



Incidence of radiation-induced hypothyroidism following head and neck irradiation: a single-center analysis

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ABSTRACT

Background: The purpose of this study was to investigate the incidence of primary hypothyroidism (HT), as well as any correlation between dosimetric parameters and thyroid dysfunctions after neck radiotherapy (RT) in head and neck cancer (HNC) patients.

Materials and methods: This study retrospectively reviewed HNC patients who finished neck RT for at least 12 months and who had available back-up treatment information. Eligible patients further received a single thyroid function test (TFT). Dosimetric parameters of the thyroid glands were retrospectively evaluated in order to detect any correlation between dose-volume parameters and primary HT.

Results: We reviewed 1,102 HNC patients. Accordingly, 64 patients were deemed eligible and were included in this study. The median time interval between RT completion and TFT was 21 months (interquartile range, 14-34 months), while 26 patients (40.6%) were diagnosed with HT. The thyroid volume spared from a dose of 50 Gy (VS50_{Gy}) was found to be statistically significant and considered an associated factor for developing HT ($p = 0.047$). Furthermore, there was an observable trend indicating a reduction in the risk of HT when VS50_{Gy} was more than 5 cm³ ($p = 0.052$).

Conclusion: In our study, VS50_{Gy} was determined to be a significant predictive parameter of radiation-induced HT.

Key words: radiotherapy; head and neck cancers; hypothyroidism

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Introduction

Radiotherapy (RT), either as a single modality or in combination with surgery and chemotherapy, has become a major component of head and neck cancer (HNC) treatment. It provides excellent disease control and is associated with improved survival rate [1-3]. In the era of advanced RT techniques, intensity-modulated radiation therapy (IMRT) has been introduced as a way to decrease radiation-induced

toxicity in HNC patients [4]. The thyroid gland is one of the largest pure endocrine glands in the body. It produces thyroid hormones that are essential for a healthy metabolism, as well as normal growth and development [5]. Any deficiency in these hormones can lead to various clinical symptoms [5, 6]. Radiation painting of the neck region can often affect the thyroid gland. The most commonly occurring radiation-induced thyroid dysfunction is primary hypothyroidism (HT), either subclinical or

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overt HT, for which the approximate incidence rate ranges from 20% to 40% [5, 7–9]. However, a definite mechanism of this dysfunction has remained unclear. Some of the possible explanations may be that it is caused by radiation-induced small thyroid vessel injuries, fibrosis, or immune-mediated damage [8, 10]. The onset of HT occurred anywhere from four weeks to 20 years after neck RT, with peak incidence at 1–3 years [8, 9]. Since recent improvement in novel systemic therapies have resulted in prolonged survival rates in HNC patients [11], complications that arise after RT should now be an even greater concern. Therefore, the improved ability to predict and detect HT could lead to further progress in developing effective prevention measures and in the development of more accurately selected specific treatment for patients. This important issue is now drawing increased amounts of attention from researchers. Correlations between radiation dose to the thyroid glands and incidences of thyroid dysfunction have been heterogeneously reported [12, 13]. Other possible factors for this outcome included younger age, female gender, and additional courses of chemotherapy [5, 9, 14, 15]. In contrast, many studies have reported no impact of these factors on primary HT [7, 8, 10, 12, 13]. Abnormal functions of the pituitary gland after RT can also affect the thyroid hormone, which has been diagnosed as secondary (central) HT. Hypothalamic–pituitary–thyroid axis deficiency has previously diagnosed after patients received intensive irradiation dose of over 50 Gy to the pituitary gland [16, 17]. An analysis of the correlation between radiation dosimetry to the pituitary gland and fatigue-related symptoms has indicated a cutoff value of 54 Gy [6, 17, 18]. A systematic review of Normal Tissue Complication Probability (NTCP) has also recommended limited radiation dose to the pituitary gland that were not greater than 40 Gy in nasopharyngeal cancer patients. This was recommended in order to reduce risk associated with radiation-induced HT [19]. However, the analysis in a study conducted by Sommat et al. revealed a non-statistically significant association between the pituitary dose and incidences of HT in nasopharyngeal cancer patients [12].

Notably, a consensus on the predictive factors of thyroid dysfunction following RT has remained inconclusive. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) does not refer to a standard set of guidelines for radiation dose con-

straint to the thyroid gland [20]. A systemic review of the NTCP model after QUANTEC reported no consensus on the dosimetric parameters that could reduce the risk of HT caused by RT [19]. The National Comprehensive Cancer Network (NCCN) panel has suggested evaluating thyroid function by monitoring the serum thyroid stimulating hormone (TSH) every 6–12 months after neck irradiation. However, in our center, a thyroid function test (TFT) was not routinely administered to patients after head and neck RT. This study was a cross-sectional retrospective analysis that aimed to detect the incidence of primary HT and any correlation between the dosimetric parameters and thyroid dysfunctions.

