RESEARCH ARTICLE

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An Analytical Study to Determine Dose-Volume Threshold for Radiation Induced Hypothyroidism

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Abstract

Objective: To determine radiation dose volume threshold in predicting the development of hypothyroidism in cancer patients following neck irradiation. **Methods:** This is a cross sectional follow up study for patients who had been previously irradiated, prior to enrolment in the study. We have done thyroid dose-volumetric analysis on 120 histologically proven cancer patients in the age group of 18-75 years who received neck irradiation as a part of their definitive or adjuvant radiotherapy with three-dimensional conformal or intensity-modulated radiotherapy technique (3D -CRT or IMRT) and completed at least six months post-radiotherapy. Primary tumor sites included carcinoma or lymphoma of the head and neck, breast, cervical, and upper thoracic esophagus, requiring neck irradiation. **Results:** The proportion of patients who tested positive for Radiation induced hypothyroidism (RIHT) was found to be 40%, with clinical hypothyroidism and subclinical hypothyroidism being 25.8% and 14.2%, respectively. Time to develop hypothyroidism peaks around two years. Mean thyroid gland dose (Dmean) >28 Gy, thyroid gland volume receiving 40 Gy dose (i.e. V40) >49% and age <50 years were found to be significant risk factors for the development of RIHT on binary logistic regression. RT dose >50 Gy and thyroid gland volume spared from 40 Gy (i.e. VS40) < 2.12cm^3 were statistically significant predictors for RIHT on chi-square and (Receiver operating characteristic) ROC curve analysis respectively but not on regression analysis. **Conclusion:** Dose-volume threshold for the thyroid gland as Dmean <28 Gy and V40 <49% may prevent the development of RIHT.

Keywords: Radiation dose-volume threshold- Radiation induced hypothyroidism- IMRT- 3D-CRT

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Introduction

Thyroid hormones are essential for the regulation of body metabolism, heart rate, thermogenesis, muscle, and digestive function (Khandelwal and Tandon, 2012). Hypothyroidism (most common), hyperthyroidism, thyroid cancer, and benign adenoma are the late radiation toxicities reported in the literature related to thyroid gland post neck irradiation (Colevas et al., 2001; Jereczek-Fossa et al., 2004; Alterio et al., 2007; Bakhshandeh et al., 2012).

Emami et al., (1991), publication on tolerance of normal tissue to therapeutic radiation in pre-three-dimensional conformal radiotherapy / Intensity-modulated radiotherapy (3DCRT/IMRT) era mentions probability of clinical hypothyroidism for whole gland irradiation only. In 3DCRT/IMRT era Qualitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report for clinical outcomes on normal tissue from numerous studies (Bentzen et al., 2010) as well as report by Emami (2013) lack dose-volume data on the thyroid gland.

There are few publications that have reported data on dose-volumetric parameters to predict the risk of radiation-induced hypothyroidism (RIHT) in the last two decades. Bisello et al., (2022) recently mentioned dose constraints for the thyroid gland in their report on dose-volume constraints for organs at risk in radiotherapy (CORSAIR). However, there is a lot of uncertainty on optimal cutoff value for reported predictors such as thyroid Dmean, V30, V45, V50, VS30, and VS60 (Bentzen et al., 2010; Johansen et al., 2011; Cella et al., 2012; Emami, 2013; Akgun et al., 2014; Kim et al., 2014; Fujiwara et al., 2015; Sachdev et al., 2017; El-Shebiney et al., 2018; Kamal et al., 2020; Zhou et al., 2021; Pal et al., 2022; Bisello et al., 2022). Despite technical advances in radiotherapy techniques over the last decades, radiation exposure of the thyroid gland remains unavoidable first due to its proximity to primary site or cervical lymph node stations and secondly unprotected thyroid gland radiation planning due to lack of consensus on dose-volume threshold data. We have conducted this institute ethics committee-approved dose-volumetric analysis study to determine the dose-volume threshold for RIHT in patients treated

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with neck radiotherapy.

