

Review Article

A review on the dosimetrical and radiobiological prediction of radiation-induced hypothyroidism in radiation therapy of head-and-neck cancer, breast cancer, and Hodgkin's lymphoma survivors

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Abstract

A review on the radiobiological modeling of radiation-induced hypothyroidism after radiation therapy of head-and-neck cancers, breast cancer, and Hodgkin's lymphoma is presented. The current review is based on data relating to dose-volume constraints and normal tissue complication probability (NTCP) as a function of either radiobiological or (pre)treatment-clinical parameters. Also, these data were explored in order to provide more helpful criteria for radiobiological optimization of treatment plans involving thyroid gland as a critical normal organ.

Key words: radiation therapy; hypothyroidism; head-and-neck cancer; breast cancer; Hodgkin's lymphoma; NTCP modelling; QUANTEC.

Introduction

Radiation therapy plays a vital role in the treatment of many cancers in conjunction with chemotherapy and surgery [1-3]. Although the aim of radiation therapy is to eradicate the tumor while sparing adjacent normal tissues as far as possible, radiation-induced complications after radiation therapy of neck region, including chronic xerostomia, osteoradionecrosis, trismus and soft tissue fibrosis can be expected. On the other hand, the importance of treatment planning in radiation therapy has been increased steadily with invention of new technologies which provide more accurate and conformal radiation dose to the tumor site and saving critical normal organs [4-7]. Estimation of tumor control probability (TCP) and normal tissue complication probability (NTCP) using radiobiological models can be a complementary tool for evaluation and optimization of treatment plans.

In radiation therapy of head-and-neck and upper thorax region, thyroid gland could be a critical organ irradiated partially or completely with high energy photon beams. In other words, this gland can be located inside the therapeutic beam due to its proximity to the gross tumor volume (GTV) in irradiation of supraclavicular lymph nodes for breast cancer (BC), cervical region for head-and-neck cancers (HNCs) and Hodgkin's lymphoma (HL) (**Figure 1**).

HNCs comprise cancers found in paranasal sinuses, nasal cavity, oral cavity, tongue, salivary glands, larynx, and pharynx (i.e. nasopharynx, oropharynx, and hypopharynx). In addition to surgery as a treatment for most of the advanced HNCs, the main treatment technique is sole radiation therapy or radiation therapy combined with chemotherapy either as concurrent or adjuvant treatment. BC is considered as the second most common cancer and the fifth most common cause of cancer-related mortalities among women. While BC rates are higher among women in more developed regions, global rates are increasing in nearly every area of the world [8,9]. Postoperative radiation therapy to the supraclavicular region is prescribed for BC patients who have lymph node metastasis [10]. Classical HL is predominantly a nodal-based disease identified by the presence of Reed-Sternberg cells residing in a mixture of non-neoplastic reactive cells. HL may scarcely express its first manifestation in the form of a disorder in extra-nodal site, such as the gastrointestinal tract, nasopharyngeal region, central nervous system, kidney or other sites [11].

Primary hypothyroidism is a known late side effect which stems from irradiation of the thyroid gland during radiation therapy of different neoplasms like HL, HNCs, and BC leading to reduction in hormonal production of thyroid gland [12-14]. Diagnosis of primary hypothyroidism is interpreted as clinical or subclinical hypothyroidism, depending on laboratory results

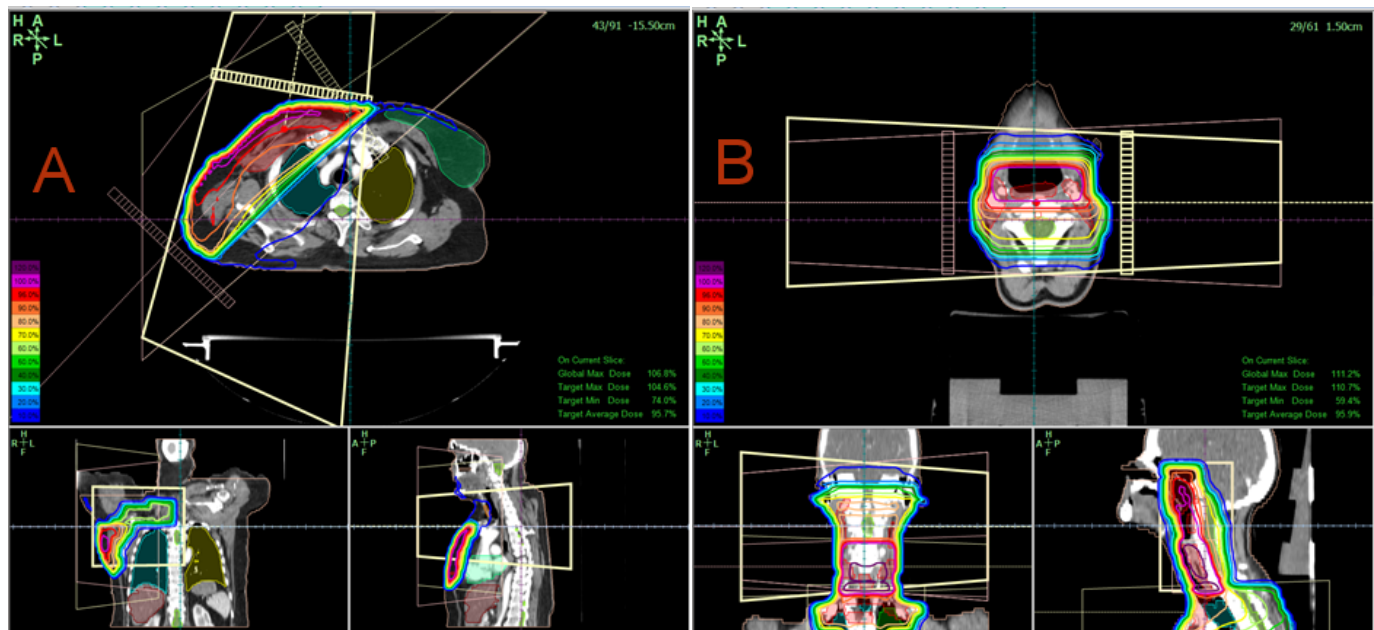


Figure 1. Representative isodose lines at different dose levels and radiation fields for treatment planning of a typical A) breast cancer, and B) head and neck cancer.

of the patient serum sample and symptoms like depression, chronic fatigue, weight gain, hoarseness, skin dryness, hair loss, forgetfulness, muscle weakness, increased sensitivity to cold, slower heart rate, hypercholesterolemia, and accelerated atherosclerosis [12,15]. Clinical hypothyroidism (CHT) is characterized by an elevated level of thyroid-stimulating hormone (TSH) and low level of free thyroxine (FT4). On the other hand, subclinical hypothyroidism (SHT) is characterized by a normal level of FT4 and high level of TSH. In SHT, symptoms like hypercholesterolemia and accelerated atherosclerosis may be manifested too [12,15,16]. Central hypothyroidism is another toxicity that happens after radiation therapy of cranial and spinal malignancies, HNCs, and lymphomas which attenuates the release or stimulation of related hormones from brain's hypothalamus or pituitary gland [17]. Moreover, other toxicities like hyperthyroidism, benign adenoma, Graves' disease and thyroid cancer have been reported in the literature [12,15,18]. However, it should be reminded here that central hypothyroidism was not considered in this review. According to studies, primary hypothyroidism following radiation therapy occurs at a median interval of 1.4-1.8 years. However, it has been reported even 3 months or 20 years with a peak of incidence within the first 1 to 3 years after radiation therapy [15,19-21]. Generally, the incidence of hypothyroidism is in the range of 3% to 92%, but it mostly varies from 20% to 50% after radiation therapy of HNCs and HL [12,15-19]. However, the incidence of hypothyroidism following irradiation to the supraclavicular region in patients with BC has been remained unclear [14,22-24]. Radiation-induced thyroid malfunction and manifestation of its symptoms can be neglected and attributed to other diseases in cancer survivors due to clinical sophistication in interpreting observed radiation complications especially in the pediatric ones.