Materials and methods

Patient selection

Patients who have been diagnosed with HNC and received RT in our center from 2013 to 2019 were retrospectively reviewed. Those who had undergone neck irradiation for a period of at least 12 months and could back up the relevant radiation dosimetric information were enrolled. All eligible patients were further administered serum TFT to evaluate thyroid function.

Other inclusion criteria included the following; age 18–75 years old at the time of diagnosis, RT intended to cure a disease, and no distant metastasis. The implementation of combined chemotherapy was also allowed. Furthermore, we included post-operative RT unless the operation involved the thyroid gland. The form of radiation technique employed in this study was intensity-modulated radiotherapy/image-guided radiotherapy (IMRT/IGRT), either conventional fractionation or simultaneous integrated boost (SIB).

The exclusion criteria were comprised of any conditions that might interfere with thyroid hormone abnormality as follows: 1 — disease extended into intracranial, 2 — radiation field involved pituitary fossa, 3 — pre-existing thyroid or pituitary disease, 4 — abnormal thyroid detected by computed tomography (CT) before RT, 5 — previous thyroid surgery, 6 — previous cranial or lower neck RT, and 7 — previous iodine radioisotope treatment.

Radiation planning

The RT process was initiated with CT simulation from the vertex to the mid-thoracic region

using 2–5 mm slice thickness. Subjects were immobilized with the use of a thermoplastic mask. All CT images were registered to the Oncentra master plan (Elekta, Sweden) contouring system. The target volume (gross tumor volume — GTV, clinical target volume — CTV, planning treatment volume — PTV) and critical structures (organs at risk, OARs) were contoured upon the primary head and neck tumors. GTV values included gross tumors and involved lymph nodes. High-risk CTV involved 5-mm expansion from the GTV or surgical bed in a postoperative setting with a prescribed dose ranging from 66 to 70 Gy. Intermediate-risk CTVs were composed of high-risk CTV and at-risk lymphatic drainage in the node-positive region with a prescribed dose within a range of 59.4 to 60 Gy. Low-risk CTV included low-risk lymphatic areas treated with a dose of 50–54 Gy. For the SIB protocol, RT was delivered in 33 daily fractions, the dose prescriptions were 66 to 70 Gy for high-risk CTV, 59.4 Gy for intermediate-risk CTV, and 54 Gy for low-risk CTV. The PTVs were established as 3–5 mm isotropic expansion from CTVs to account for any technical errors.

Thyroid glands, including both thyroid lobes and the isthmus, were re-delineated on each CT slice by the principal investigator. The accuracy of the delineation was then confirmed by a radiologist.

Dosimetric analysis

Radiation dosages delivered to the thyroid glands were re-evaluated and recorded. The mean dose (D_{mean}) and the percentage of thyroid volume receiving doses of 30, 40, 45 and 50 Gy [$V_{30\text{Gy}}$, $V_{40\text{Gy}}$, $V_{45\text{Gy}}$ and $V_{50\text{Gy}}$ (%), respectively] were calculated from the dose-volume histograms (DVHs). The absolute volume (cm^3) of the thyroid gland spared from dose levels of 45, 50, and 60 Gy [$VS_{45\text{Gy}}$, $VS_{50\text{Gy}}$ and $VS_{60\text{Gy}}$ (cm^3), respectively] were also collected. Because of our planning program limitations [helical tomotherapy (TomoTherapy, Accuray) and volumetric modulated arc therapy (VMAT, Monaco, Elekta)], a new region of interest (ROI) could not be added to the previously established plans that were delivered to the patients (actual delivered plan). Our study analyzed the radiation dosages to the thyroid glands by applying the Computational Environment for Radiotherapy Research (CERR) program (Fig. 1) [21]. The accuracy of the CERR program was compared with

the actual delivered plan by analyzing the dosimetric parameters of high-risk PTVs, which included D_{mean} , dose coverage 95% of PTV ($D_{95\%}$), median dose ($D_{50\%}$), near-minimum dose ($D_{98\%}$), and near-maximum dose ($D_{2\%}$). Once the radiation plan obtained from the CERR program revealed certain non-statistical differences compared to the actual delivered plan, the radiation dosages delivered to the thyroid gland were further recorded.