Materials and Methods

This is a cross sectional follow up study for patients who had been previously irradiated, prior to enrolment in the study. We have done thyroid dose-volumetric analysis on one hundred and twenty histologically proven cancer patients who received neck irradiation and completed at least six months post-radiotherapy.

Eligibility criteria

Patient eligibility criteria included: histologically proven cancer patients in the age group of 18 - 75 years with no apparent history of hypothyroidism before the start of radiotherapy (RT); who underwent neck irradiation with 3D-CRT or IMRT, with radiotherapy fractionation schedule of 1.8 Gy to 2.2 Gy per fraction; where whole or part of the thyroid gland was in the planned radiation field and were attending follow-up clinic from 6 months onwards post-RT. Primary tumor sites included carcinoma or lymphoma of the head and neck, breast, cervical, and upper thoracic esophagus, requiring neck irradiation. Patients diagnosed with nasopharyngeal carcinomas, other head and neck malignancies in which the radiation field extends till the pituitary gland, history of pituitary or thyroid tumor/disorder, or prior pituitary/thyroid irradiation and pregnancy were excluded from the study. Eligible patients who attended the follow-up clinics from November 2019 – January 2022 and agreed to participate in this study were included.

Thyroid function assessment

Eligible patients attending follow-up clinics from six months onward post-radiation were tested for hypothyroidism. Three ml of blood sample was taken for thyroid function test (TFT) evaluation. TFTs were measured in the Endocrinology laboratory. TFT included assessment of free T3 (normal value: 2.3 - 4.2 pg/mL), free T4 (normal value: 0.89 – 1.76 ng/dL), thyroid stimulating hormone (TSH) (for age ≤ 55years: normal value 0.35 - 5.5 microIU/mL; for age > 55years: normal value 0.5 - 8.9 microIU/mL). The diagnosis of subclinical hypothyroidism was based on the TSH value greater than the maximum value of the laboratory range with the normal level of circulating free T4 with/without symptoms. The diagnosis of overt hypothyroidism was based on the increase in TSH with a concomitant reduction in free T4 with or without clinical symptoms/signs such as weight gain, cold intolerance, fatigue, bradycardia, hypotension, and slow reflexes. Patients with abnormal TFTs were advised to visit the Endocrinology department for thyroid replacement therapy or close monitoring depending upon clinical hypothyroidism or subclinical hypothyroidism status. Time to develop hypothyroidism was defined as the duration between the end of radiotherapy and the first recorded abnormal value of TFT.

Radiation dose and Thyroid volume parameters

Thyroid gland was contoured manually on the computed tomography (CT) simulation images of patients treated with 3D-CRT or IMRT. Uniform CT window level parameter setting was used for all the patients. Absolute thyroid volume and radiation dose-volumetric parameters such as doses to the thyroid gland (mean, maximum and minimum), percentage of thyroid volume receiving 10 Gy, 20 Gy, 30 Gy, 40 Gy, 45 Gy, and 50 Gy, i.e. (V10, V20, V30, V40, V45, V50) and the thyroid volume (cm3) spared (VS) from 10 Gy - 50 Gy exposure, i.e. (VS10, VS20, VS30, VS40, VS45, VS50) were calculated using dose-volume histograms on ECLIPSE radiation treatment planning software.

Statistical analysis

Categorical variables were summarized as frequency/ proportion with percentage. Continuous variables were summarized as mean +/- standard deviation or median with interquartile range. The association of dose-volumetric parameters with the development of hypothyroidism was evaluated using independent t-test or the Mann-Whitney test, depending up on the normality distribution and in case of categorical variables using Chi-square test. Receiver operating characteristic (ROC) curve was used to assess the radiation dose-volumetric parameters in predicting the development of radiation-induced hypothyroidism. Max Youden index was applied to the ROC curve to choose the optimal cut-off values for mean thyroid dose, V10-V50, and VS10-VS50. Factors that were found to be in statistical significant association with the development of RIHT were further tested using binary logistic regression. Statistical package for social sciences (SPSS) version 25 was used for statistical analysis.