Hence, by considering increased risk of morbidity and mortality associated with inappropriate or lack of treatment of hypothyroidism, such as cardiac disease, congenital birth defects, and myxedema, it is crucial to diagnose and treat this disease timely in cancer survivors and most notably, regard its risk when planning radiation treatment techniques in cancer patients.

This review covers the papers from 2010 to the end of 2017 indexed in PubMed and Scopus database which focused on NTCP modeling of primary hypothyroidism induced by ionizing radiation in patients who received 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) for BC, HNCs and HL. The papers discussing possible risk factors concerning radiation-induced hypothyroidism (RHT) are also included. Any papers included in this study other than the mentioned publication date are also used to provide primary knowledge about the subject.

Radiation-induced pathophysiology of thyroid gland

The most harmful effect of ionizing radiations is their ability to induce biochemical changes in cells' genetic integrity which may then cause malignancy or produce other functional damages in irradiated tissues and organs. Generally, chronic damage of ionizing radiation can be detected by the rate of mitotic divisions occurring in the irradiated tissues, by the amount of damage to vascular tissues, and by the duration of the observation period. In radiation therapy, radiation dose levels of several grays may lead to 'cell death' event which occurs later, usually as the cell re-enters mitosis cycle [25]. The endocrine tissues, except for ovaries, are defined as typical radio-resistant tissues in which mitosis does not happen

frequently, i.e. they usually manifest minimal damage after therapeutic radiation dose levels. According to initial experimental and clinical studies, thyroid gland has been demonstrated as relatively resistant organ to external beam irradiation [25]. From radiobiological point of view, thyroid gland is a typical organ with a parallel arrangement of its functional subunits (FSUs) [26,27]. The pathophysiology of iatrogenic diseases of this gland is influenced by multiple mechanisms and it is supposed to be associated with destruction of vessels. However, the mechanisms of this complication are mostly unknown [28,29]. Concisely, function of epithelial follicle cells is inhibited and endothelium is modified in stages by radiation. This process leads to necrosis of cells, disturbance of follicles, degeneration and thrombosis of vessels, acute and chronic inflammation (thyroiditis), and partial new formation of epithelial cells [28,29]. Additionally, echogenicity changes of thyroid gland and blood vessels have been displayed by diagnostic ultrasound during radiation therapy and ensuing development of acute thyroiditis pertains to vessel changes [30]. Morphological changes of great importance include atrophy, chronic thyroiditis with spread of lymphocytes, fibrosis of vessels, imbalanced and focal hyperplasia of follicular cells [15,31,32].

Risk factors affecting thyroid gland

Risk factors affecting the function of thyroid gland can be categorized into two groups of patient-based and treatment-based. Potential patient-based risk factors affecting the development of hypothyroidism include younger age, gender [12,33,34], genetic proneness [35] and such typical environmental factors as iodine intake and cigarette smoking [36-38].

In treatment-based factors, higher radiation volume or bilateral neck irradiation [20,39], addition of chemotherapy or neck surgery [12,33,34], mantle field irradiation, radiotherapy of spine from C2-T2, Waldeyer's tonsillar ring and neck, irradiation of brain stem, radiotherapy of supraclavicular and nasopharyngeal regions augments the risk of hypothyroidism [12,19,20,34,40,41]. Likewise, higher radiation dose to thyroid gland further increases the risk of hypothyroidism [17,42,43].

Determination of a clear dose-volume threshold value for thyroid gland

Thyroid gland is located below the larynx on each side and anterior to the trachea. It is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. In treatment planning for radiation therapy, the volume of thyroid gland can be readily defined and contoured by radiation oncologist using images acquired from different imaging modalities including computed tomography (CT) and magnetic resonance (MR) imaging. A typical representative contour of thyroid gland and the related cumulative DVHs (Dose-volume Histograms) are shown in **Figure 2**.

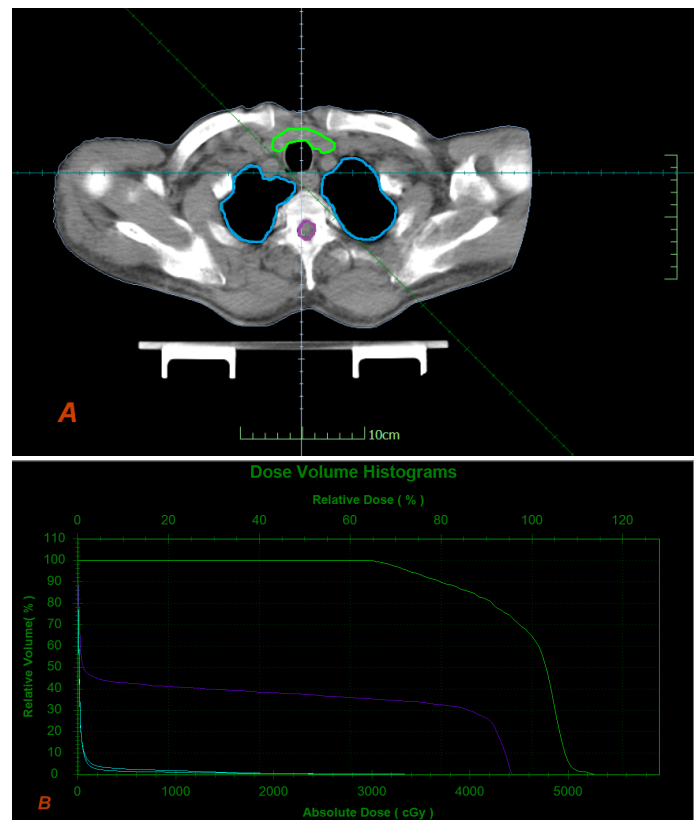


Figure 2. A) Representative Axial neck computed tomography image at the level of the thyroid gland, the lungs, and the spinal cord. The thyroid gland is contoured in lime green, the spinal cord is in violet, and the lungs are contoured in blue. B) Related cumulative dose volume histograms for the contoured organs which was generated from a plan composed of two lateral parallel-opposed fields of nasopharyngeal cancer (open field, 6 MV photon beam). The dose constraint of 4400 cGy was considered for spinal cord.

In order to reduce the complication, it is essential to determine the dose-volume threshold of RHT during treatment planning in radiation therapy. In this regard, several studies have been implemented to define and optimize dose-volume constraints [44-49]. However, there are relatively noticeable variations in the reported dose-volume thresholds for RHT among different modalities of radiation therapy. This variability of dose-volume constraints was specially shown in a recent systematic review based on five studies, declaring that defining a clear relationship between dose-volume parameters and hypothyroidism was not easily achievable and may need further well-planned studies [19]. Over and above that, qualitative analyses of normal tissue effects in the clinic (QUANTEC) reports did not tabulate required information on dose-volume constraints for thyroid gland [50].

Dose-volume predictors for hypothyroidism in treatment of HNCs and HL

In the seminal study by Emami *et al.* tolerance dose values for uniform whole-and-partial irradiation of 28 critical organs were compiled in a five-year period. For incidence of CHT, they reported values of $D_{50} = 45$ Gy, $D_{50} = 60$ Gy and $D_{50} = 70$ Gy

in 8%, 13%, and 35% of patients, respectively [51]. However, the main aim of that study was a direction to a clinical need according to information and technology up to that time. For example, external beam radiation therapy with conventional fractionation used to be the only treatment modality and DVHs were not in routine clinical use at that time.