Assessment of thyroid function

Serum TFT was composed of TSH, free triiodothyronine (FT3), and free thyroxine (FT4). Primary HT was defined as a TSH value greater than the upper normal limit of our institutional reference in combination with either normal FT3/FT4 (subclinical hypothyroidism) or FT3/FT4 values less than the lower normal limits of our institutional reference (overt hypothyroidism). The normal range for TFT at our institution was as follows: TSH 0.270–4.200 $\mu\text{IU/mL}$, FT3 2.04–4.40 pg/mL , and FT4 0.93–1.71 ng/mL . Patients who had secondary HT (normal or low level of TSH in combination with low FT4 level) were excluded from the analysis.

All patients who developed subclinical or overt HT in this study were referred to an endocrinologist for further appropriate management and/or treatment.

Statistical analysis

The primary endpoint of this study was to identify incidence of primary HT after neck irradiation. The secondary endpoint was to determine any correlation between primary HT and radiation painting to the thyroid gland. Descriptive statistical analyses were used to evaluate the characteristic data of the patients.

The accuracy of the radiation dosage established by the CERR program was compared to the actual delivered plan by Man-Whitney U test. The laboratory results of TFT were used to categorize patients into two groups; euthyroid and hypothyroid. Binary logistic regression analysis was used to detect any relationships between characteristic variables (age at diagnosis, gender, combined chemotherapy, and follow-up period) and incidence of primary HT. The correlations between dosimetric parameters and primary HT were analyzed by logistic regression analysis using backward variable selec-

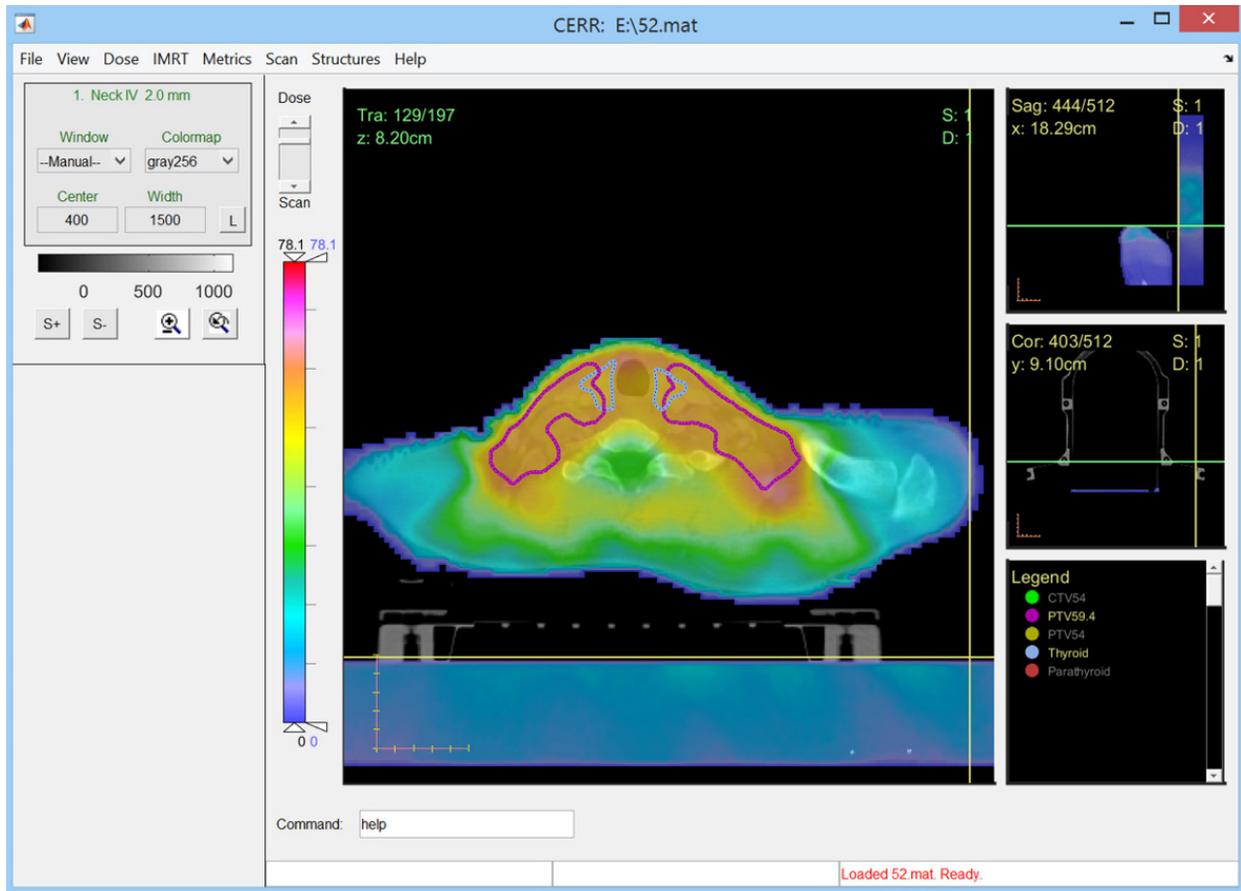


Figure 1. Interface of the Computational Environment for Radiotherapy Research (CERR) program was used for dosimetric analysis. Planning target volumes (PTVs) (purple) were used as controls. Thyroid glands (light blue) were evaluated the dose by CERR-program-generating dose-volume histograms (DVHs)