Results

Patient Characteristics (Demographic, Clinical & Treatment related)

A total of 120 patients, six months post-neck radiation attending follow-up clinic, were analyzed to test for hypothyroidism. Demographic, clinical, and treatment related parameters of 120 patients are summarized in Table 1. Radiotherapy doses delivered to head and neck cancer sites were usually in the range of 50 Gy –70 Gy for subclinical disease/gross disease in radical/adjuvant setting, 50 Gy for breast site including the ipsilateral supraclavicular fossa in the adjuvant setting, and 30 Gy for lymphomas requiring cervical lymph node radiation as part of combined modality treatment.

Proportion of patients tested positive for hypothyroidism and Time duration to develop hypothyroidism

In our study, the proportion of blood samples testing positive for radiation-induced hypothyroidism was 48 out of 120 (40%), with overt hypothyroidism being 25.8% and subclinical hypothyroidism being 14.2%. Cold intolerance was reported by 19 patients, fatigue by 36 patients, weight gain by two patients, and slow reflexes were observed in 3 patients. Other thyroid abnormalities found among 120 blood samples were isolated hypothyroxinemia (low T4 only) in 11 patients, sick euthyroid syndrome (low T3) in one patient, and subclinical hyperthyroidism in one patient. Euthyroid status was documented in 59 blood samples out of 120 blood samples. Median follow-up period was 1.79 years (Range -6.5 years, Minimum-6 months and maximum follow-up-7 years). The peak period for RIHT was observed between 1-3 years, as shown in Figure 1.

Site (HN vs. Non-HN), RT technique (IMRT vs. Non-IMRT) and Total RT Dose effect (>50 Gy vs. <50 Gy) on hypothyroidism

As per the site, 49.27% (34 out of 69) of head & neck cancer patients developed hypothyroidism compared to 27.4%, i.e. (14 out of 51) breast cancer patients. Chi-square test was found to be statistically significant between site and development of hypothyroidism (p-value 0.016).

As per the RT technique, 45.9% of IMRT treated patients (34 out of 74) developed hypothyroidism compared to 30.4% of 3D-CRT treated patients (14 out of 46). Chi-square test was found to be statistically insignificant between the RT technique and the development of hypothyroidism (p-value 0.092). Radiation dose >50 Gy was found to be statistically significant (p-value 0.03) in the development of hypothyroidism – 47.4% (36 out of 76) positive cases compared to 27.3% (12 out of 44) positive cases in patients treated with radiation dose <50 Gy.

Radiation dose-Thyroid gland volume analysis

On statistical analysis, absolute thyroid volume was found to be statistically insignificant for the development of hypothyroidism (as shown in Table 2). Overall,