Considering 3D-CRT for HNCs, Akgun *et al.* retrospectively evaluated radiation dose-volume factors for a median follow-up of 47 months in 106 patients with HNCs (fraction size of 1.8 or 2 Gy and a total median dose of 60 Gy; range, 36–70 Gy). They emphasized V30 as a possible useful tool for evaluating the risk of RHT during an individual patient's treatment planning [44]. Also, in a retrospective study by Fujiwara *et al.*, dose-volume threshold was determined for developing thyroid dysfunctions in 116 patients with HNCs (fraction sizes 2 Gy) after a median follow-up of two years. In this study, a mean thyroid dose of 30 Gy was reported as a useful threshold for predicting the development of RHT [47].

There are several studies about IMRT of HNCs and HL which evaluated the threshold dose for RHT. For example, Cella *et al.* retrospectively studied dose-volume constraints in 53 patients with HL (median tumor dose, 32 Gy; range, 30–36 Gy) after sequential chemo-radiotherapy during a median follow-up period of 32 months. In their study, V30 of thyroid gland predicted the risk of developing RHT which can be regarded as a useful dose constraint during HL treatment planning [45]. Chyan *et al.* followed 123 patients with oropharyngeal cancer (OPC) (fraction sizes 2.12 Gy) during a median follow-up of 4.6 years to define dosimetric predictors for development of RHT. The volume fraction of thyroid gland receiving over 45 Gy (V45) was estimated to increase the risk of developing RHT significantly [46].

Sachdev *et al.* examined dosimetric and clinical parameters after a median follow-up period of 50 months in 75 patients with head-and-neck squamous cell cancer (HNSCC). The parameter of V50 was the marker that highly predicted the risk of developing RHT [48].

Kim and Yeo evaluated dosimetric advantages of VMAT compared to conventional radiation therapy for incidence of RHT in 15 patients with early stage squamous cell carcinoma of the larynx (fraction sizes 2.25 Gy). For thyroid gland, the dosimetric parameters of treatment plans including Dmean, V30 and V50 were compared. Consequently, they found that these parameters were significantly lower in VMAT than in conventional RT. Regarding the NTCP model developed for prediction of RHT by Boomsma *et al.* [52], Kim and Yeo indicated that the VMAT yielded remarkably better dose volume parameters for the thyroid gland. In conclusion, one of the dosimetric advantages of VMAT was lower probability of RHT following RT in patients with early stage glottic cancer [53].

Dose-volume predictors for hypothyroidism in treatment of BC

Akyurk *et al.* prospectively investigated thyroid disorders in 28 patients with BC at a median follow-up of 25 months. In this study, V₂₀, V₃₀, V₄₀ and D_{mean} of thyroid ≥ 36 Gy were found to influence significantly on development of RHT, whereas V_{mean} of thyroid was not associated with development of RHT. Additionally, the incidence of RHT was reported 21% in their patient population [22].

Kikawa *et al.* prospectively surveyed the influence of radiation on thyroid in 42 patients with BC whose supraclavicular region was irradiated. In this survey, after a median follow-up of 30 months, patients with thyroid volume less than 8 cm³ were observed with a higher prevalence of RHT. Thus, lower volumes of thyroid gland were identified as a predictive factor of both CHT and SHT. In this cohort, the prevalence of RHT in Japanese patients was relatively low compared with similar previous reports [23].

Other studies from 2010 to 2017 with respect to possible factors and the risk of RHT are listed in **Table 1**.

NTCP modeling for radiation-induced hypothyroidism

In the most general sense, the dose-response relationship for tumors and normal tissues are described by a variety of mathematical functions demonstrated by sigmoidal curves. Among the radiobiological models, three major ones including Probit, Logistic, and Poisson have been widely used in the literature (**Figure 3**). As illustrated in **Figure 3**, there is a sigmoid dose-response relationship for these models. The differences basically originate from the mathematical algorithm and considered parameters of models.

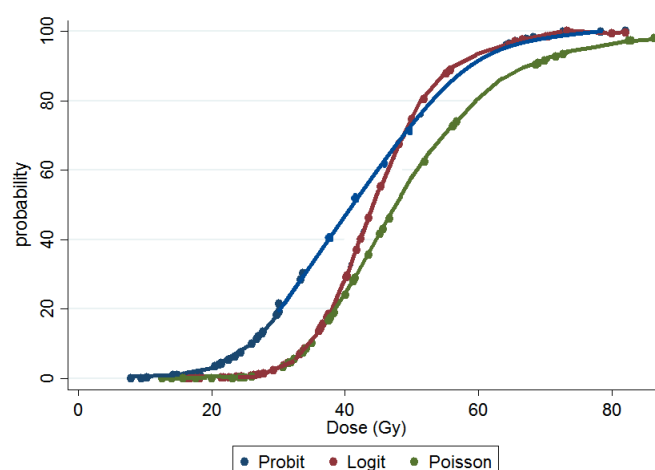


Figure 3. The three statistical functions frequently used in NTCP models to demonstrate the shape of the dose-response curve for hypothyroidism endpoint. The data were derived from head-&-neck and breast cancer patients (unpublished data), the radiobiological parameters of D50= 44 Gy and γ_{50} = 1.49 were considered.

Table 1. Selected studies based on dose-volumetric data for development of RHT after treatment of HNC, BC and HL (continued on the next page).

| Study | No of patients surveyed | Cancer site | Surgery involved | Radiation therapy technique | Endpoint | Thyroid dose determined (Gy) | Dose per fraction (Gy)/total dose (Gy) | Incidence risk of HT | Risk factors of HT | Restrictions |
|---|--------------------------------------|---------------------------------------|------------------|-----------------------------|---------------------------------------|------------------------------|---|---|--|------------------------|
| Diaz <i>et al.</i> ⁺ (2010)[69] | 144 | HN | No | IMRT | Biochem. HT | Yes | 2.1 | 1-year: 23% 3-years: 53% | Age, V _T | NA |
| Wu <i>et al.</i> [*] (2010)[70] | 408 | NPC | No | - | SHT, overt HT | No | - | 5-years: 15.7% SHT, 9% overt HT, 10-years: 19% overt HT | Age<30, 3D-CRT (overt HT), gender, low T-stage, 3D-CRT (SHT) | NA |
| Lin <i>et al.</i> [*] (2011)[71] | 45 | NPC | No | - | Biochem. HT | Yes | - | Crude: 27% after 18 months | RT mean dose | NA |
| Srikantia <i>et al.</i> [*] (2011)[72] | 45 | 43 HN, 2 NPC | n=2 | Cobalt 60 teletherapy | Clinical HT, SHT | Yes | 1.8-2 | Crude: 42.2% (31.1% clinical HT) after 9 months | Elder age, D _T | D _T <40 Gy |
| Siala <i>et al.</i> ⁺ (2011)[73] | 239 | NPC | No | 3D-CRT | Biochem. HT, clinical HT & central HT | No | 2 (3D-CRT), 1.6 (Hyperfractionated regimen) | 24% (73% biocem. HT, 19% clinical HT), 8% central HT | Gender (univariate) | NA |
| Vogelius <i>et al.</i> ^m (2011)[68] | Published studies based on OR for HT | studies reporting data on HT after RT | - | - | - | - | - | a dose-response relation with a 50% risk at TD=45Gy | Gender, race, neck surgery, surgery involving thyroid | NA |
| Johansen <i>et al.</i> [*] (2011)[60] | 32 | BC | MRM (12) BCS (4) | 3D-CRT | Biochem. HT, overt HT | Yes | 50 (13) 50+10 (3) | Not reported | V _T , V ₃₀ | V ₃₀ |
| Boomsma <i>et al.</i> ^δ (2011)[21] | 57-390 based on 5 studies | HN | - | - | - | Yes | - | 23-53% | - | NA |
| Cella <i>et al.</i> ⁺ (2012)[45] | 53 | LH | No | IMRT | Biochem. HT | Yes | Median total dose: 32 | 2-year: 43.5%, 5-years: 49.1% | V ₃₀ >62.5% | V ₃₀ <62.5% |
| Rønjom <i>et al.</i> ⁺ (2013)[58] | 203 | HNSCC | No | IMRT | Biochem. HT | Yes | 2 | | V _T & D _{mean} | NA |
| Lo Galbo <i>et al.</i> [*] (2013)[32] | 137 | HN | n =40 | - | SHT, overt HT | No | - | Crude: 47.4% (27.7% SHT, 19.7% overt HT) | Neck dissection, laryngectomy, hemithyroidectomy & elder age | NA |
| Lin <i>et al.</i> [*] (2013)[74] | 65 | NPC | No | - | Biochem. HT, overt, SHT & central HT | Yes | - | 18-months incidence: 23% | D _{mean} >50 Gy to thyroid and pituitary gland and thyroid gland only | NA |
| Lin <i>et al.</i> [*] (2014)[75] | 50 | NPC | No | - | Biochem. HT, overt, SHT & central HT | No | - | 1-year: 22% | No report | NA |