tion. The variance inflation factor (VIF) was determined in order to avoid any multicollinearity issue [22]. Factors that were associated with VIF values exceeding 2.5 indicated multicollinearity [23]. All dosimetric parameters that reported p-value of less than 0.25 on the univariable analysis and revealed VIF values lower than 2.5 were selected for multivariable analysis. In multivariable logistic regression analysis, a p-value of < 0.05 was defined as statistically significant. All statistical analyses were performed using IBM SPSS statistical software ver. 23.0 (IBM, NY, USA).

Results

Patient characteristics

A total of 1,102 HNC patients were reviewed in this study. Accordingly, 64 patients with sufficient treatment plan information were determined to be eligible and enrolled in this study (Fig. 2). Patient

characteristics are presented in Table 1. The primary tumor sites included nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, and carcinoma of unknown primary origin. Most of the patients were treated as definitive RT/CCRT (85.9%). Concurrent chemoradiation was delivered to 90.6% of the patients.

Clinical characteristics and incidence of primary hypothyroidism

The median time interval between RT completion and laboratory test for thyroid function was 21 months [interquartile range (IQR) 14–34 months], for which 26 patients (40.6%) had developed primary HT. Thirteen out of 26 patients (20.3% of the whole cohort) were first diagnosed with overt HT without clinical symptoms and were prescribed oral levothyroxine supplement by an endocrinologist. According to univariable logistic regression analysis, surgery and chemother-

