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Dose-volumetric Predictors for Thyroid Dysfunction after 3D Conformal Radiotherapy: An Observational, Prospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author MAJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AAE and HMHRE managed the analyses of the study. Author AEB supervised and performed the radiological work in the study. Author RO performed the dose-volumetric calculations in the study. Author EA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study was conducted to assess the dose-volumetric threshold of radiation induced hypothyroidism (RIHT) in patients receiving radiotherapy (RT) to the neck.
Study Design: This is a prospective cohort observational study.
Place and Duration of the Study: The study was conducted at Mansoura University Hospital, Mansoura, Egypt, between April 2016 until March 2019.
Methods: We have completed 2 years of follow up to 50 patients with different malignancies who were treated by radiotherapy to the neck. Baseline assessment of the thyroid clinically and radiologically was done prior to the start of radiotherapy. Periodic testing of the cohort through the follow up period was done by clinical examination, measurement of TSH, fT4 and thyroid ultrasonography.

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Results: The incidence of RIHT was 26%. No statistical significance for the clinical risk factors. The dose-volumetric risk factors were studied and showed positive results. A mean dose of 5185 cGy was found a significant risk factor. Also, $V_{40} \geq 89\%$, $V_{45} \geq 63.5\%$, $V_{50} \geq 22.5\%$ were found to be the cutoff predictors for the threshold radiation dose to induce hypothyroidism. Also decreasing the size of the gland by ≥0.7 cm^3, fT_4 value by ≥ 3.5 pmol/L and TSH by ≥ 0.75 uIU/L after one year from the end of EBRT is the cutoff value for prediction of occurrence of RIHT within the 2nd year of follow up.

Conclusion: RIHT is a considerable late adverse effect for patients receiving RT to the neck. Mean dose, V_{40}, V_{45} and V_{50} were found significantly related to RIHT. Mean dose of ≥ 5185 cGy, $V_{40} \geq 89\%$, $V_{45} \geq 63.5\%$, $V_{50} \geq 22.5\%$ were proven to be the dose-volumetric threshold.

Keywords: Radiotherapy; hypothyroidism; prospective; cohort; predictors.

1. INTRODUCTION

Radiation induced hypothyroidism (RIHT) is the most common late effect of radiation to the thyroid gland, commonly in head and neck cancer. Recent reports state the incidence of RIHT to be between 17- 47.7% [1-3]. The median interval after radiotherapy until RIHT development ranged from 1.4 to 1.8 years [4].

Thyroid function assessment is not routine in cancer patients despite that hypothyroidism has a significant impact on the quality of life [5]. Serum thyroid stimulating hormone (TSH) level is the most sensitive test for hypothyroidism (HT). It is recommended to obtain another test within 5-6 weeks from first test [6]. Free T4 (FT4) level is recommended for diagnosis of HT while T3 level testing is not recommended routinely [7].

Clinical (HT) is manifested with increased TSH and decreased fT4, and with classic symptoms of HT. Subclinical HT has elevated TSH and normal fT4 with nonspecific symptoms apparently. The treatment of clinical or subclinical HT is levothyroxine replacement therapy aiming to turn the TSH and fT4 back to normal levels with overcoming symptoms [1].

The positive predictors for risk factors related to dose-volume relationship for the thyroid gland have been unclear despite various reports about various risk factors. The application of 3D conformal radiotherapy (3DCRT) now enables us to measure the volume and the dose delivered to this volume of the thyroid gland and to correlate the dose-volume relationship with RIHT after external beam radiotherapy (EBRT) [2].

The main radiological finding that is consistent in most studies of patients who have received RT to head and neck was reduced thyroid size after radiotherapy. Follow up thyroid ultrasound when compared to pre-radiotherapy ultrasound has shown significant reduction in the thyroid gland size [8].

We aimed at our study to correlate radiation dose delivered to the thyroid gland with the incidence of RIHT, based on the analysis of dose-volume histograms (DVHs), which leads to identification of the threshold dose required to induce RIHT. The post-radiotherapy (Post-RT) sonographic appearance of the thyroid gland was correlated with the thyroid function in patients who developed RIHT.