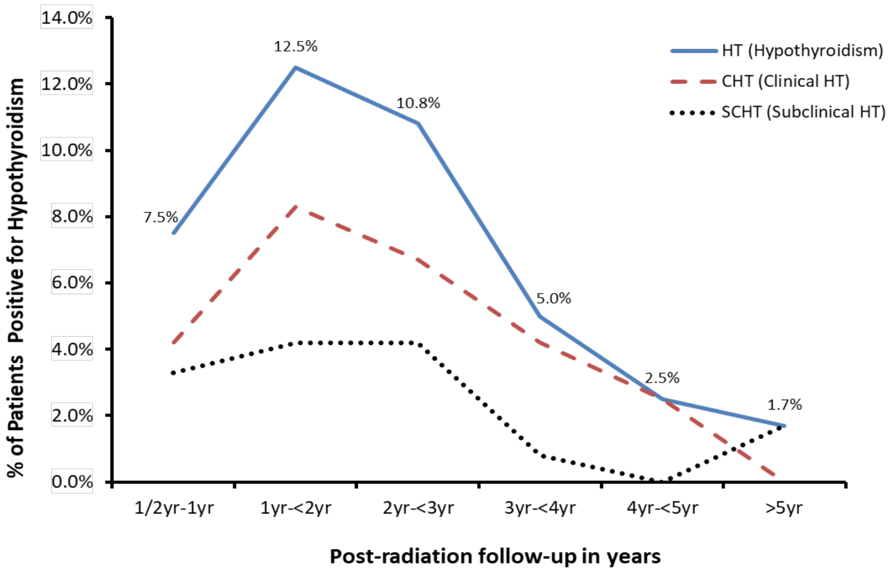

Figure 1. Proportion of Patients Tested Positive for Hypothyroidism as Per Post-Radiation Time Period

Table 1. Demographic, Clinical & Treatment Related Parameters

Variables	Categories	Total (N=120)	Frequency/ Interquartile Range (IQR)
Age (years)	-	Median: 54.5	45-59.75
Gender	Male	54	45%
	Female	66	55%
Site of tumor	Breast	50	41.60%
	Head & Neck (HN)	69	57.50%
	Lymphoma	1	0.80%
Neck Surgery	Yes	25	20.80%
	No	95	79.10%
Chemotherapy	Yes	90	75%
	No	30	25%
RT Techniques	3DCRT-HN & Lymphoma	13	10.80%
	3DCRT-Breast	33	27.50%
	IMRT- HN & Lymphoma	56	46.70%
	IMRT- Breast	18	15%
Cumulative RT Dose	≤50 Gy	44	36.60%
	>50 Gy	76	63.30%
Thyroid gland volume (cm^3)	All	Mean- 7.83	Standard deviation +3.18