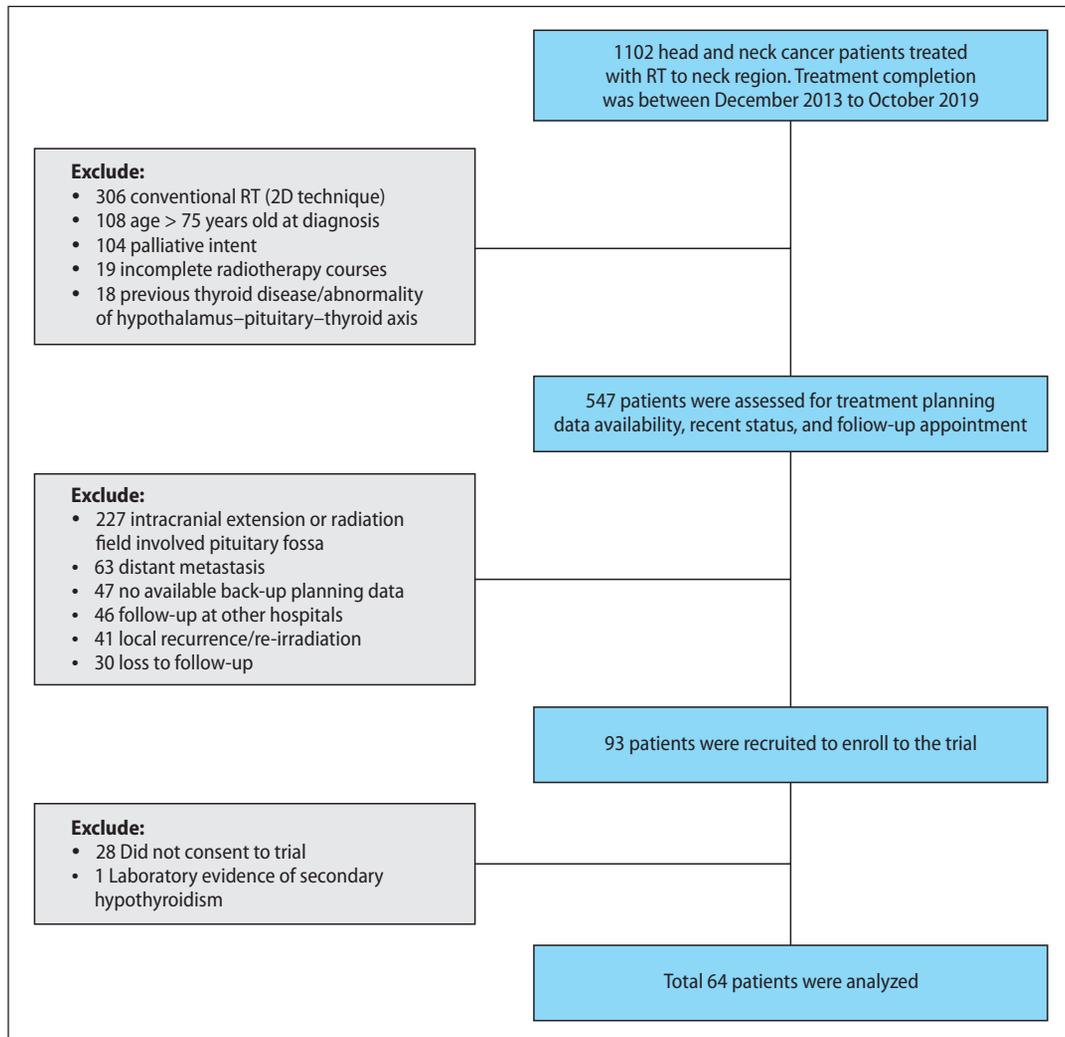


Figure 2. Patient selection diagram. We reviewed 1,102 head and neck cancer patients that had received radiotherapy (RT) at our hospital. Accordingly, 64 patients were determined to be qualified and included in the analysis

apy were indicative of a statistical correlation with an incidence of primary HT. However, none of them reached statistical significance in our multivariable logistic regression analysis. Radiation painting to the pituitary gland was not found to have an impact on the incidence of HT. Results are shown in Table 2 and the incidence of patients who had developed hypothyroidism over time is demonstrated in Figure 3.

IMRT/IGRT planning and CERR program substitution

CERR program was used to evaluate radiation dosimetry of new ROIs (thyroid gland). Dosimetric parameters of the thyroid gland obtained from the CERR program are shown in Table 3. An analysis of high-risk PTVs established from Man-Whit-

ney U test revealed non-statistical difference between the data of the CERR program and the data of the actual delivered plan, as presented in Table 4. Therefore, all data achieved from the CERR program were established as a surrogate in order to evaluate the dose to the thyroid gland.

Correlation between dosimetric parameters and primary hypothyroidism

According to univariable logistic regression analysis, total thyroid volume, the mean dose to the thyroid, and doses of $V_{40\text{Gy}}$, $V_{45\text{Gy}}$, $V_{50\text{Gy}}$, $VS_{45\text{Gy}}$, $VS_{50\text{Gy}}$, and $VS_{60\text{Gy}}$ were associated with primary HT. With regard to multicollinearity, the value of VIF showed a strong correlation between Dmean and various dosimetric parameters. Therefore, Dmean and doses of V_{40} , V_{45} , V_{50} ,

Table 1. Patient characteristics

Variables	N (%)
Age (years)	
Median	52
Range	29–74
Gender	
Male	49 (76.6)
Female	15 (23.4)
Primary site	
Nasopharynx	32 (50)
Oral cavity	8 (12.5)
Oropharynx	20 (31.3)
Hypopharynx/Larynx	3 (4.7)
Unknown primary	1 (1.5)
Chemotherapy	
Induction/Adjuvant	38 (59.4)
Concomitant	58 (90.6)
Surgery	
Yes	9 (14.1)
No	55 (85.9)
Time interval between RT completion and laboratory test [mo]	
Median	21
Interquartile range	14–34
Pituitary gland dose (Dmax)	
≤ 50 Gy	51 (79.7)
> 50 Gy	13 (20.3)

VS45, and VS60 were not included in the multivariable analysis. Only absolute thyroid volume spared from a dose of 50 Gy (VS50_{Gy}) remained statistically significant ($p = 0.047$) according to multivariable logistic regression analysis as is presented in Table 5. We also attempted to determine the cutoff value of VS50_{Gy} by using binary logistic regression analysis as is shown in Table 6. The results revealed a trend to reduce an incidence of HT when VS50_{Gy} was more than 5 cm³ ($p = 0.052$).