2. PATIENTS AND METHODS

This is a prospective cohort study that included 50 patients with head and neck cancer, breast cancer and lymphoma presented to Clinical Oncology and Nuclear Medicine Department at Mansoura University Hospital (MUH) from the period of April 2016 to March 2017 inclusive. 3D conformal radiotherapy (3DCRT) was used, with or without concurrent chemotherapy. The follow up period was 24 months duration after RT or until diagnosis of secondary hypothyroidism. Last follow up was in March 2019.

Eligibility criteria included adult patients (Age > 18 years), euthyroid state and normal sonographic findings of the thyroid, no history of thyroid dysfunctions or surgical manipulation of the gland before treatment, expected lifespan of at least 12 months then finally; oral and written informed consent were taken from patients before enrollment in the study.

2.1 Pre-treatment Evaluation

All patients were evaluated by full history, clinical examination and radiological investigations as indicated. All patients had pre-treatment evaluation of the thyroid gland radiologically by duplex ultrasound (US) of the thyroid and

laboratory assessment by TSH (normal range 1.39- 4.49 uIU), free T4 (normal range 9-23 pmol/L). Patients with thyroid gland abnormalities were excluded.

2.2 Radiotherapy

All patients were treated by 3DCRT. Head and neck cancer patients as well as neck lymphoma patients had CT simulation and immobilization with thermoplastic masks. Breast cancer patients were simulated using the breast board and the conventional breast position, where the head is tilted to the contralateral side and the arms are raised above the head.

Localization was done with CT cuts of 5mm thickness. Contouring of target volumes and OARs was done. Radiotherapy was delivered on daily basis using conventional fractionation (180-200 cGy/ fraction) to all head and neck cancer and lymphoma patients. Breast cancer patients were treated with hypo-fractionated schedule of 4000 cGy/ 3weeks/ 15 fractions, 267 cGy /fraction. Biological effective dose (BED) delivered was calculated after using alpha/beta ratio NTCP and TCP based software (IsoBED) [9]. Patients were treated by 6MV photon by linear accelerator (Elekta). Treatment duration lasted between 3 to 7 weeks and radiation doses ranged from as low as 24 Gy (lymphoma cases) to 70 Gy (advanced head and neck cancer cases).

Thyroid gland was delineated as an organ at risk (OAR) using the planning system for 3D conformal radiotherapy. The mean thyroid dose and the percentage of thyroid volume receiving >10, 20, 25, 30, 35, 40, 45, 50 Gy (V10, V20, V25, V30, V35, V40, V45 and V50) were calculated.

2.3 Chemotherapy

Out of 50 patients, 43 patients have received chemotherapy as part of their treatment. Breast cancer patients and lymphoma patients have received chemotherapy prior to radiotherapy according to indication.

Sixteen breast cancer patients have received adjuvant chemotherapy regimen as AC followed by weekly paclitaxel 12 weeks. Two out of three lymphoma patients have received chemotherapy prior to RT using the CHOP regimen. The 3rd case was treated by involved site radiotherapy (ISRT) alone. Among thirty-one patients of head and neck cancer twenty-five where indicated for concurrent chemoradiation and received weekly cisplatin 40 mg/m^2 for 6 to 7 weeks starting on day 1 of RT.

2.4 Post- treatment Evaluation

Repeated laboratory and sonographic evaluation, at 3, 6, 12, 18 and 24 months, were performed at follow up. Hypothyroidism was defined as TSH value > the maximum value of laboratory range. Thyroid ultrasound was done to evaluate thyroid gland size during follow up. Replacement therapy with levo-thyroxin was given to patients with RIHT.

2.5 Statistical Analysis

Data were entered and analyzed using: IBM-SPSS software (version 25), Medcalc software (version 18.9.1). Qualitative data were expressed as count and percent. Quantitative data were initially tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk's test with data being normally distributed if P > .05. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not.

Qualitative data for two groups (2X2 table): Chi-Square test (or Fisher's exact test) was used. Qualitative data for more than two groups (e.g., 2X3 table): Chi-Square test (with Bonferroni method to adjust p values when comparing column proportions) was used. Quantitative data between two groups: Independent-Samples t-test was used if data were normally distributed in both groups. The non-parametric alternative Mann-Whitney U test was used if not.

The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases was evaluated using Receiver Operating Characteristic (ROC) curve analysis [10]. ROC curves were also used to compare the diagnostic performance of two or more diagnostic test [11].