Abbreviations:

MRM: Modified radical mastectomy;

BCS: Breast conserving surgery (lumpectomy);

SHT: Subclinical hypothyroidism;

Biochem. HT: Biochemical hypothyroidism;

V_x: The volume of the thyroid gland receive doses ≥x Gy;

VS_x: The volume of the thyroid gland spared from doses ≥x Gy;

V_T: Thyroid gland volume;

DT: Thyroid gland dose;

OR: Odds ratio;

ENI: Elective node irradiation;

NA: Not applicable;

^m: Meta-analysis study;

^{*}: Prospective methodology;

⁺: Retrospective methodology;

^δ: Systematic review.

Table 1 (cont'd). Selected studies based on dose-volumetric data for development of RHT after treatment of HNC, BC and HL.

| Study | No of patients surveyed | Cancer site | Surgery involved | Radiation therapy technique | Endpoint | Thyroid dose determined (Gy) | Dose per fraction (Gy)/total dose (Gy) | Incidence risk of HT | Risk factors of HT | Restrictions |
|--|-------------------------|-----------------------|---------------------|-----------------------------|--------------------------|------------------------------|--|--|--|--|
| Murthy <i>et al.</i> * (2014)[76] | 89 | HN | No | 3D-CRT, IMRT | Biochem. HT, overt & SHT | Yes | 2 (3D-CRT), 2.25 (IMRT) | Crude: 55% (16% overt, 39% SHT) | Younger age, primary site, node ⁺ & D _{min} =100 & higher dose/fraction in IMRT cohort | NA |
| Akgun <i>et al.</i> ⁺ (2014)[44] | 100 | 88 HN, 12HL | n=30 | 3D-CRT | Biochem. HT | Yes | 2 | Crude: 52% | V _T , D _{mean} & V ₃₀ (univariate) | V ₃₀ |
| Akyurek <i>et al.</i> ⁺ (2014)[24] | 28 | BC | MRM (19) BCS (9) | 3D-CRT | Clinical HT, SHT | Yes | 50+10 (19) 50 (9) | 1-year: 14% 2-years:21% | D _{mean} , V ₂₀ , V ₃₀ & V ₄₀ | D _{mean} <36 Gy |
| Kim <i>et al.</i> * (2014)[63] | 114 | 85 HN, 29 NPC | n=33 | 3D-CRT (50), IMRT (64) | Biochem. HT | Yes | 2 (3D-CRT), 2.25 (IMRT) | Crude: 46% | V ₄₅ >65% | V ₄₅ <50% |
| Chyan <i>et al.</i> ⁺ (2014)[46] | 123 | OPC | n=27 | IMRT | Biochem. HT, overt & SHT | Yes | 2.12 | Crude: 61% (54% overt) | V _T (univariate) | V ₄₅ |
| Sachdev <i>et al.</i> ⁺ (2014)[48] | 75 | 70 HN, 5 NPC | n=16 | IMRT | Biochem. HT | Yes | Median total dose: 70 | Crude: 33% | V ₅₀ >60% | V ₅₀ <60% |
| Lauro <i>et al.</i> ⁺ (2014)[77] | 22 | Pediatric brain tumor | No | 3D-CRT | Clinical HT, SHT | Yes | Total dose: 18-36 | Crude: 59% | D _{mean} of thyroid | NA |
| Kim & Yeo (2014)[53] | 15 | HN | No | VMAT | Primary HT | Yes | 2.25 | - | | NA |
| BernÅjt <i>et al.</i> ⁺ (2014)[78] | 83 | HN | 40 | - | Bioche. HT | - | - | Crude: 35% | RT dose | NA |
| Fujiwara <i>et al.</i> ⁺ (2015)[47] | 101 | 93 HN, 8 NPC | n=22 | 3D-CRT | SHT | Yes | 2 | 1-year: 21.1%, 2-years: 36.4%, 3-years: 48.3% | ENI group & chemotherapy (univariate) ENI group (multivariate) VS ₁₀ , VS ₂₀ VS ₃₀ , VS ₄₀ D _{mean} | D _{mean} = 30 Gy |
| Lee <i>et al.</i> * (2016)[79] | 149 | NPC | - | IMRT | Biochem. HT, clinical HT | Yes | - | Crude: 36.2% (14.1% Clinical HT) | V _T , VS ₄₅ & VS ₆₀ (multivariate) | VS ₆₀ & VS ₄₅ |
| Sommat <i>et al.</i> ⁺ (2017)[62] | 102 | NPC | No | IMRT | SHT, overt HT | Yes | 1.8-2 | 2-years: 43.1% | V ₄₀ >85% | V ₄₀ ≤85% |
| Tunio <i>et al.</i> * (2017)[61] | 40 | BC | MRM: (15) BCS: (25) | 3D-CRT | Clinical HT, SHT | Yes | 2 | Crude: 15% | V _T , V ₃₀ >50% | V ₃₀ ≤50% |
| Kikawa <i>et al.</i> * (2017)[25] | 42 | BC | Not reported | 3D-CRT | SHT, Clinical HT | No | 2 | 5-years prevalence: Clinical HT: 14.3% SHT: 2.4% | V _T < 8cm ³ | V ₃₀ |
| Zhai <i>et al.</i> * (2017)[49] | 135 | NPC | n=3 | IMRT | Primary HT | Yes | 1.7-2.2 | 2-years: 29.6%, 3-years: 44% | Younger age, D _{mean} for thyroid gland≥45Gy | V ₄₅ <0.5 & V ₅₀ <0.35 |

Abbreviations:

MRM: Modified radical mastectomy;
BCS: Breast conserving surgery (lumpectomy);
SHT: Subclinical hypothyroidism;
Biochem. HT: Biochemical hypothyroidism;
Vx: The volume of the thyroid gland receive doses ≥x Gy;
VSx: The volume of the thyroid gland spared from doses ≥x Gy;
VT: Thyroid gland volume;

DT: Thyroid gland dose;
OR: Odds ratio;
ENI: Elective node irradiation;
NA: Not applicable;
^m: Meta-analysis study;
*: Prospective methodology;
+: Retrospective methodology;
^δ: Systematic review.

