gradually after completion of RT and the greatest decrease at 6–12 months up to 24 months, followed by a decreasing trend (6,8,13). The possible explanation for the phenomenon was the shrinkage of thyroid gland, caused by radiation damage and autoimmune reaction, occurred in the first 6 months and led to reduced production of thyroid hormones. Based on feedback mechanism, the reduction of circulating free T4 triggered pituitary gland to secrete more TSH to stimulate thyroid gland to produce more thyroid hormones until reaching normal level in the blood circulation. Evidences also showed that the thyroid gland and function were partially recovered after 2–3 years but long follow-up study was still needed on complete recovery ability of thyroid gland (13).

Factors associated with RIHT

In pre-IMRT era. Emami found that clinical hypothyroidism was associated with damage to large fraction of the whole thyroid gland (2/3 or more). Irradiation to the whole gland volume at 45 Gy resulted in the estimated probability of 8% clinical hypothyroidism at 5 years (tolerance dose (TD) 8/5). The estimated TD 13/5 and 35/5 were 60 and 70 Gy, respectively (23). But no TD for subclinical hypothyroidism was reported.

Currently, IMRT, an inverse treatment planning algorithm that maximizes dose conformity to tumor while minimizing unnecessary dose to surrounding critical structures, is considered as a standard RT technique for NPC in view of both dosimetric and clinical benefit (24-27). However, the benefit of IMRT comes with a potential drawback. With no specific dose constraint during plan optimization, IMRT contributed to a higher dose and irradiated volume of thyroid gland which might result in higher incidence and shorter latency of RIHT, compared with three-dimensional conformal radiotherapy (3D-CRT) in which midline shield in the anterior lower neck field usually applied (3).

With attempts to define threshold dose to the thyroid gland, a systematic review of 5 dosimetric studies based on RIHT was performed. They analyzed the relationship between the occurrence of RIHT and thyroid gland volume absorbing 10–70 Gy (V10–V70), mean dose (Dmean), minimal dose (Dmin), maximum dose (Dmax) to the thyroid gland. However, the results failed to define a clear threshold dose and dose-volume effect between thyroid dose distribution and the incidence of RIHT due to heterogeneity among studies including study design and parameters (28).

Apart from dosimetric factors, another systematic review and meta-analysis from 37 articles showed that significant clinical risk factors were female gender [Odds ratio (OR) =1.57; 95% confidence interval (CI), 1.30–1.88], partial or hemithyroidectomy (OR =8.28; 95% CI, 5.71–12.02), and Caucasian *vs.* African American descent (OR =4.84; 95% CI, 2.76–8.49). By fitting dose-response functions using logistic model from data of 4 dosimetric studies, the author showed a dose-response effect with a 50% risk of RIHT at mean thyroid dose of 45 Gy (95% CI, 28–62 Gy) (TD50 =45 Gy) (29). According to IMRT studies in NPC, mean thyroid dose was ranging from 43-54 Gy resulting in high incidence of RIHT up to 54% (12,13,30,31). Thus far, no consensus for IMRT dose constraint of thyroid gland has been established.
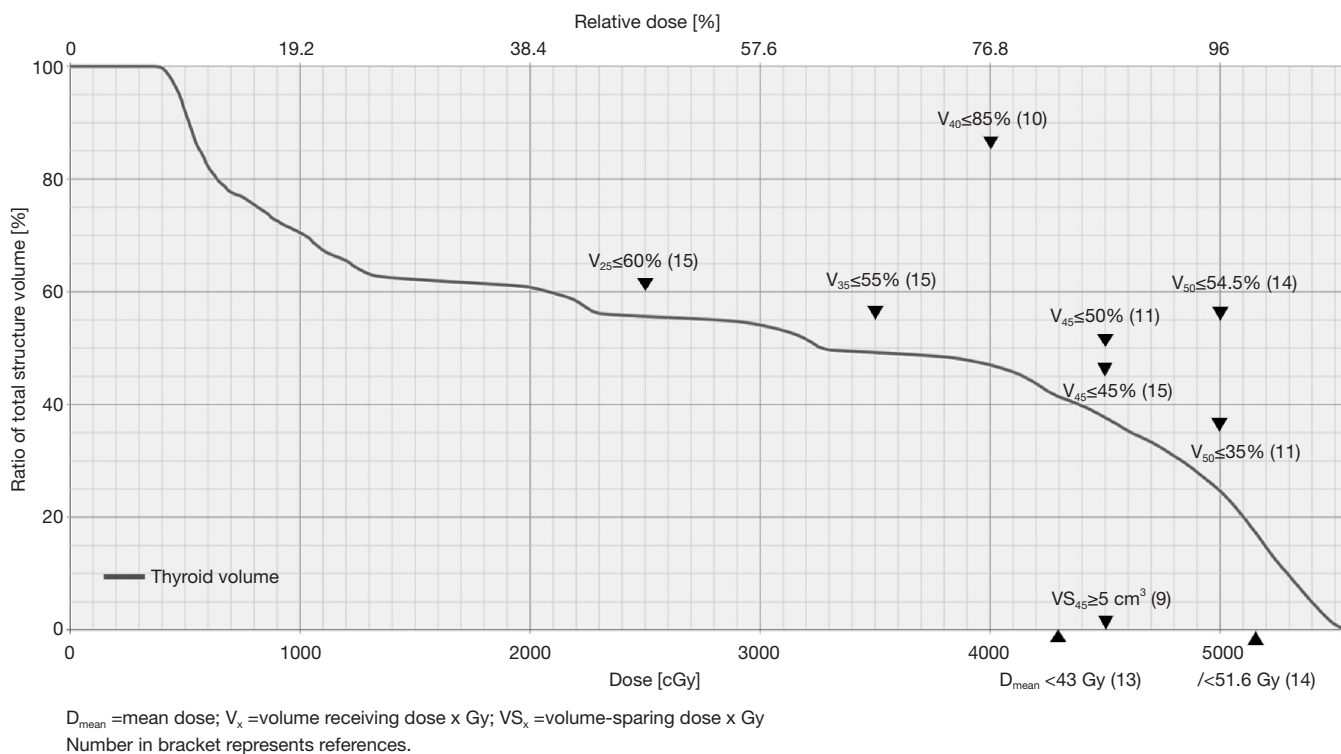
Table 1 Clinical and dosimetric predictors for radiation-induced hypothyroidism in nasopharyngeal carcinoma