The Kaplan-Meier method [12] is a non-parametric method used to estimate the probability of survival past given time points (i.e., it calculates a survival distribution). The survival distributions of two or more groups were compared for equality using log-rank test. Cox regression analysis was used to predict the occurrence of an event by calculating the hazard ratio. For any of the used tests, results were

considered as statistically significant if p value ≤ 0.050.

3. RESULTS

The study has involved 50 patients. Their mean age ± SD was 50.5 ± 9.6 years and 52% (26) were males compared to 48% (24) who were females. Head and neck cancer patients were the majority of cases (62%). All baseline results of thyroid function tests were within normal laboratory range. Other characteristics are summarized in Table 1.

Two patients were confirmed to develop RIHT after 6 months from the end of EBRT, 3 patients at 12 months, 4 patients at 18 months and 4 patients at 24 months. By the end of 24 months, 13 patients had the established diagnosis of RIHT and started their levo-thyroxin replacement therapy. The 37 euthyroid patients were advised to continue follow up. The median time to develop RIHT was 18 months (range 6-24 months). Neither age, sex, cancer type, chemotherapy or surgical neck dissection had statistically significant effect on development of RIHT. Also, there was no statistically significant difference between baseline TSH, fT4 levels and thyroid gland size between euthyroid and hypothyroid groups (Table 2).

All 50 patients have received 3DCRT. The thyroid gland was contoured on the planning system and the dose delivered to the thyroid gland was calculated. The assumed predictors were the mean thyroid dose and the V10, V20, V25, V30, V35, V40, V45, V50. After 2 years of follow up, the patients who have developed RIHT were identified as the hypothyroid group. The cutoff values for each of the volumes as well as for the mean thyroid dose were measured statistically. The statistical results were obtained by using ROC curve (Fig. 1). The mean dose delivered to the thyroid gland in the cohort was 4466 cGy ± 818.316. Data obtained from ROC curve analysis have shown that mean dose ≥ 5185 cGy was statistically significant as a cutoff value to predict RIHT, with specificity of 94.6%, sensitivity of 61.5%, PPV of 80% and NPV of 87.5% (Table 3).

Table 1. Pre-treatment patient characteristics

Character	No.	%
Age (years)		
• Mean ± SD	50.5 ± 9.6	
• Median	51	
• Range	33-69	
Sex		
• Male	26	52%
• Female	24	48%
Cancer type		
• Head and neck cancer	31	62%
• Breast cancer	16	32%
• Non-Hodgkin lymphoma	3	6%
Chemotherapy		
• Yes	43	86%
• No	7	14%
Surgery		
▪ **yes**	24	48%
▪ **no**	26	52%
Baseline TSH		
• Mean ± SD	2.49 ± 0.85 uIU/L	
• Range	2.3 – 2.8 ul U/L	
Baseline fT4		
• Mean ± SD	16.25 ± 2.86 pmol/L	
• Range	11.1 - 22.0 pmol/L	
Baseline thyroid gland size		
• Mean ± SD	10.18 ± 0.75 cm^3	
• Range	8.8 – 11.7 cm^3	

Table 2. Analysis of clinical, laboratory, radiological and treatment factors in relation to thyroid function status

Parameter	Euthyroid group (n = 37)	Hypothyroid group (n = 13)	P
Mean age ± SD (years)	50.81 ± 9.3	49.46 ± 10.7	.67
Sex			
▪ Male	20 (54.05%)	6 (46.15%)	.75
▪ Female	17 (45.94%)	7 (53.85%)	
Diagnosis			
▪ Head& neck cancer	21 (56.76%)	10 (76.92%)	.19
▪ Breast cancer	13 (35,14%)	3 (23.08%)	
▪ Lymphoma	3 (8.1%)	0	
Chemotherapy received			
▪ Yes	31 (83.78%)	12 (92.3%)	.66
▪ No	6 (16.22%)	1 (7.69%)	
Neck surgery			
▪ **yes**	16 (43.24%)	8 (61.54%)	.39
▪ **no**	21 (53.76%)	5 (38.46%)	
Baseline Mean TSH	2.46 uIU/L	2.96 uIU/L	.22
Baseline Mean fT4	16.06 pmol/L	16.8 pmol/L	.42
Baseline Mean size by ultrasound	10.16 cm	10.24 cm	.89