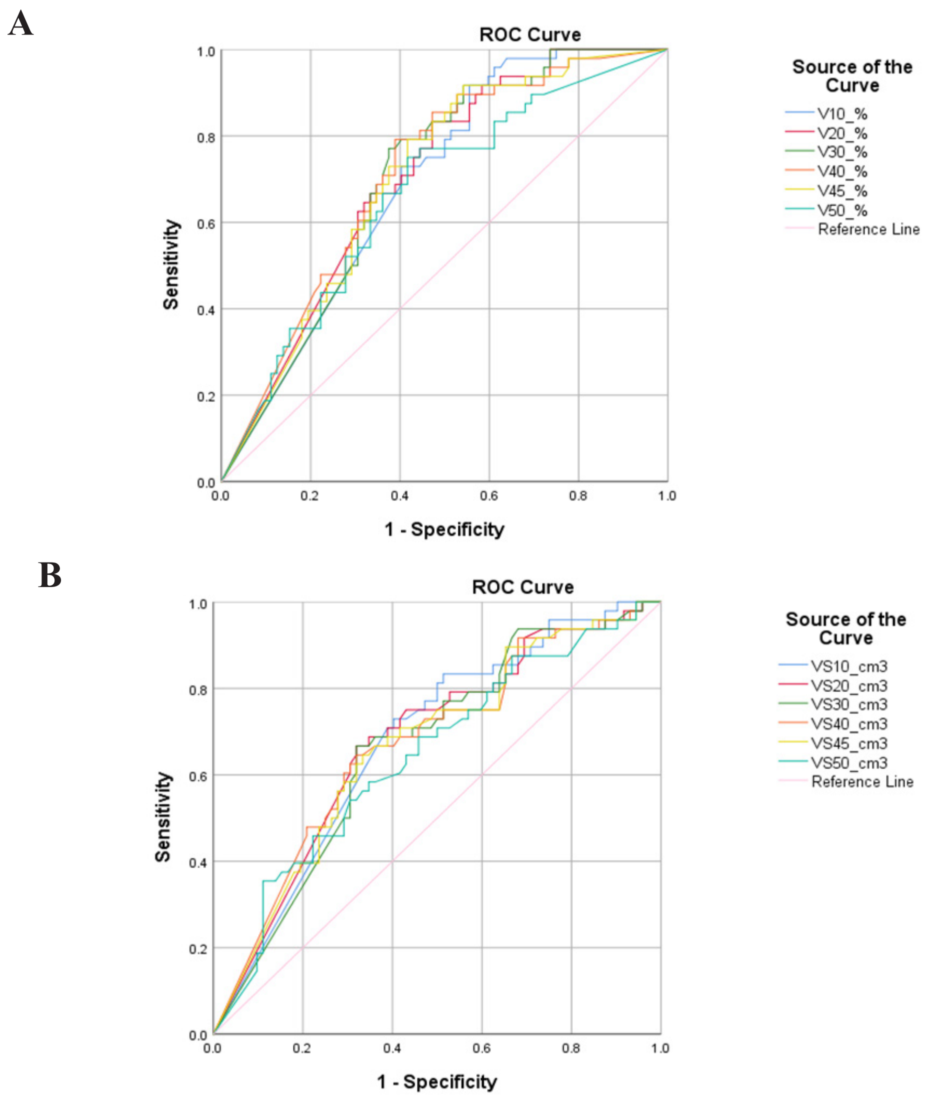

Figure 2. A & B - ROC Curve Analysis for V10-V50 (2A) and VS10-VS50 (2B)

radiation dose-volumetric parameters- such as Dmin, Dmax, Dmean; V10 – V50, VS10 – VS50; were non-normal in distribution and were statistically significant for the development of RIHT (p-value <0.05) (as shown in Table 3).

ROC curve analysis for optimal cut-off value –

Thyroid Dmean - Thyroid Dmean was analyzed further with the ROC curve, and a cut-off value of 28 Gy was obtained after applying the max Youden index. Forty-two out of 78 patients with Dmean >28 Gy, developed hypothyroidism compared to 6 out of 42 patients with Dmean ≤28 Gy. Dmean >28 Gy was found to have a statistically significant association with the development of hypothyroidism (p-value 0.001).

Thyroid V10 -V50- ROC curve and Youden index were applied to get the best cut-off value for the individual dose-volumetric parameters. Among V10 – V50, the highest AUC was found for V40 (Table 4), corresponding to a 49.3% cut-off value calculated with max Youden index with a sensitivity of 79.2% and a specificity of 61.1%. (Figure 2A)

Thyroid VS10-VS50 - Dose volumetric parameters- Among VS10 – VS50, the highest AUC was found for VS10 (Figure 2B), corresponding to the best cut-off value of 0.08cm3 with a sensitivity of 72.9% and specificity of 59.7% (Table 4).

Binary logistic regression analysis

Factors found to have statistical significant association with development of RIHT were chosen for regression analysis. Due to a correlation coefficient of > 0.7 between V40 and mean thyroid dose (>28 Gy vs. <28 Gy) and between V40 and VS40, V40 and mean thyroid dose were

Table 2. Association of Absolute Thyroid Volume in the Development of Radiation-Induced Hypothyroidism

	No Hypothyroidism Mean (Standard Deviation)	Hypothyroidism Mean (Standard Deviation)	p-value
Absolute Thyroid volume (cm^3)	8.07 (3.38)	7.46 (2.86)	0.302

Table 3. Association of Radiation Dose-Volume Parameters in the Development of Radiation-Induced Hypothyroidism