Study	N	Median follow-up (year)	Treatment	RIHT definition	Incidence of RIHT	Significant predictor (s)*	Suggestions by authors
Ulger et al., 2007 (5)	85	2.8	Conventional RT	↑TSH, ↔ or ↓FT4	14%	Age	–
Lee et al., 2016 (9)	149	3.1	IMRT	↑TSH or ↓FT4	30.9%, 1Y =5.3%, 2Y =29.6%, 3Y =36.2%	thyroid volume*, thyroid Dmin, Dmean, D5, V30, V35, V40, V45, VS30, VS40, VS45*, VS60*	Thyroid VS45 ≥5 cm³; Thyroid VS60 ≥10 cm³
Luo et al., 2017 (30)	164	2	3D-CRT + IMRT 80.5%	↑TSH	23.2%, 1Y =14.3%, 2Y =24.6%	gender*, chemotherapy, thyroid Dmin, Dmean, V25, V30, V35, V40, V45, V50*, V55, V60	Nomogram (gender, chemotherapy, V50)
Sommat et al., 2017 (10)	102	4.1	IMRT	↑TSH, ↔ or ↓FT4	43.1%, 1Y =33%, 2Y =44.5%	younger age*, early T stage*, thyroid volume, thyroid Dmin, V40*, V45, V50, Pituitary Dmax	Thyroid V40 ≤85%
Zhai et al., 2017 (11)	135	2.8	IMRT	↑TSH, ↔ or ↓FT4	28.9%, 1Y =13.2%, 2Y =39.9%, 3Y =53.5%	female, younger* age, thyroid volume, thyroid Dmin, Dmean*, V35, V40, V45*, V50*, thyrotoxicosis	Thyroid V45 ≤50%; Thyroid V50 ≤35%
Lin et al., 2018 (13)	56	2	IMRT	↑TSH, ↔ or ↓FT4	28.6%	Dmean*, D50	Thyroid Dmean <43 Gy
Lertbutsayanukul et al., 2018 (12)	178	3.5	IMRT	↑TSH, ↔ or ↓FT4	53.9%	female, thyroid volume, pretreatment TSH*, VS60*,	Thyroid VS60 ≥10 cm³
Xu et al., 2018 (14)	52	1.4	IMRT	↑TSH, ↔ or ↓FT4; ↓TSH, ↓FT4	53.8%, 1Y =33%, 2Y =51%, 3Y =71%	female, Dmean, V50, thyroid volume	Thyroid Dmean <51.6 Gy; Thyroid V50 <54.5%
Luo et al., 2018 (31)	174	2	3D-CRT + IMRT 81.6%	↑TSH, ↔ or ↓FT4		gender*, Dmin, Dmean, V30, V35, V40, V45, V50*, V55, V60, chemo*, Pituitary Dmax*	Logistic regression model (Table 2)
Huang et al., 2019 (15)	345	3.8	IMRT	↑TSH, ↔ or ↓FT4	44.1%, 1Y =10.7%, 2Y =25.8%, 3Y =36.3%	age, gender, nodal status, thyroid volume*, Dmean, Dmin, V25, V35, V45	Thyroid V25 ≤60%; Thyroid V35 ≤55%; Thyroid V45 ≤45%