Table 2. Studies based on treatment-clinical and radiobiological NTCP modeling

| Study | No of patients surveyed | Radiation therapy technique | Cancer site | Endpoint | Baseline thyroid function | Incidence risk of HT/ risk factors | Model | Parameter | Value |
|--|-------------------------|-----------------------------|-------------|-------------|---------------------------|---|-------------------------|---------------|---|
| Boomsma <i>et al.</i> *, (2012)[52] | 105 | 3D-CRT (70), IMRT (35) | HN | Biochem. HT | Yes | 2-years: 36% | $\frac{1}{1+e^{-s}}$ | S | $0.011 + (0.062 * D_{mean}) + (-0.19 * V_T)$ |
| Cella <i>et al.</i> +, (2012)[57] | 53 | 3DCRT | HL | Biochem. HT | Yes | 2-year: 43.5%, 5-years: 49.1% / V_{30} , gender and V_T | $\frac{1}{1+e^{-g(x)}}$ | g(x) | $1.94 + (0.265 * V_{30} (cc)) - (2.21 * gender) - (0.268 * V_T)$ |
| Rønjom <i>et al.</i> + (2013)[58] | 203 | IMRT | HNSCC | Biochem. HT | Yes | 1-year: 12%, 5-years: 26% / V_T & D_{mean} | $\frac{1}{1+e^{-s}}$ | S | Logistic model: $S=-2.019 + (0.0821 * D_{mean}) - (0.189 * V_T)$ Mixture model: $S= -1.235 + (0.1162 * D_{mean}) - (0.2873 * V_T)$ |
| Bakhshandeh <i>et al.</i> * (2013)[12] | 54 HN, 11 NPC | 3D-CRT | HN | SHT | Yes | 1-year: 45% | Lyman EUD | D_{50} | 44.3 |
| | | | | | | | | m | 0.25 |
| | | | | | | | | n | 0.92 |
| | | | | | | | Logit EUD | D_{50} | 43.9 |
| | | | | | | | | k | 6.16 |
| | | | | | | | | n | 0.85 |
| | | | | | | | RS | D_{50} | 43.5 |
| | | | | | | | | γ | 1.49 |
| | | | | | | | | s | 0.05 |
| | | | | | | | Mean dose | D_{50} | 44.1 |
| m | 0.26 | | | | | | | | |
| Bakhshandeh <i>et al.</i> * (2013)[12] | 54 HN, 11 NPC | 3D-CRT | HN | Clinical HT | Yes | | CV individual | D_s | 24 |
| | | | | | | | | m | 0.03 |
| | | | | | | | | N_{FSU} | 80 |
| | | | | | | | | N_0 | 7 |
| | | | | | | | | α | 0.08 |
| | | | | | | | | λ | 0.8 |
| | | | | | | | CV population | D_{50} | 38.5 |
| | | | | | | | | γ_{50} | 1.05 |
| | | | | | | | | σ | 0.76 |
| | | | | | | | | μ_{cr} | 0.64 |
| Bakhshandeh <i>et al.</i> * (2013)[12] | 54 HN, 11 NPC | 3D-CRT | HN | Clinical HT | Yes | | Mean dose | D_{50} | 60 |
| | | | | | | | | m | 0.27 |
| | | | | | | | Lyman EUD | D_{50} | 60 |
| | | | | | | | | m | 0.24 |
| | | | | | | | | n | 0.49 |
| | | | | | | | Logit EUD | D_{50} | 60 |
| | | | | | | | | k | 6.39 |
| | | | | | | | | n | 0.45 |
| RS | D_{50} | 60 | | | | | | | |
| | γ | 1.48 | | | | | | | |
| | s | 0.33 | | | | | | | |
| D'Avino <i>et al.</i> , (2016)[13] | 100 | 3DCRT | HL | Biochem. HT | Yes | Crude: 28% | LKB | D_{50} | 37.3 ± 0.6 |
| | | | | | | | | m | 0.62 ± 0.02 |
| D'Avino <i>et al.</i> , (2016)[13] | 100 | 3DCRT | HL | Biochem. HT | Yes | Crude: 28% | RS | n | 0.99 ± 0.01 |
| | | | | | | | | D_{50} | 36.1 ± 0.7 |
| D'Avino <i>et al.</i> , (2016)[13] | 100 | 3DCRT | HL | Biochem. HT | Yes | Crude: 28% | RS | γ | 0.538 ± 0.015 |
| | | | | | | | | s | 0.006 ± 0.01 |

Abbreviations:

Baseline thyroid function: Normal serum thyroid function tests

as starting point used for comparisons;

EUD: Equivalent uniform dose;

RS: Relative seriality;

LKB: lyman-Kutcher-Burman;

CV: Critical volume;

*: Prospective methodology;

+: Retrospective methodology.

The realm of study in mathematical models for normal tissue responses to absorbed doses is broad and beyond the scope of this paper to discuss in detail. Several NTCP models with their inherent parameters have been explained in the literature, e.g. in Tsougos *et al.* [54].

Following “Emami’s paper”, Burman *et al.* published an accompanying article in which they fitted the Lyman-Kutcher-Burman model to tolerance data reported by Emami *et al.* for the clinical thyroiditis as the endpoint. The fitted parameters of

n, m, and D50 for the whole volume of thyroid gland were obtained 0.22, 0.26, and 80 Gy, respectively [55]. Nevertheless, there are some limitations which make Emami’s paper not to be considered as a comprehensive and applicable guideline for all cases [56]. However, up to now, few published papers have focused on NTCP modeling of thyroid gland for hypothyroidism endpoint. Related studies on NTCP modeling of thyroid gland are listed in **Table 2**.

Recently, Bakhshandeh *et al.* [26] prospectively determined the dose-response relationship of the thyroid gland for RHT in 65 HNC patients (fraction sizes 1.8-2 Gy with consideration of $\alpha/\beta=3$ Gy). They applied up to six different radiobiological models for estimation of NTCP, and analyzed the data obtained from one-year post-radiotherapy follow-up based on laboratory results of the patient serum samples (TSH, T3, T4, FT3 and FT4 levels). They found the best-fit parameters of the models by evaluating SHT and CHT separately. In their study, all of the models were in agreement with follow-up data according to goodness of fit measures. Finally, among the studied models, the mean dose model was introduced as the robust model to describe the dose-response relationship for RHT, whereas Lyman equivalent-uniform-dose (LEUD) model ranked second. For SHT endpoint, tolerance dose parameter was reported for 5 NTCP models ranging from 38.5 Gy (for the population critical volume model) to 44.3 Gy (for the Lyman EUD model). In addition, analyzing the parameters responsible for volume effect in all of six models showed a parallel structure for the thyroid gland (i.e. n in the Lyman EUD and logit EUD models, s in the relative seriality model, λ in the individual critical volume model, and μ_{cr} in the population critical volume model). The fitted value of m parameter was 0.25 in the LEUD model. Optimal values of the parameters for each model with 95% confidence intervals are shown in **Table 2**. For CHT endpoint, they performed another fitting on the obtained follow-up data using four models including mean dose, Lyman EUD, logit EUD, and relative seriality (RS). The fitted value for tolerance dose parameter was estimated as 60 Gy. Their reported optimal values of the parameters for each model with 95% confidence intervals are shown in **Table 2**.

More recently, D'Avino *et al.* [27] retrospectively estimated the parameters of Lyman-Kutcher-Burman (LKB) and RS models for RHT in 100 HL patients based on laboratory results of the patient serum samples (TSH, FT3 and FT4 levels) at a median follow-up of 73.5 months (fraction sizes 1.5-1.8 Gy). Parameters of volume effect in both models showed a parallel structure for the thyroid gland. Then, they compared the prediction results of the models with that of a 3-variable logistic model published by Cella *et al.* [57]. In brief, a good prediction was offered by LKB and RS models while a little high effectiveness was shown by the logistic NTCP model for predicting RHT. Their obtained optimal values of the parameters for each model with 95% confidence intervals are given in **Table 2**.