Parameters (%)	No Hypothyroidism Median (IQR)	Hypothyroidism Median (IQR)	p-value
Minimum Thyroid dose (Gy)	5.2 (1.22 – 33.47)	32.14 (68.62 – 46.18)	<0.001
Maximum Thyroid dose (Gy)	54.18 (49.43 – 64.20)	62.43 (53.38 – 68.90)	<0.001
Mean Thyroid dose (Gy)	28.37 (16.02 – 52.45)	50.75 (30.69 – 59.05)	<0.001
V10 (%)	79.82 (36.75 - 100)	100 (84.05 - 100)	<0.001
V20 (%)	55.3 (29.66 - 100)	100 (60.42 - 100)	<0.001
V30 (%)	48.4 (25.68 - 100)	99.26 (56.1 - 100)	<0.001
V40 (%)	43.6 (21.68 – 97.4)	95.2 (49.92 - 100)	<0.001
V45 (%)	39.95 (16.17 – 92.17)	81.45 (45.15 - 100)	<0.001
V50 (%)	19.85 (0 – 75.45)	67.3 (31.12 – 98.82)	0.002
VS10(cm^3)	1.39 (0 – 3.96)	0 (0 – 0.63)	0.001
VS20 (cm^3)	2.42 (0 – 4.63)	0 (0 – 2.35)	0.001
VS30 (cm^3)	2.87 (0 – 4.95)	0.05 (0 - 3)	0.002
VS40 (cm^3)	3.19 (0.25 – 5.33)	0.35 (0 -3.96)	0.001
VS45 (cm^3)	3.45 (0.79 – 5.78)	1.17 (0 – 4.15)	0.002
VS50 (cm^3)	4.1 (2.47 – 6.52)	2.81 (0.1 – 4.92)	0.008

analyzed individually with other factors such as age (<50 years vs.>50years), RT dose (>50 Gy vs. <50 Gy), (site HN vs. NHN), adjuvant chemo (Yes or No). Mean thyroid dose >28 Gy, V40, and patients with age <50 years were found to be statistically significant for the development of hypothyroidism.

Discussion

In our study population, the proportion of blood samples tested positive for hypothyroidism was 40%; clinical hypothyroidism was 25.8%, and subclinical hypothyroidism was 14.2%. Within the first year 7.5% of patients, 12.5% in 1-2 years (peak period), 10.8% in 2-3 years, and 5% in 3-4 years with declining trend developed hypothyroidism. Our results find similarity with published literature on post-radiotherapy overall hypothyroidism incidence in the range of 20-46% (Jereczek-Fossa et al., 2004; Kim et al., 2014; Kumari et al., 2017; El-Shebiney et al., 2018; Das et al., 2018). Minimum period to develop RIHT was reported as early as three months (Kumari et al., 2017; Pal et al., 2022). Our patients diagnosed with hypothyroidism did not have any significant signs/ symptoms related to altered TFT. Fatigue was the major symptom reported, but patients considered this as a normal side effect after cancer diagnosis and treatment.

RT dose >50 Gy was statistically significant in the development of hypothyroidism in our study. Grande (1992) observed thyroid dysfunction in cases receiving >60 Gy radiation dose compared to <60 Gy on multivariate analysis. As per metanalysis by Vogelius et al., (2011), a steep dose-response curve was achieved while evaluating the radiation dose effect on the development of hypothyroidism, i.e., the risk of RIHT increases with an increase in radiation dose. D50 i.e. Dose at 50% probability of developing hypothyroidism was synthesized

Table 4. Receiver Operating Characteristics (ROC) Curve Analysis of Radiation Dose - Volumetric Parameters

Variable	Area under the curve (AUC)	p- Value	95% Confidence Interval (CI)		Cut off value (%)	Sensitivity	Specificity	Youden index
V10 (%)	0.692	<0.001	0.6	0.784	57.35	0.917	0.444	0.361
V20 (%)	0.705	<0.001	0.614	0.797	56.05	0.833	0.528	0.361
V30 (%)	0.704	<0.001	0.612	0.796	55.8	0.771	0.625	0.396
V40 (%)	0.712	<0.001	0.62	0.804	49.3	0.792	0.611	0.403
V45 (%)	0.702	<0.001	0.61	0.795	44.45	0.792	0.583	0.375
V50 (%)	0.665	0.002	0.567	0.764	32.3	0.75	0.583	0.333
VS10 (cm^3)	0.678	0.001	0.582	0.774	0.08	0.729	0.597	0.326
VS20 (cm^3)	0.677	0.001	0.58	0.775	0.48	0.667	0.681	0.347
VS30 (cm^3)	0.663	0.003	0.565	0.761	1.72	0.667	0.681	0.347
VS40 (cm^3)	0.672	0.001	0.574	0.771	2.12	0.646	0.681	0.326
VS45 (cm^3)	0.667	0.002	0.568	0.765	2.45	0.646	0.667	0.313
VS50 (cm^3)	0.644	0.008	0.543	0.745	0.24	0.354	0.111	0.243
VS50 (cm^3)	0.644	0.008	0.543	0.745	3.68	0.688	0.542	0.229*