*, significant variables in multivariate analysis. RIHT, radiation-induced hypothyroidism; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; TSH, thyroid-stimulating hormone; FT4, free thyroxine; Dmin, minimal dose; Dmean, mean dose; Dmax, maximal dose; Dx, dose that volume x% of thyroid gland received; Vx, volume receiving dose x Gy; VSx, volume-sparing dose x Gy.

However, it is worth noting that there was no NPC study in the first dosimetric systematic review and only 2 NPC studies included in the second systematic review. In this review, *Table 1* summarized clinical and dosimetric predictors for RIHT in NPC and recommendations for dose constraint of thyroid gland from the reported literatures. And, other than using only one or two dosimetric constraints, multiple points of dose volume constraint should be concerned during the process of IMRT plan optimization. *Figure 2* demonstrated the recommended cut points in treatment planning software. The biological optimization such as equivalent uniform dose (EUD) is

D_{mean} =mean dose; V_x =volume receiving dose x Gy; VS_x =volume-sparing dose x Gy
Number in bracket represents references.

Figure 2 The recommended cut points for thyroid gland dose constraint from the reported literatures.

beyond the scope of this review.

Considering there are many unmodifiable factors, e.g., gender, age, thyroid volume, and pretreatment TSH levels, minimizing unnecessary radiation dose to the thyroid gland is of paramount. This could be accomplished by many approaches, for example (I) matching the IMRT plan to a conventional anterior low-neck field with midline shield, so-called split-filed IMRT (36), (II) omitting treatment of lymph node level IV in T1 disease (37,38), and (III) diminishing overlapping between low-risk planning target volume (PTV-LR) and thyroid gland. *Figure 3* demonstrates dose distribution and contour of thyroid gland and PTV-LR in stage T2N2M0 NPC patient. Of note, with minimal overlapping of thyroid and PTV-LR, 40 Gy of isodose line encompassed nearly half of thyroid gland.

Predictive models for RIHT

Although there is no QUANTEC report that covers RIHT, there has recently been proposing the use of normal tissue complication probability (NTCP) model to estimate risk of complication. Furthermore, it has been an increasing interest to evaluate and compare treatment modalities,

such as x-ray *vs.* proton therapy, using NTCP model-based approach (39,40).

Purpose of NTCP model is translating dosimetric input into a clinically relevant outcome. In other words, "irradiated dose to organ" is depicted as "a probability or risk of developing toxicity of that organ". Various mathematical models have been proposed to estimate the risk of complication as a function of assorted parameters of the treatment plan, tissue architecture and radiosensitivity (33). The most common types of NTCP models are Lyman model, logistic model, and logistic regression model.

Although there were many studies on dose-response model for predicting RIHT in HNC (19,29,32,34,35,41) but they excluded NPC patients or those whose pituitary gland dose >40 Gy due to possible damage to the HPT axis. To dates, there have been only two studies focusing on development of predictive tools for RIHT in NPC patients (30,31). *Table 2* summarizes NTCP models for RIHT endpoint in overall HNC.