Apart from dose-volume parameters as previously presented, a set of other clinical and (pre)treatment variables may be associated with the development of RHT inclusive of age, diabetes mellitus [17], (hemi-) thyroidectomy, laryngectomy, neck dissection, and chemotherapy [17,31,34]. To this end, three studies have been conducted on developing multivariate NTCP models based on clinical and (pre)treatment parameters to predict RHT in HNC, BC, and HL patient cohorts [52,57,58]. Boomsma *et al.* [52] prospectively pioneered a

multivariate NTCP model during 2.5 year follow-up of 105 HNC patients based on laboratory results of the patient serum samples (TSH and T4 levels). Their constructed multivariate NTCP model based on two variables included the mean dose and volume of thyroid gland (**Table 2**). Higher mean dose for thyroid gland resulted in larger values of NTCP ($P<0.001$), with an odds ratio of 1.064/Gy (95% confidence intervals). Besides, larger volume of thyroid gland exhibited smaller values of NTCP ($P=0.001$) with an odds ratio of 0.826/cm³ (95% confidence intervals). In other similar study, Cella *et al.* [57] retrospectively developed two multivariate NTCP models for RHT in 53 HL patients with a median follow-up of 32 months (1.5–1.8 Gy). The 3-variable model including absolute thyroid volume exceeding 30Gy (V30(cc)), thyroid gland volume (VT) and gender ($P<0.001$) provided an optimal prediction compared with the 2-variable model including the thyroid volume exceeding 30Gy (V30(%)) and gender. Their multivariate logistic regression model for the risk of RHT are given in **Table 2**. In their study, the two models were compared with Boomsma's NTCP model for RHT. As a consequence, the 3-variable model seemed to work out better for predicting RHT in other external patient populations.

Rønjom *et al.* [58] retrospectively derived an NTCP model from 203 patients with HNSCC with a median follow-up of 25.1 months (fraction size of 2 Gy) for RHT development. Data were analyzed with both a logistic and a mixture model (including latency time correction) to determine risk factors of RHT. Mixture model defined thyroid gland volume, thyroid gland mean dose, and latency time as predictive parameters. In this survey, the five-year incidence of RHT was 26%. In order to maintain the risk percentage below 26%, dose constraints of 26 Gy, 38 Gy, 48 Gy and 61 Gy (Dmean) for thyroid gland volumes of 10, 15, 20 and 25 cm³ was proposed respectively on the basis of the mixture NTCP model. Both models are listed in **Table 2**. In another study by Rønjom *et al.* [59] variations of their previously developed NTCP mixture model in relation to changes in delineation of the thyroid gland were inspected for RHT estimation. In this study, the thyroid gland was outlined in 246 treatment plans of patients with HNSCC. Ultimately 46 of these plans were arbitrarily selected for blinded re-delineation to survey intra- and inter-observer variability of thyroid gland volume, thyroid gland mean dose and NTCP estimations for RHT. Consequently, the variation resulted from NTCP model for prediction of RHT risk in HNC patients was small, thereby the model was robust opposed to observer variations in delineation of the thyroid gland. Despite this, large differences may exist in estimated risk for an individual patient which make it necessary to contour the thyroid gland more precisely for acquisition of accurate dose and NTCP estimations in treatment planning of individuals.

Conclusions and perspectives

Incidence of RHT, its clinically acceptable risk level, and certain factors associated with RHT have been studied by

numerous studies. However, its radiobiological modeling for radiation therapy purpose has been the subject of few investigators. Different mathematical models have been used to predict the response of thyroid gland after radiation therapy. However, it needs more detailed research to provide a comprehensive model for prediction of thyroid response to radiation therapy.

Comparing the NTCP models developed by Boomsma *et al.*, Cella *et al.*, and Rnjom *et al.* which provided noticeable results, indicates that these NTCP models had 'thyroid volume' parameter in common and all the three studies identified the importance of this parameter in developing RHT. In other words, larger thyroid volume caused a significant decrease in the incidence of RHT [52,57,58]. On the other hand, the observed variations in the values of D_{50} , n , and m can be ascribed to other factors like sample size, race, cancer type, treatment planner's skill, accuracy in delineation of thyroid gland by a radiation oncologist, and choice of endpoint.

From the reviewed studies, it can be concluded that logistic NTCP models offer slightly higher effectiveness for predicting RHT compared to other radiobiological NTCP models [27].

Finally, in all NTCP modeling studies, statistical analyses and developing NTCP models were dependent on the choice of endpoint. Assessment of the hormone levels of thyroid gland for endpoint definition determines its dose-response relationships [26,27,58].

Different dose-volume constraints have been reported by the current studies. For instance, volumes of V_{30} [23,44,45,60,61], V_{40} [62], V_{45} [46,49,63] and V_{50} [48] in patients with BC, LH, and HNC have been considered as useful dose constraints for treatment planning optimizations, though higher certainty in the threshold value of dose-volume for thyroid gland will require more comprehensive studies. While D'Avino *et al.* [27] reported the value of $D_{50} = 37.3$ Gy for biochemical hypothyroidism, the threshold doses of $D_{50} = 44$ Gy for SHT and $D_{50} = 60$ Gy for CHT were estimated by Bakhshandeh *et al.* [26] which were approximately compatible with the values of $D_{50} = 45$ Gy, $D_{50} = 60$ Gy and $D_{50} = 70$ Gy reported by Emami *et al.* for induction of CHT within five years [51]. In the same study, it was shown that at least two-thirds of the volume should be injured in order to induce CHT [51]. In radiobiological modeling for hypothyroidism, the volume effect was considered as "n" parameter in all the studies in which the values of $n = 0.99$ and $n = 0.92$ were applied for

estimation of SHT by the LKB model. These data were completely in agreement with the concept of volume effect in parallel structures [64-66].

In total, among potential clinical factors of developing RHT, neck surgery can substantially influence the risk of RHT, thus, the presence of post-surgery patients in the study population will increase the likelihood of RHT incidence [67,68]. Also, authors found no impact of adjuvant chemotherapy with agents such as cisplatin, 5Fluoro-Uracil, epirubicin, and cyclophosphamide on thyroid gland function [26,60], while gender and age were found to be the most significant predictors of developing RHT [26,57,68]. According to the conclusion by Jereczek-Fossa *et al.*, it is still controversial whether chemotherapy has an effective role as a risk factor for RHT development [16].

It should also be noted that other causes of hypothyroidism such as medications which interfere with thyroid hormone production have not been considered in all reviewed studies. With respect to the knowledge resulted from reviewed papers, more studies are needed to determine certain variables and develop new multivariate NTCP models in order to demonstrate their external validation in independent datasets for RHT prediction.

As little information is in hand on modeling for RHT, it is still demanding to conduct more studies in both prospective and retrospective methodology by considering other potential methods such as artificial neural network. Besides, application of other imaging technologies such as MRI, PET, and 4DCT data in future studies can provide more accurate data for efficient radiobiological modeling.

In the end, it seems that the incidence of hypothyroidism could further increase with a longer follow-up time [19]. However, the developed NTCP models can be used exclusively in the follow-up time mentioned by investigators to estimate the risk of RHT [52].

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References

- [1] Mirinezhad SK, Somi MH, Jangjoo AG, *et al.* Survival rate and prognostic factors of esophageal cancer in East Azerbaijan province, North-west of Iran. *Asian Pac J Cancer Prev.* 2012;13(7):3451-3454.
- [2] Mirinezhad SK, Somi MH, Seyednezhad F, *et al.* Influence of chemoradio therapeutic strategies and factors on the five year survival of patients with esophageal cancer. *Journal of Isfahan Medical School* 2014;32(291):982-990.
- [3] Mohammadzadeh M, Faramarzi E, Mahdavi R, *et al.* Effect of conjugated linoleic acid supplementation on inflammatory factors and matrix metalloproteinase enzymes in rectal cancer patients undergoing chemoradiotherapy. *Integr Cancer Ther.* 2013;12(6):496-502.