Discussion

Radiation-induced primary hypothyroidism

The thyroid gland is an important endocrine gland that is frequently affected by RT during HNC treatment. According to the outcomes of our study, the incidence of primary HT was 40.6%, which is comparable to that of previous studies (approximately 20–50%) [7, 10, 12, 14, 24, 25]. The median time interval after complete RT and TFT was 21 months (IQR, 14–34 months). The follow-up time was determined to be a similar period as that needed to detect thyroid dysfunction after irradiation, as has been reported in many studies [19, 24]. However, some published studies have reported an increase in the cumulative incidence of HT after 2–3 years [26]. Therefore, a longer follow-up

Table 2. Logistic regression for primary hypothyroidism and clinical characteristics

Clinical variables	Univariable		Multivariable	
	Odds ratio (95% CI)	p-value [†]	Odd ratio (95% CI)	p-value*
Age at diagnosis	0.996 (0.948–1.047)	0.871		
Gender Female (vs. Male)	0.667 (0.198–2.243)	0.513		
Surgery Yes (vs. No)	3.500 (0.788–15.543)	0.100 [†]	2.123 (0.342–13.171)	0.419
Induction/adjuvant chemotherapy Yes (vs. No)	0.520 (0.188–1.442)	0.209 [†]	0.919 (0.238–3.550)	0.902
Concurrent chemotherapy Yes (vs. No)	0.114 (0.012–1.038)	0.054 [†]	0.091 (0.007–1.128)	0.062
Time interval from RT completion (months)	1.013 (0.982–1.046)	0.413		
Pituitary gland dose (Dmax) ≤ 50 Gy vs. >50 Gy	0.509 (0.149–1.740)	0.282		

[†]significant at p-value < 0.25; *significant at p-value of < 0.05; CI — confidence interval

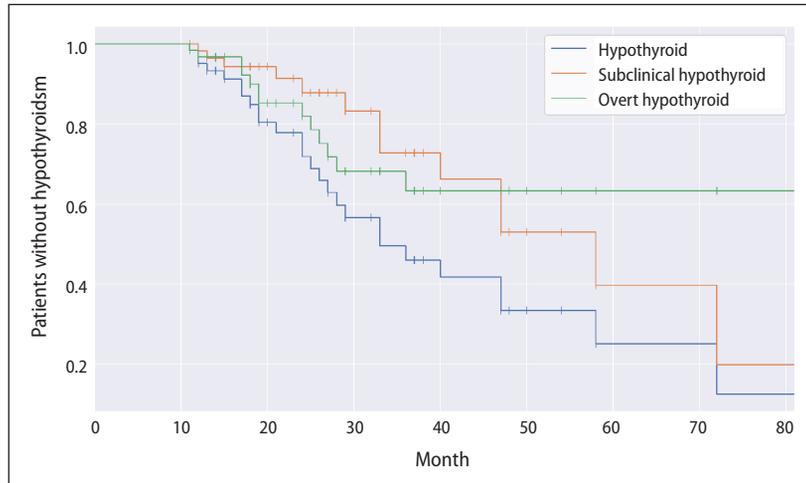


Figure 3. Kaplan-Meier curve showing a rate of hypothyroidism (HT) over time. The cumulative incidence (blue line), subclinical HT (green line), and overt HT (orange line) of patients after completion of radiotherapy (RT) are presented

Table 3. Dosimetric parameters of the thyroid gland obtained by Computational Environment for Radiotherapy Research (CERR) program

Dosimetric parameters of thyroid gland	Median	IQR
Thyroid volume [cm ³]	14.9 (6.4)	11.8–18.2
Dmean thyroid dose [Gy]	53.9 (4.4)	51.3–55.8
V30 _{Gy} (%)	100 (0.1)	99.9–100.0
V40 _{Gy} (%)	99.9 (8.4)	91.6–100.0
V45 _{Gy} (%)	97.5 (14.7)	85.1–100.0
V50 _{Gy} (%)	90.4 (26.5)	72.7–99.6
VS45 _{Gy} [cm ³]	0.4 (2.13)	0.0–2.2
VS50 _{Gy} [cm ³]	1.6 (4.0)	0.1–4.1
VS60 _{Gy} [cm ³]	12.9 (7.1)	10.1–17.4

IQR — interquartile range

period might be required to better define an incidence of HT.

Radiation combined with neck dissection was reported as a significantly related factor to induce HT in pharyngeal cancer according to the outcomes of a study conducted in Japan [27]. From our analysis, an association between an incidence of HT and surgery was found to be statistically significant in the univariable logistic regression analysis. Unfortunately, we did not observe this correlation in our multivariable analysis. Notably, systemic chemotherapy did not increase the incidence of HT in our study. More modern adjuvant immune checkpoint inhibitors were also not found to be related to higher incidence of HT [28].