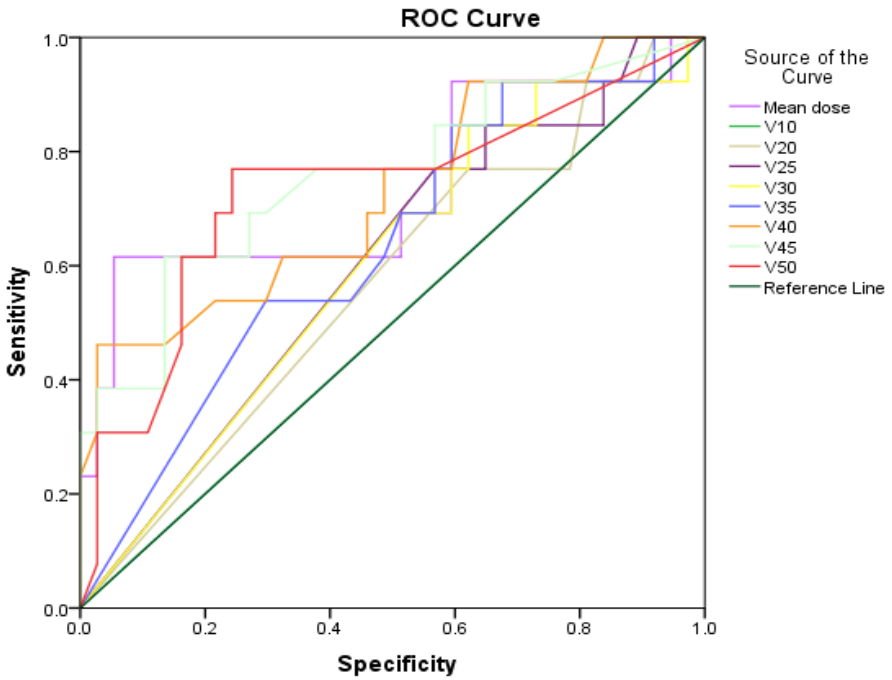

Fig. 1. ROC curve of different V_x

Baseline and serial measurements of fT4, TSH and thyroid gland size were done to predict early changes in each predictor. The change of TSH value occurred earlier than the change of fT4 in the hypothyroid group (Figs. 2 & 3). The hypothyroid group showed a statistically significant change compared to the euthyroid group after 6 months from RT for TSH and after 12 months from RT for fT4. Shrinkage of the size of the size of the thyroid gland was more recognizable in the hypothyroid group and became statistically significant 24 months after radiotherapy (Fig. 4), (Table 4).

The cutoff value for TSH change as a predictor for RIHT was considered to be Increased TSH by 0.75 uIU/L after 1 year from radiotherapy. Similarly, the cutoff value for free T4 change as a predictor for RIHT was considered to be decreased free T4 by 3.5 pmol/L after 1 year from radiotherapy.

Regarding thyroid size, most hypothyroid patients had a change of decreased size by ≥ 0.7 cm^3 after one year of follow up. A reduction in size by ≥ 0.7 cm^3 after one year from RT was considered to be the cutoff value for thyroid gland size change. ROC curve analysis (Fig. 5) was done for the three clinical predictors as seen below. It was done to identify as well as to compare the sensitivity and specificity of each predictive cutoff value.

We have found that the TSH change was the most sensitive predictor for development of RIHT (99.9%). The most specific predictor was size reduction (97.3%). It also had the highest positive predictive value (90%). The fT4 change had the highest negative predictive value (96.7%). The findings of these cutoff values are summarized in (Table 5).

Table 3. The cutoff values for dose-volumetric parameters associated with RIHT

Variable	AUC	95% CI	P	Cutoff value	Sensitivity	Specificity	PPV	NPV
Mean dose	0.734	0.550-0.917	**.013**	**≥ 5185 cGy**	61.5%	94.6%	80%	87.5%
V10	0.5	0.316-0.684	.99	-	-	-	-	-
V20	0.569	0.390-0.747	.465	-	-	-	-	-
V25	0.600	0.426-0.774	.288	-	-	-	-	-
V30	0.598	0.422-0.773	.299	-	-	-	-	-
V35	0.634	0.461-0.807	.154	-	-	-	-	-
V40	0.728	0.558-0.897	**.015**	**≥ 89 %**	46.1%	97.3%	85.7%	83.7%
V45	0.759	0.594-0.924	**.006**	**≥ 63.5%**	61.5%	86.5%	61.5%	86.5%
V50	0.731	0.553-0.908	**.014**	**≥ 22.5%**	76.9%	75.7%	52.6%	90.3%