0.229*-Nearest value to the Youden index for a better trade-off of sensitivity and specificity for VS50 (cm^3)

to be approximately 45 Gy; 95% CI (28 Gy – 62 Gy), but they have mentioned this synthesized number likely to be too high due to lack of prospective studies correlating TSH increase with radiation dose.

IMRT planning technique with no dose constraints to the thyroid gland resulted in more hypothyroidism cases compared to 3DCRT where the gland was centrally shielded in the lower neck if the primary site is away from the lower neck, e.g., oral cavity or when gross nodes are not present near to lower neck. Reason for more cases of hypothyroidism in head and neck cancer patients than in breast cancer patients can be attributed to bilateral neck radiation and high RT dose (50 Gy -70 Gy) in a majority of HN patients compared to breast cancer cases who received unilateral neck radiation and low total RT dose (46 Gy -50 Gy).

Thyroid Dmin, Dmax, Dmean, V10–V50, and VS10 – VS50 were all statistically significant for the development of hypothyroidism except absolute thyroid gland volume, which was statistically insignificant in the current study. However, on multivariate analysis, Kamal et al., (2020) study reported smaller thyroid gland volume as the strongest predictor in addition to higher Dmean for the increased risk of clinical hypothyroidism.

In this study, as per ROC curve analysis, V40 had the highest AUC among V10-V50 parameters. Optimal cut-off value V40 of 49.3% was determined as per the Youden index obtained from the ROC curve, i.e., >49.3% of thyroid gland receiving 40 Gy was found to be at risk for developing hypothyroidism. In our study, we found the best cut-off values for V30, V45, and V50 as 55.8%, 44.45%, and 32.3% compared to V30 as 42.1% by El-Shebiney et al., (2018), V45 as 50% by Kim et al., (2014) and V50 as 60% by Sachdev et al., (2017) respectively from ROC curve analysis.

We obtained thyroid Dmean <28 Gy as the optimum cut-off protective value after the Youden index application on the ROC curve. This value is almost similar to the Dmean thyroid dose of <30 Gy reported by Fujiwara et al., (2015) as a predictor for lower incidence of RIHT.

Thyroid gland is considered under the parallel category rather than serial category of organs at risk (OAR), so the number of follicle cells spared by higher isodose curves can be determining factor for the maintenance of thyroid gland function (Lee et al., 2016). Although VS10 and VS20 had the highest AUC on ROC curve analysis in the current study, it may not be feasible for low isodose curves to spare the gland in clinical practice. VS30 or VS40 may be opted as restricting higher isodose of 30 Gy or 40 Gy, sparing at least 1.72cm3 and 2.12cm3 of the thyroid gland, respectively, to prevent the development of RIHT, as analyzed from the current study. In contrast, other studies reported a cut-off volume for thyroid gland volume spared by 30 Gy dose (VS30) as 5cm3 on retrospective analysis of breast cancer patients and 7cm3 VS30 on retrospective analysis of lymphoma patients (Johansen et al., 2011; Cella et al., 2012).