The radiation dose constraint to the thyroid gland has been investigated over years, but definitive data have not been well established yet. In the three-dimension conformal radiotherapy (3D-CRT) era, Emami et al. estimated an 8% incidence of clinical HT at five years when the entire

Table 4. Man-Whitney U Test Statistics between intensity-modulated radiotherapy/image-guided radiotherapy (IMRT/IGRT) planning and Computational Environment for Radiotherapy Research (CERR) program. The high-risk planning target volumes (PTVs) of each individual plan were used as a control

Dosimetric variables	CERR	Actual plan	p-value*
	Median (IQR)	Median (IQR)	
Volume	166.3 (84.4–277.6)	162.8 (86.0–277.7)	0.780
Dmean	69.6 (69.4–70.3)	69.7 (69.5–70.2)	0.446
D98	66.7 (66.4–67.6)	66.9 (66.5–67.4)	0.207
D95	67.6 (67.2–68.2)	67.7 (67.4–68.3)	0.266
D50	69.7 (69.6–70.2)	69.8 (69.6–70.1)	0.248
D2	71.8 (71.3–72.8)	71.8 (71.4–72.9)	0.559

*Man-Whitney U test; †significant at p-value of < 0.05; IQR — interquartile range; Dmean — mean dose to target

Table 5. Logistic regression for primary hypothyroidism and dosimetric parameters

Variables	Univariable		Multivariable	
	Odds ratio (95% CI)	p-value	Odd ratio (95% CI)	p-value
Volume [cc]	0.859 (0.757–0.976)	0.020 [†]	0.892 (0.783–1.017)	0.089
Dmean [Gy]	1.096 (0.978–1.228)	0.113		
V30 (%)	1.026 (0.976–1.078)	0.318		
V40 (%)	1.044 (0.991–1.099)	0.106		
V45 (%)	1.045 (0.998–1.093)	0.060		
V50 (%)	1.038 (1.003–1.074)	0.032		
VS45 [cc]	0.721 (0.527–0.988)	0.042		
VS50 [cc]	0.734 (0.572–0.940)	0.014 [†]	0.777 (0.606–0.997)	0.047*
VS60 [cc]	0.901 (0.818–0.993)	0.036		

[†]only covariates found to be significant in the univariate analysis (p-value < 0.25) were analyzed in the multivariable analysis. Dmean, V40, V45, V50, VS45, and VS60 were not included in the multivariable analysis to avoid multicollinearity as the variance inflation factor (VIF) values exceeded 2.5; *significant at p-value of < 0.05; Dmean — mean radiation dose to the thyroid gland; Vxx (%) — percentage of volume receiving a dose of xx Gy to the thyroid gland; VSxx (cm³) = absolute volume (cm³) of thyroid glands spared from a dose level of xx Gy; CI — confidence interval

Table 6. Binary logistic regression analysis for VS50_{Gy} cutoff

Thyroid volume spared from dose 50 Gy [cm ³]	Number of patients (n = 64)*	Odds ratio (95% CI)	p-value
≤ 2	18/36	1	0.083
> 2	8/28	0.40 (0.14–1.14)	
≤ 3	20/41	1	0.076
> 3	6/23	0.37 (0.12–1.13)	
≤ 4	22/47	1	0.094
> 4	4/17	0.35 (0.10–1.23)	
≤ 5	25/55	1	0.052
> 5	1/9	0.15 (0.02–1.28)	

VS50_{Gy} — absolute volume (cm³) of thyroid glands spared from a dose of 50 Gy; *Indicates the number of patients who developed hypothyroidism/the total number of patients who received VS50_{Gy} at each specified volume; CI — confidence interval

thyroid gland received a dose of 45 Gy, increased to 13% with the radiation dose over 60 Gy [29]. Various dosimetric parameters have been reported as possible correlation factors with radiation-induced HT according to findings published in more modern studies. A possible dosimetric factor that is related to higher incidence of HT in nasopharyngeal cancer was a V40_{Gy} value less than 85% [12]. A V45_{Gy} over 50% was another possible parameter for HT after head and neck irradiation as has been reported in a study conducted in Korea [10]. Published data on pharyngeal cancer would also indicate that a V45_{Gy} over 67% was associated with a higher incidence of HT [27]. Furthermore, some published studies have identified V50_{Gy} as a predictive factor with a cutoff value at 50–60% [14, 25, 30]. Thyroid mean dose was found to be another predictive parameter that was previously identified

in oropharyngeal cancer patients [31]. However, the results of our study indicated a strong correlation between Dmean and doses of V40_{Gy}, V45_{Gy} and V50_{Gy} in our univariable analysis which was not included into the multivariable analysis. These outcomes reveal an indeterminate association between primary HT and percentage of thyroid volume receiving HT and percentage of thyroid volume receiving doses of 40, 45, and 50 Gy.