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

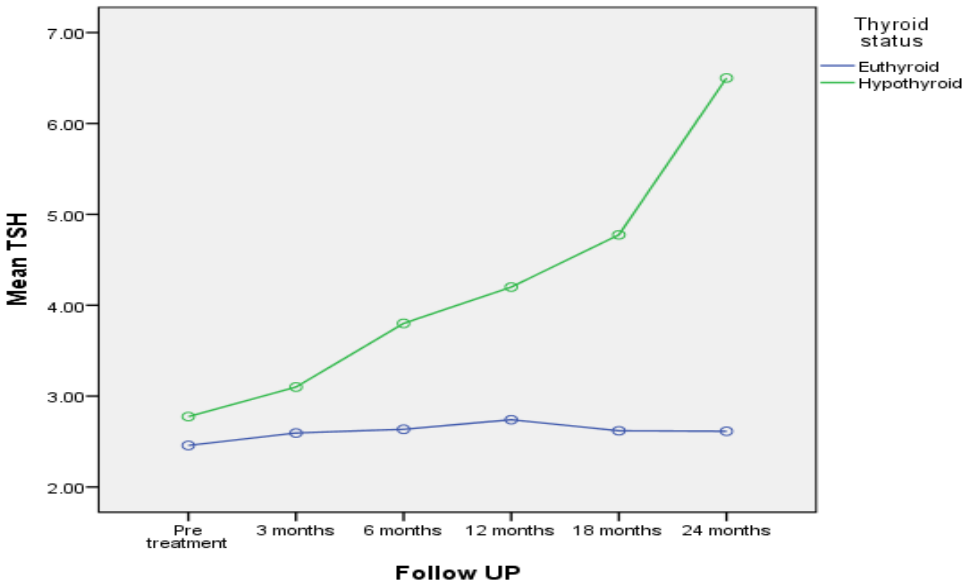

Fig. 2. TSH change during 24 months for each group

Table 4. TSH, fT4 and thyroid size in both groups

Time	Thyroid status	TSH		fT4		Thyroid size	
		Mean	P	Mean	P	Mean	P
Baseline	Euthyroid	2.457	.48	16.057	.24	10.165	.63
	Hypothyroid	2.775		18.200		10.350	
3 months	Euthyroid	2.595	.273	14.638	.98	10.049	.46
	Hypothyroid	3.100		14.667		10.350	
6 months	Euthyroid	2.635	**.013**	15.095	.71	9.954	.68
	Hypothyroid	3.800		14.667		10.125	
12 months	Euthyroid	2.741	**.02**	15.073	**.016**	9.892	.97
	Hypothyroid	4.200		12.333		9.875	
18 months	Euthyroid	2.619	**.001**	14.919	**.05**	9.778	.52
	Hypothyroid	4.775		12.333		9.525	
24 months	Euthyroid	2.614	**> .001**	14.892	**> .001**	9.727	**.05**
	Hypothyroid	6.500		8.867		9.000	

Table 5. Laboratory and radiological predictors for RIHT

Predictor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
TSH increase by ≥ 0.75 uIU/ml after 1 year	99.9%	91.9%	80%	100%
Free T4 decrease by ≥ 3.5 pmol/L after 1 year	90.9%	78.4%	55.6%	96.7%
Size decrease by ≥ 0.7 cm^3 after 1 year	75%	97.3%	90%	92.3%