In our study, maximum radiation dose exposure ranges in 50 Gy-70 Gy with a large sample size compared to Johansen et al., (2011) and Cella et al., (2012) studies where total radiation doses were less. Zhai et al., (2022) suggested Dmean thyroid gland >45 Gy, V40 - >80%, and VS45 <5cm3 to be predictors for developing RIHT after analysis of nasopharyngeal carcinoma patients. However, these numbers are very high compared to Dmean thyroid gland >28 Gy, V40 - >50%, VS45 - 2.45cm3 cut-off values determined in our study of head and neck cancer patients where we excluded nasopharynx cancer cases to avoid bias for central hypothyroidism in view of pituitary irradiation.

As per Pal et al., (2022), thyroid gland volume receiving 50 Gy (V50), dose received to 50% volume (D50), and the mean dose (more than 50 Gy) were found to be significantly associated with hypothyroidism on univariate and multivariate analysis, with no mention on any cut-off value V50 and D50 of the thyroid gland for clinical hypothyroidism. In this study, only 38 patients were treated with IMRT out of 71 Head and Neck cancer patients, and these 38 patients were analyzed with dose-volume parameters for the development of clinical hypothyroidism in comparison to the present study with a larger sample size. Our results are for the combined risk of hypothyroidism, i.e., subclinical as well as clinical hypothyroidism, compared to the above study, whose results are particularly for clinical hypothyroidism.

There is conflicting evidence in the published literature regarding the role of confounding factors such as age, gender, chemotherapy, neck surgery, and the presence of autoantibodies in the development of hypothyroidism (Aich et al, 2005; Wu et al., 2010; Vogelius et al.,2011; Kim et al., 2014; Kumari et al., 2017; Lin et al., 2019). On logistic regression analysis, we found age <50 years at approximately 2.5-3 times higher risk for the development of hypothyroidism in addition to mean thyroid dose (>28 Gy) and V40. Wu et al., (2010) and Zhai et al., (2022) also found younger age to be at risk of developing clinical hypothyroidism after radiation therapy, but other studies results failed to confirm this association (Mercado et al., 2001; Kim et al., 2014; Lee et al., 2016).

Limitations of the study

The highest proportion of development of hypothyroidism seen in our study was around 1-3 years, which is in concurrence with other studies that reported a peak period for the development of hypothyroidism in the first five years post-radiotherapy (Colevas et al., 2001; Jereczek-Fossa et al., 2004; Vogelius et al.,2011; El-Shebiney et al., 2018; Lin et al., 2018). However, the current study is a cross-sectional and single institutional study; therefore, cumulative incidence and time to develop hypothyroidism cannot be accurately determined.

The second limitation is that we did not have baseline TFT results prior to RT, so the patients were recruited based on no history of proven hypothyroidism as per medical case record data maintained in our department or no thyroid abnormality on simulation CT scans taken at the time of radiation treatment planning.

In conclusion, the proportion of patients who tested positive for RIHT was found to be 40%, with clinical hypothyroidism and subclinical hypothyroidism being 25.8% and 14.2%, respectively. Time to develop hypothyroidism peaks around two years. Overall, as per the results of statistical analysis and clinical relevance, we suggest the dose constraints for the thyroid gland as Dmean <28 Gy and V40 <49% of the thyroid gland to prevent RIHT. Younger age <50 years was found to be at high risk for RIHT. RT dose >50 Gy and VS40 >2.12cm3 were statistically significant predictors on UVA but not on MVA.

Author Contribution Statement

Dr Pravesh Kumar- Data collection, Manuscript writing. Dr Pooja Sethi- Manuscript Conception, Study design, editing, statistical analysis. Dr. Sadishkumar Kamalanathan – Lab testing, Manuscript editing and review. Dr. Manavalan Manivannan- Manuscript review.

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Ethical Declaration

This study was approved by JIPMER, Institute ethics committee, as student MD thesis.

Funding Statement

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Approval

This study was approved by JIPMER, Scientific Committee and Institute ethics committee, as student MD thesis

Data Availability

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Conflict of Interest

None.

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