- [4] Mesbahi A, Dadgar H, Ghareh-Aghaji N, Mohammadzadeh M. A Monte Carlo approach to lung dose calculation in small fields used in intensity modulated radiation therapy and stereotactic body radiation therapy. *J Cancer Res Ther.* 2014;10(4):896-902.
- [5] Mesbahi A, Dadgar H. Dose calculations accuracy of TiGRT treatment planning system for small IMRT beamlets in heterogeneous lung phantom. *Int J Radiat Res.* 2015;13(4):345-354.
- [6] Mesbahi A, Akcay D, Tekcan IV, Alikus ZA. The impact of residual geometric inaccuracies on normal organ doses in image guided-radiation therapy of prostate cancer using on-board kilovoltage Cone-Beam computed tomography. *Iran J Med Phys.* 2017;14(2):104-113.
- [7] Mohammadzadeh M, Mesbahi A. MC estimation of out-of-field organ doses from scattered photons, photoneutrons, and capture gamma rays in prostate radiation therapy. *Nuclear Technology and Radiation Protection.* 2010;25:78-84.
- [8] Boyle P, Levin B: World Cancer Report 2008. International Agency for Research on Cancer.
- [9] Jemal A, Siegel R, Ward E, *et al.* Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57:43-66.
- [10] NCCN Clinical Practice Guidelines in Oncology. Breast cancer. ver.2. 2016. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 2017.
- [11] Wang SA, Rahemtullah A, Faquin WC, *et al.* Hodgkin's lymphoma of the thyroid: a clinicopathologic study of five cases and review of the literature. *Mod Pathol.* 2005;18(12):1577-1584.
- [12] Alterio D, Jereczek-Fossa BA, Franchi B, *et al.* Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. *Int J Radiat Oncol Biol Phys.* 2007;67(1):144-150.
- [13] Bethge W, Guggenberger D, Bamberg M, *et al.* Thyroid toxicity of treatment for Hodgkin's disease. *Ann Hematol.* 2000;79(3):114-118.
- [14] Reinertsen KV, Cvancarova M, Wist E, *et al.* Thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. *Int J Radiat Oncol Biol Phys.* 2009;75(3):764-770.
- [15] Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1165-1170.
- [16] Jereczek-Fossa BA, Alterio D, Jassem J, *et al.* Radiotherapy-induced thyroid disorders. *Cancer Treat Rev.* 2004;30(4):369-384.
- [17] Bhandare N, Kennedy L, Malyapa RS, *et al.* Primary and central hypothyroidism after radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* 2007;68(4):1131-1139.
- [18] Kuten A, Lubochitski R, Fishman G, *et al.* Postradiotherapy hypothyroidism: radiation dose response and chemotherapeutic radiosensitization at less than 40 Gy. *J Surg Oncol.* 1996;61(4):281-283.
- [19] Boomsma MJ, Bijl HP, Langendijk JA. Radiation-induced hypothyroidism in head and neck cancer patients: a systematic review. *Radiother Oncol.* 2011;99(1):1-5.
- [20] Mercado G, Adelstein DJ, Saxton JP, *et al.* Hypothyroidism: a frequent event after radiotherapy and after radiotherapy with chemotherapy for patients with head and neck carcinoma. *Cancer.* 2001;92(11):2892-2897.
- [21] Tell R, Lundell G, Nilsson B, *et al.* Long-term incidence of hypothyroidism after radiotherapy in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2004;60(2):395-400.
- [22] Akyurek S, Babaoglu I, Kose K, Gokce SC. Thyroid Dysfunction Following Supraclavicular Irradiation in the Management of Carcinoma of the Breast. In *J Hemat Oncol.* 2014;24(2):139-144.
- [23] Kikawa Y, Kosaka Y, Hashimoto K, *et al.* Prevalence of hypothyroidism among patients with breast cancer treated with radiation to the supraclavicular field: a single-centre survey. *ESMO Open* 2017;2:e000161.
- [24] Smith GL, Smith BD, Giordano SH, *et al.* Risk of hypothyroidism in older breast cancer patients treated with radiation. *Cancer.* 2008;112(6):1371-1379.
- [25] Fuks Z, Glatstein E, Marsa GW, *et al.* Long-term effects on external radiation on the pituitary and thyroid glands. *Cancer.* 1976;37(2Suppl):1152-1161.
- [26] Bakhshandeh M, Hashemi B, Mahdavi SR, *et al.* Normal tissue complication probability modeling of radiation-induced hypothyroidism after head-and-neck radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;85(2):514-521.
- [27] V.D'Avino, Conson M, Palma G, *et al.* Normal Tissue Complication Probability Models for Radiation-Induced Hypothyroidism in Hodgkin Lymphoma Survivors. *Int J Radiat Oncol Biol Phys.* 2016;96(2):E638.
- [28] Goldberg RC, Chaikoff IL, Lindsay S, Feller DD. Histopathological changes induced in the normal thyroid and other tissues of the rat by internal radiation with various doses of radioactive iodine. *Endocrinology.* 1950;46(1):72-90.
- [29] Nishiyama K, Tanaka E, Tarui Y, *et al.* A prospective analysis of subacute thyroid dysfunction after neck irradiation. *Int J Radiat Oncol Biol Phys.* 1996;34(2):439-444.
- [30] Bakhshandeh M, Hashemi B, Mahdavi SR, *et al.* Evaluation of thyroid disorders during head-and-neck radiotherapy by using functional analysis and ultrasonography. *Int J Radiat Oncol Biol Phys.* 2012;83(1):198-203.
- [31] Carr RF, LiVolsi VA. Morphologic changes in the thyroid after irradiation for Hodgkin's and non-Hodgkin's lymphoma. *Cancer.* 1989;64(4):825-829.