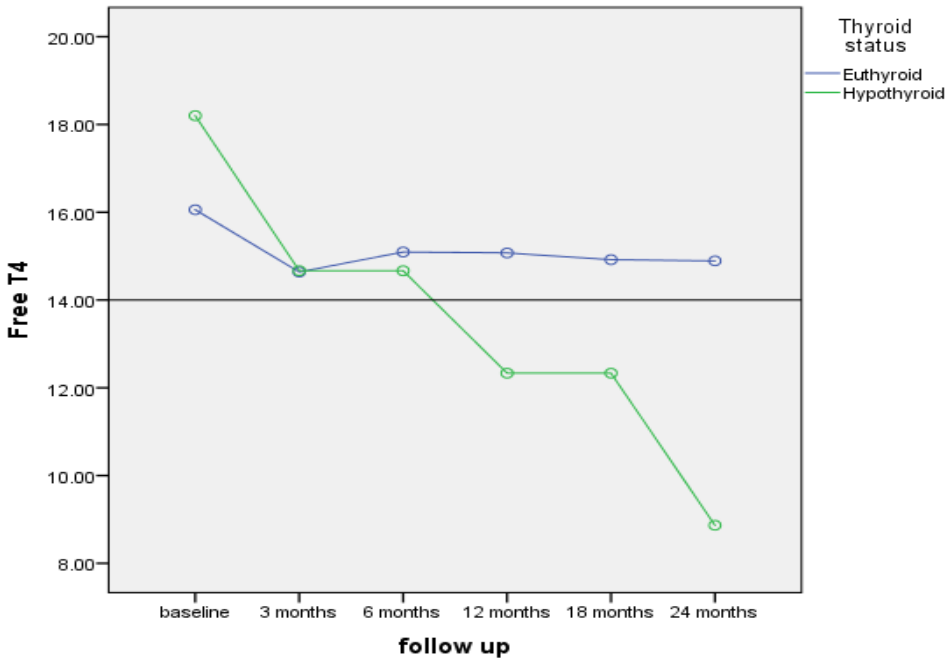

Fig. 3. Change of fT4 in both groups

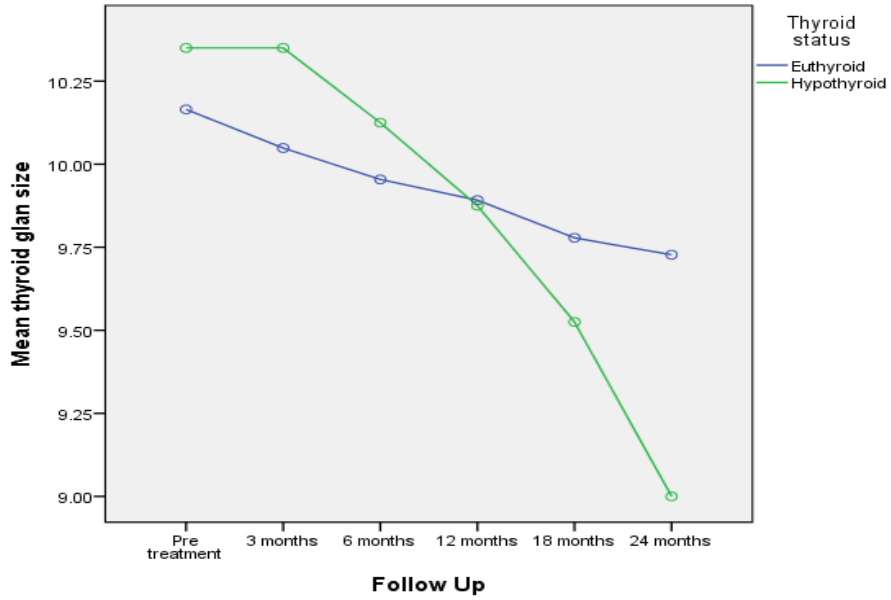

Fig. 4. Gland size change within both groups in first 24 months

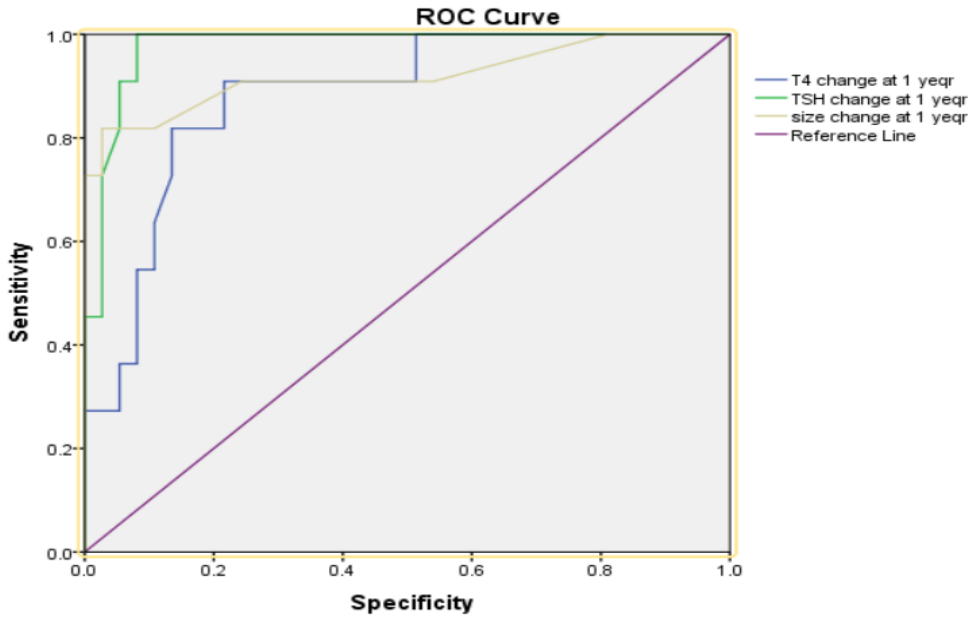

Fig. 5. ROC curve for fT4 change, TSH change and thyroid size change as clinical predictors

4. DISCUSSION

Radiation induced hypothyroidism (RIHT) is a consequence to EBRT that has been classified as one of the late effects of radiation. Oncologists may overlook this late effect as they focus on patients' survival and prevention of recurrence of the disease as their main priority. Both clinical and subclinical RIHT have been associated with poor quality of life for patients surviving cancer. This study was designed to obtain a model for early detection and prediction of this condition.

The study has evaluated RIHT among 50 patients with different diagnosis and types of cancer. Among the patients 31 had head and neck cancer with a range of etiologies. Also, the

staging was not uniform where some patients had early stage disease that required a single modality treatment with radiotherapy alone without concurrent chemotherapy. While other patients needed radiotherapy as a part of multimodality treatment plan for advanced disease together with surgery and chemotherapy. The study also included 16 patients with breast cancer who were candidates to regional lymph node irradiation. The remaining 3 patients were NHL patients who received IFRT to the neck lymph nodes. This heterogenicity in patient selection was needed to gather data from a sizable population during a relatively short duration of follow up (24 months) for a late effect of radiotherapy. However, this heterogenicity may have had its impact on the statistical findings.

Various authors have conducted similar studies on patients who have the same cancer type like nasopharyngeal carcinoma [13], laryngeal carcinoma [14] or oropharyngeal carcinoma [2]. Other authors have studied the same topic on cohorts with variable malignancies [3,15].