Most studies were retrospective and confounded with heterogeneity of disease and patient characteristics, variety of treatment techniques/regimens, and different follow-up protocol among studies. These limitations inevitably
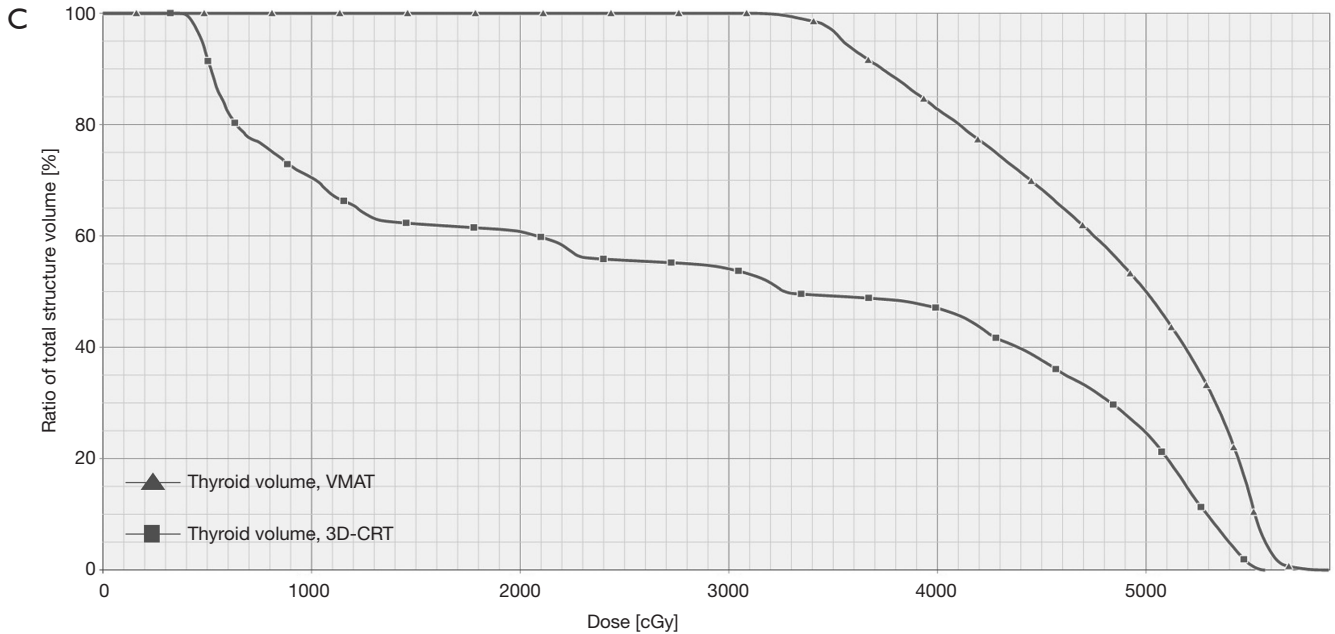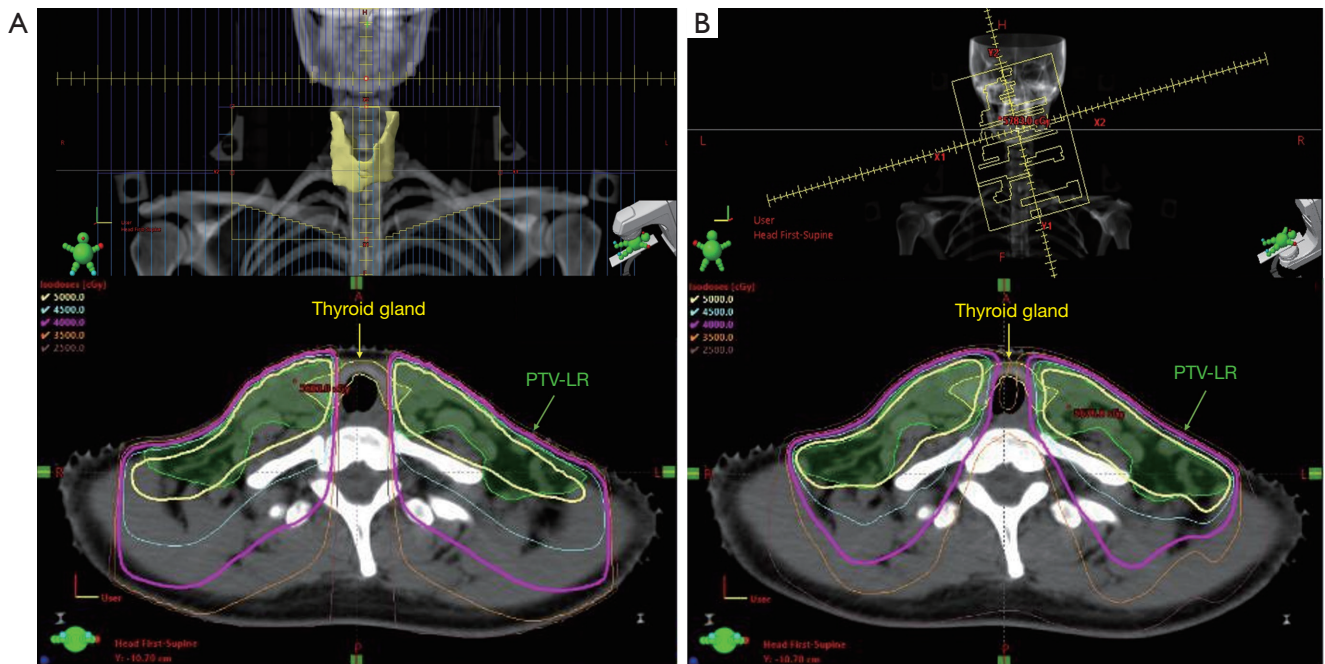
	Dmean (Gy)	VS$_{45}$ (cm^3)	V$_{25}$ (%)	V$_{35}$ (%)	V$_{40}$ (%)	V$_{45}$ (%)	V$_{50}$ (%)
3D-CRT	30	12.6	56	49	47	38	24
VMAT	48	6.5	100	97	83	68	50
Suggested in literatures	<43 (13) <51.6 (14)	≥5 (9)	≤60 (15)	≤55 (15)	≤85 (15)	≤45 (15) ≤50 (15)	≤35 (15) ≤54.5 (15)