- [32] Lo Galbo AM, Kuik DJ, Lips P, *et al.* A prospective longitudinal study on endocrine dysfunction following treatment of laryngeal or hypopharyngeal carcinoma. *Oral Oncol.* 2013;49(9):950-955.
- [33] Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med.* 1991;325(9):599-605.
- [34] Norris AA, Amdur RJ, Morris CG, Mendenhall WM. Hypothyroidism when the thyroid is included only in the low neck field during head and neck radiotherapy. *Am J Clin Oncol.* 2006;29(5):442-445.
- [35] Brix TH, Kyvik KO, Hegedus L. A population-based study of chronic autoimmune hypothyroidism in Danish twins. *J Clin Endocrinol Metab.* 2000;85(2):536-539.
- [36] Brix TH, Hansen PS, Kyvik KO, Hegedus L. Cigarette smoking and risk of clinically overt thyroid disease: a population-based twin case-control study. *Arch Intern Med.* 2000;160(5):661-666.
- [37] Brix TH, Hegedus L. Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. *Clin Endocrinol (Oxf).* 2012;76(4):457-464.
- [38] Laurberg P, Cerqueira C, Ovesen L, *et al.* Iodine intake as a determinant of thyroid disorders in populations. *Best Pract Res Clin Endocrinol Metab.* 2010;24(1):13-27.
- [39] Kumpulainen EJ, Hirvikoski PP, Virtaniemi JA, *et al.* Hypothyroidism after radiotherapy for laryngeal cancer. *Radiother Oncol.* 2000;57(1):97-101.
- [40] Bonato C, Severino RF, Elnecave RH. Reduced thyroid volume and hypothyroidism in survivors of childhood cancer treated with radiotherapy. *J Pediatr Endocrinol Metab.* 2008;21(10):943-949.
- [41] Garcia-Serra A, Amdur RJ, Morris CG, *et al.* Thyroid function should be monitored following radiotherapy to the low neck. *Am J Clin Oncol.* 2005;28(3):255-258.
- [42] Grande C. Hypothyroidism following radiotherapy for head and neck cancer: multivariate analysis of risk factors. *Radiother Oncol.* 1992;25(1):31-36.
- [43] Sklar C, Whitton J, Mertens A, *et al.* Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab.* 2000;85(9):3227-3232.
- [44] Akgun Z, Atasoy BM, Ozen Z, *et al.* V30 as a predictor for radiation-induced hypothyroidism: a dosimetric analysis in patients who received radiotherapy to the neck. *Radiat Oncol.* 2014;9:104.
- [45] Cella L, Conson M, Caterino M, *et al.* Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* 2012;82(5):1802-1808.
- [46] Chyan A, Chen J, Shugard E, *et al.* Dosimetric predictors of hypothyroidism in oropharyngeal cancer patients treated with intensity-modulated radiation therapy. *Radiat Oncol.* 2014;9:269.
- [47] Fujiwara M, Kamikonya N, Odawara S, *et al.* The threshold of hypothyroidism after radiation therapy for head and neck cancer: a retrospective analysis of 116 cases. *J Radiat Res.* 2015;56(3):577-582.
- [48] Sachdev S, Refaat T, Bacchus ID, *et al.* Thyroid V50 Highly Predictive of Hypothyroidism in Head-and-Neck Cancer Patients Treated With Intensity-modulated Radiotherapy (IMRT). *Am J Clin Oncol.* 2017;40(4):413-417.
- [49] Zhai RP, Kong FF, Du CR, *et al.* Radiation-induced hypothyroidism after IMRT for nasopharyngeal carcinoma: Clinical and dosimetric predictors in a prospective cohort study. *Oral Oncol.* 2017;68:44-49.
- [50] Marks LB, Yorke ED, Jackson A, *et al.* Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys.* 2010;76:S10-S19.
- [51] Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21(1):109-122.
- [52] Boomsma MJ, Bijl HP, Christianen ME, *et al.* A prospective cohort study on radiation-induced hypothyroidism: development of an NTCP model. *Int J Radiat Oncol Biol Phys.* 2012;84:e351-e356.
- [53] Kim ES, Yeo SG. Volumetric modulated arc radiotherapy sparing the thyroid gland for early-stage glottic cancer: A dosimetrical analysis. *Oncol Lett.* 2014;7(6):1987-1991.
- [54] Tsougos I, Mavroidis P, Rajala J, *et al.* Evaluation of dose-response models and parameters predicting radiation induced pneumonitis using clinical data from breast cancer radiotherapy. *Phys Med Biol.* 2005;50(15):3535-3554.
- [55] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys.* 1991;21(1):123-135.
- [56] Emami B. Tolerance of Normal Tissue to Therapeutic Radiation. *Rep Radiother Oncol.* 2013;1(1):123-127.
- [57] Cella L, Liuzzi R, Conson M, *et al.* Development of multivariate NTCP models for radiation-induced hypothyroidism: a comparative analysis. *Radiation Oncology.* 2012;7:224.
- [58] Ronjom MF, Brink C, Bentzen SM, *et al.* Hypothyroidism after primary radiotherapy for head and neck squamous cell carcinoma: normal tissue complication probability modeling with latent time correction. *Radiother Oncol.* 2013;109(2):317-322.
- [59] Ronjom MF, Brink C, Lorenzen EL, *et al.* Variation of normal tissue complication probability (NTCP) estimates of radiation-induced hypothyroidism in relation to changes in delineation of the thyroid gland. *Acta Oncol.* 2015;54(8):1188-1194.

- [60] Johansen S, Reinertsen KV, Knutstad K, *et al.* Dose distribution in the thyroid gland following radiation therapy of breast cancer--a retrospective study. *Radiat Oncol.* 2011;6:68.
- [61] Tunio MA, Al AM, Bayoumi Y, *et al.* Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. *J Cancer Res Ther.* 2015;11(4):684-689.
- [62] Sommat K, Ong WS, Hussain A, *et al.* Thyroid V40 Predicts Primary Hypothyroidism After Intensity Modulated Radiation Therapy for Nasopharyngeal Carcinoma. *Int J Radiat Oncol Biol Phys.* 2017;98(3):574-580.
- [63] Kim MY, Yu T, Wu HG. Dose-volumetric parameters for predicting hypothyroidism after radiotherapy for head and neck cancer. *Jpn J Clin Oncol.* 2014;44(3):331-337.
- [64] Jackson A, Kutcher GJ, Yorke ED. Probability of radiation-induced complications for normal tissues with parallel architecture subject to non-uniform irradiation. *Med Phys.* 1993;20(3):613-625.
- [65] Niemierko A, Goitein M. Modeling of normal tissue response to radiation: the critical volume model. *Int J Radiat Oncol Biol Phys.* 1993;25(1):135-145.
- [66] Yorke ED, Kutcher GJ, Jackson A, Ling CC. Probability of radiation-induced complications in normal tissues with parallel architecture under conditions of uniform whole or partial organ irradiation. *Radiother Oncol.* 1993;26(3):226-237.
- [67] Lo Galbo AM, de BR, Kuik DJ, *et al.* The prevalence of hypothyroidism after treatment for laryngeal and hypopharyngeal carcinomas: are autoantibodies of influence? *Acta Otolaryngol.* 2007;127(3):312-317.
- [68] Vogelius IR, Bentzen SM, Maraldo MV, *et al.* Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. *Cancer.* 2011;117(23):5250-5260.
- [69] Diaz R, Jaboin JJ, Morales-Paliza M, *et al.* Hypothyroidism as a consequence of intensity-modulated radiotherapy with concurrent taxane-based chemotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2010;77(2):468-476.
- [70] Wu YH, Wang HM, Chen HH, *et al.* Hypothyroidism after radiotherapy for nasopharyngeal cancer patients. *Int J Radiat Oncol Biol Phys.* 2010;76(4):1133-1139.
- [71] Lin Z, Wu VW, Lin J, *et al.* A longitudinal study on the radiation-induced thyroid gland changes after external beam radiotherapy of nasopharyngeal carcinoma. *Thyroid.* 2011;21(1):19-23.
- [72] Srikantia N, Rishi KS, Janaki MG, *et al.* How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients? *Indian J Med Paediatr Oncol.* 2011;32(3):143-148.
- [73] Siala W, Mnejja W, Abid M, *et al.* Thyroid toxicity after radiotherapy of nasopharyngeal carcinoma. *Annales d'Endocrinologie.* 2011;72(1):19-23.
- [74] Lin Z, Wang X, Xie W, *et al.* Evaluation of clinical hypothyroidism risk due to irradiation of thyroid and pituitary glands in radiotherapy of nasopharyngeal cancer patients. *J Med Imaging Radiat Oncol.* 2013;57(6):713-718.
- [75] Lin Z, Chen L, Fang Y, *et al.* Longitudinal study on the correlations of thyroid antibody and thyroid hormone levels after radiotherapy in patients with nasopharyngeal carcinoma with radiation-induced hypothyroidism. *Head Neck.* 2014;36(2):171-175.
- [76] Murthy V, Narang K, Ghosh-Laskar S, *et al.* Hypothyroidism after 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for head and neck cancers: Prospective data from 2 randomized controlled trials. *Head Neck.* 2014;36(11):1573-1580.
- [77] Lauro C, Macy ME, Zeitler P, *et al.* The relationship between thyroid dose and diagnosis of primary hypothyroidism in pediatric brain tumor patients receiving craniospinal irradiation. *J Pediatr Endocrinol Metab.* 2014;27(3-4):299-303.
- [78] Bernat L, Hrusak D. Hypothyroidism after radiotherapy of head and neck cancer. *J Craniomaxillofac Surg.* 2014;42(4):356-361.
- [79] Lee V, Chan SY, Choi CW, *et al.* Dosimetric Predictors of Hypothyroidism After Radical Intensity-modulated Radiation Therapy for Non-metastatic Nasopharyngeal Carcinoma. *Clin Oncol.* 2016;28(8):e52-e60.