In our study 3DCRT was used for all patients. IMRT was not available at MUH and therefor was not implemented. No dose constraints to the thyroid gland were adopted and therefore the thyroid gland was not actively protected from higher doses of radiation. A similar radiotherapy technique was taken by El-Sherbiney et al. [16]. However, IMRT was used in other studies like [14,17]. Dose constraints and active protection to the thyroid gland with IMRT was adopted by Lee et al. [14].

Our results have shown that the incidence of RIHT after maximum follow up of 24 months was 26%. The range of reported incidence from similar studies ranged from 17- 47% [2,5,15,16, 18,19]. Our follow up period is relatively short and the incidence is expected to increase with longer follow up periods. In a retrospective study performed by chyan et al. [20] the median follow-up period was 4.6 years and the incidence of RIHT was 61%. Other authors [4,21,22] have stated the importance of monitoring RIHT within the first 2 years after EBRT where they recorded that the median interval to develop RIHT was 1.4 to 1.8 years. This is consistent with our results where the median interval between RT and development of HT was 18 months.

The prospective nature of our study is considered as an advantage, where the pre-RT TSH monitoring allowed to prevent the possibility of missing pre-RT subclinical HT status. However, the retrospective studies may allow some bias.

Another value of TSH monitoring after EBRT is that temporary rise of TSH may return to normal with longer follow up [23]. In this study repeated confirmatory TSH and free T4 measurements were done after the initial rise of TSH to overcome the possibility of spontaneous recovery of acute or subacute clinical or subclinical HT to confirm the occurrence of RIHT and the need to replacement therapy.

In this study none of the clinical predictors (age, sex, chemotherapy, surgical dissection) had statistical significance to correlate to RIHT. In contrast to other authors who suggested combined surgery and EBRT [24], female sex [25], concurrent chemoradiation [26] had higher risk of RIHT. The current study is a prospective study while all of these studies were retrospective studies. Other prospective studies [16,17] showed that patient age, sex, comorbidities, combined surgery , and concurrent chemotherapy did not contribute to the risk of RIHT.