3D-CRT, 3D conformal radiotherapy; VMAT, volumetric arc therapy; Dmean, mean dose; V$_x$, volume receiving dose x Gy; VS$_x$, volume-sparing dose x Gy Number in bracket represents references.

Figure 3 Radiation treatment field and dose distribution from 3D conformal radiotherapy (A) and volumetric modulated arc therapy (B) in stage T2N2M0 nasopharyngeal carcinoma with dose-volume histogram of the thyroid gland showing less thyroid dose in anterior lower neck with midline shield as compared to VMAT (C).

Table 2 Normal tissue complication probability (NTCP) models for radiation-induced hypothyroidism

Study	N	RIHT definition	Time point	Significant non-dosimetric factors	Model and parameters (95% CI)
Vogelius et al., 2011 (29)	Meta-analysis of 4 studies	↑TSH	between 1–11 y		Logistic model
					D_{50}, thyroid mean dose =45 [28,62]
					$\gamma\,50$, thyroid mean dose =1.40 [0.50,2.20]
					AUC =N/A
Bakhshandeh et al., 2013 (32)	65 HNC (NPC=11)	CTCAE version 4.02	within 1 y after RT		Lyman EUD mean dose model
		Grade 1 (↑TSH, ↔ FT4) or higher			D_{50}, thyroid mean dose =60 [56,73]
					m thyroid mean dose =0.27 [0.20,0.39]
					AUC=N/A
Boomsma et al., 2012 (33)	105 HNC	↑TSH, ↔ or ↓FT4	within 2 y after RT	Thyroid volume	Logistic regression model
					β thyroid mean dose =0.062 [0.029,0.096]
					β thyroid volume =−0.19 [−0.30, −0.08]
					Constant [β_0] =0.011
					AUC =0.85 [0.78, 0.92]
Cella et al., 2012 (34)	53 HL	↑TSH, ↓FT3 or ↓FT4	median follow-up 2.7 y	Thyroid volume, gender	Logistic regression model
					β thyroid V30 [cc] =0.26 [0.08,0.44]
					β thyroid volume =−0.27 [−0.49, −0.05]
					β gender =−2.21 [−3.88,−0.54]
					Constant [β_0] =1.94
					AUC =0.87 [0.75, 0.95]
Rønjom et al., 2015 (35)	198 HNC	↑TSH, ↔ or ↓FT4	within 2.1 y after RT	Thyroid volume	Logistic regression model
					β thyroid mean dose =0.18 [0.10,0.37]
					β thyroid volume =−0.30 [−0.62,−0.15]
					Constant [β_0] =−4.92
					AUC =N/A
Luo et al., 2017 (30)	164 NPC	↑TSH	Median, follow-up 2 y	Gender, chemotherapy	Nomogram
Luo et al., 2018 (31)	174 NPC	↑TSH, ↔ or ↓FT4	Median, follow-up 2 y	Gender, chemotherapy	β thyroid V50 =0.050
					β pituitary Dmax =−0.026
					β gender =1.280
					β chemotherapy =2.902
					Constant [β_0] =−2.695
					AUC =0.79 [0.73, 0.85]
					β thyroid V50 =0.050

RIHT, radiation-induced hypothyroidism; HNC, head-and-neck cancer; HL, Hodgkin's lymphoma; NPC, nasopharyngeal carcinoma; RT, radiotherapy; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; EUD, equivalent uniform dose; CI, confidence interval; AUC, area under the receiver operating curve; N/A, not applicable.