The absolute thyroid volume spared from each dose level (VSxx_{Gy}) has increasingly been reported as a correlative factor with primary HT. The results of a previous study on oropharyngeal cancer suggested that the VS45_{Gy} value should be more than 3 cm³ [13]. The outcomes of a study conducted in Hong Kong also recommended value of VS45_{Gy} and VS60_{Gy} over 5 cm³ and 10 cm³, respectively [32]. These dosimetric values were associated with prolonged freedom from HT as follows;

91.5 vs 75.9 months for $VS_{45Gy} \geq 5 \text{ cm}^3$, and 91.5 vs. 73.3 months for $VS_{60Gy} \geq 10 \text{ cm}^3$. Similarly, the outcomes of a study conducted by Lertbutsayanukul et al. indicated a cutoff value of VS_{60Gy} over 10 cm^3 as an associated factor with prolonged freedom from HT at three years, 50.8% vs. 33.5% [33]. The results from our multivariable logistic regression analysis demonstrated that VS_{50Gy} is a significant dosimetric parameter. Unfortunately, we could not identify an appropriate cutoff point value of VS_{50Gy} . However, we did observe the trend of a decrease in the incidence of HT when VS_{50Gy} was more than 5 cm^3 in a binary logistic analysis ($p = 0.052$).

Individual thyroid volume was also reported to be an associated factor of radiation-induced HT. Published data in oropharyngeal patients estimated that a thyroid volume $\geq 8 \text{ cm}^3$ could be prolonged 3-year freedom from HT (48.5% vs. 25.0%) [13]. A study conducted in Croatia identified a total thyroid volume below 14 cm^3 as a predicting factor of HT [30]. Moreover, thyroid volume over 20 cm^3 was associated with a lower 2-year incidence of HT in some study of nasopharyngeal cancer [34]. Another report originated from Poland in oropharyngeal cancer treated by IMRT also validated the NTCP model for thyroid volume as a predictor of HT [31, 35]. However, the analysis from this study did not reveal any correlation between thyroid volume and HT. Thyroid volume was determined to be statistically significant in univariable analysis but not in multivariable logistic regression analysis.

Another predictor was pre-treatment TSH. Some published study has indicated that a pre-treatment TSH value less than $1.55 \mu\text{IU/mL}$ was associated with a longer 3-year freedom from HT (58.8% vs. 27.6%) [33]. Unfortunately, our center did not routinely evaluate TFT before RT. The relatively high incidence of HT reported in this current study should be of particular concern and applied in modifications to our further practice. Pre-treatment TFT, thyroid volume, and VS_{50Gy} constraint of the thyroid gland should be regularly assessed for early detection and prevention of radiation-induced HT.

Although the most common form of HT after irradiation was subclinical HT, the result of this study indicated that 13 out of 26 patients (50%) with thyroid dysfunction had overt HT without clinical symptoms. The data reported by Lee et al. revealed

that 24.2% of patients diagnosed with subclinical HT later developed overt HT [32]. The management guidelines for subclinical HT recommend thyroid hormone replacement when $\text{TSH} > 10 \mu\text{IU/mL}$ [36, 37]. Remarkably, patients who had subclinical HT and TSH value less than $10 \mu\text{IU/mL}$ should be closely monitored for potential early detection or treatment of overt HT.

A major limitation of this study was its retrospective manner. We reviewed 1,102 patients who received RT in our center from 2013 to 2019. However, only 64 patients were enrolled. Most patients were excluded from the analysis according to the following conditions; 306 patients (28%) were treated by conventional RT technique, 227 patients (20.6%) had intracranial extension or radiation field involved pituitary fossa, and 104 patients (9.4%) were treated for palliative intent. Moreover, this study collected data during the COVID-19 pandemic which restricted the patients' ability to re-visit the hospital and fully participate in the trial. This situation led to a smaller number of enrolled patients being involved in our overall analysis. Furthermore, our cross-sectional study also limited the dynamic change evaluation of thyroid function after neck irradiation.

Conclusion

The incidence of HT after neck RT in our institute was relatively high (40.6%). Notably, the radiation dose constraint to the thyroid gland without compromising target coverage is of great importance. From our analysis, the thyroid volume spared from a dose of 50 Gy (VS_{50Gy}) was identified as a significant factor of radiation-induced HT. Even though we could not suggest an appropriate cutoff point value of VS_{50Gy} , a trend to reduce the risk of HT was observed when VS_{50Gy} was more than 5 cm^3 . Importantly, a smaller initial thyroid volume might be associated with an increased risk of HT as it was determined to be a significant factor in univariable analysis.

Ethical approval

Ethical approval was granted by the Institutional Research Board (grant number 155/2563).

Clinical Trial Registration Number:
TCTR20210204008.

Conflict of interest

None declared.

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