affected the predictive power of model (42). Therefore, prior to clinical application, it is necessary to perform external validation, especially in different clinical entity. More importantly, a well-designed prospective study with long-term follow-up period would accomplish precise and accurate information. Baseline thyroid function test is required to exclude preexisting thyroid dysfunction and not to overestimate the incidence of RIHT after radiation. Due to different fractionation regimen, DVH data of the thyroid gland should be converted to an equivalent dose in 2 Gy/fraction because different parts of the thyroid gland received heterogeneous fractionation dose. Besides, the novel predictive markers including circulating thyroid immune-mediated factors and radiogenomic data have potential to be integrated into the NTCP model for improving prediction ability and further implementing in treatment plan optimization.

Acknowledgments

Footnote

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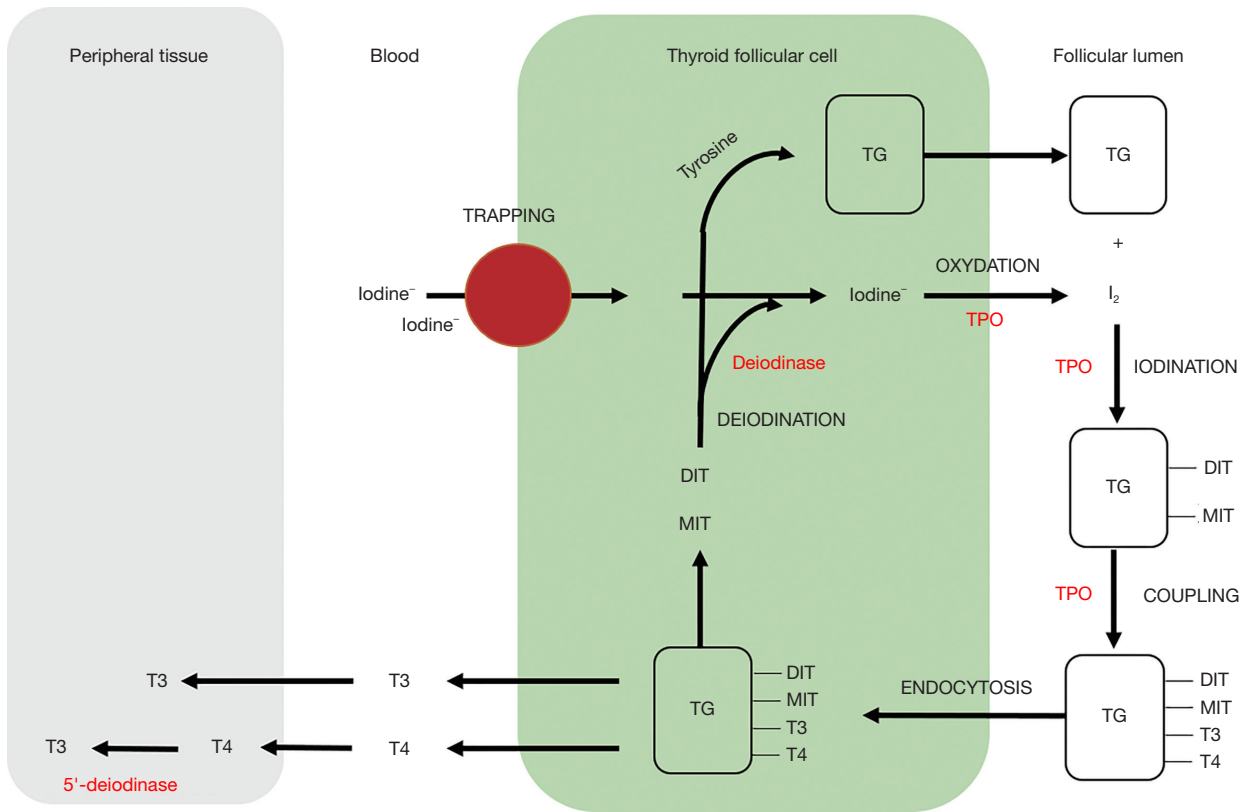
I⁻=iodide; I₂=iodine; NIS=sodium-iodide symporter; TG=thyroglobulin; TPO=thyroid peroxidase enzyme; DIT=diiodothyrosine; MIT=monoiodothyrosine; T3= triiodothyronine; T4= thyroxine

Figure S1 Thyroid hormone synthesis.