In our study we analyzed multiple dosimetric variables that include the mean thyroid dose, V_{10}, V_{20}, V_{25}, V_{30}, V_{35}, V_{40}, V_{45}, V_{50}. However, only the mean dose and V_{40}, V_{45}, V_{50} had statistically significant relationship with RIHT. The threshold mean dose was mean dose ≥ 5185 cGy (P = .013). Threshold for V_{40} is V_{40} ≥ 89 % (P = .015), V_{45} threshold is V_{45} ≥ 63.5 % (P= .006), and for V_{50} is V_{50} ≥ 22.5% (P = .014). There was no statistical significance for any one of the four predictors over the others.

Other authors have defined V_{30} > 62.6% [19], V_{30} > 42.1% [16], D_{50} of 44 Gy [27], V_{50}> 60% [20] as the threshold for RIHT. Mean dose ≥ 50 Gy was considered a considerable cutoff [2]. This wide range of cutoff predictors can be explained with varying methodology. Longer follow up periods will allow to record higher incidence of RIHT cases. The sample size plays a major role as well as homogeneity of the sample and thus different results with wide range of dose volumetric parameters are seen in the literature. Also, the retrospective nature of some studies contributed to this variation. Using 3DCRT alone like our study and El-Sherbiney et al. study [16] may contribute to different outcomes than using IMRT in other studies [2,14,15,28].

With periodic ultrasonographic follow up we found that the size of the thyroid gland has been shown to decrease in all patients throughout the follow up period with more prominent decrement in the hypothyroid group. A similar study [29] has also found that patients who received EBRT to the neck have had substantial decrease in size. However, the authors have reported that no correlation between the size change and the incidence of RIHT. On the other hand more studies [8,30] have stated that hypothyroid patients had more significant decrease in size of the thyroid gland compared to euthyroid patients. The inconsistency between the first and the latter studies can be explained by the different methodology, where the 1st study implemented CT imaging while the latter studies implemented thyroid US. In our study we used ultrasonographic evaluations similar to the latter studies and thus we have the same conclusion. More recently, Lin et al. have applied serial CT scans on 6 months intervals until 48 months of follow up and found that shrinking thyroid volume was significantly associated with RIHT [31].

Some authors have studied the predictability of RIHT based on other sonographic findings. Low echogenicity index of the thyroid gland was found to be a positive predictive risk factor for subclinical and clinical RIHT by Cheng et al. [8]. They found that echogenicity index of 1.8 was the optimum cutoff to identify thyroid glands with reduced function, with sensitivity and specificity values of 55.3% and 69.5%, respectively. Although using this cutoff had low sensitivity and only moderate specificity, it could provide complementary information to that obtained by thyroid function testing. They also investigated the impact of changing vascularity index but found no correlation between increased vascularity index and the incidence of RIHT. In our study, only a very few patients have showed a change in echogenicity index and/ or vascularity index and didn't have statistical significance in correlation to normal or hypothyroid state.

Furthermore, we have found that decreasing the size of the gland by ≥ 0.7 cm^3 after one year from the end of EBRT is the cutoff value for prediction of occurrence of RIHT within the 2nd year of follow up with 75% sensitivity, 97.3% specificity. In the literature available we have not found studies that defined a similar predictor to RIHT. Similarly, for fT_4, the cutoff value is decreasing fT_4 value by ≥ 3.5 pmol/L after one year from pre-treatment value with 90.9% sensitivity and 78.4% specificty. For TSH, the cutoff is increasing the TSH by ≥ 0.75 uIU/L after one year from pre-treatment value with 99.9% sensitivity, and 91.9% specificity.

The limitations of the study include the relatively short follow up duration and heterogenicity of the study population. It is recommended to continue follow up of the cohort in further studies as it is expected to have higher incidence of RIHT as a late effect for EBRT.

5. CONCLUSION

RIHT is a considerable late adverse effect for patients receiving RT to the neck. Mean dose, V_{40}, V_{45}, and V_{50} were found significantly related to RIHT. Mean dose of ≥ 5185 cGy, V_{40} ≥ 89%, V_{45} ≥ 63.5%, V_{50}≥ 22.5% were proven to be the dose-volumetric threshold. Also, decreasing the size of the gland by ≥0.7 cm^3, increasing TSH by ≥ 0.75 uIU/L, decreasing fT4 by ≥ 3.5 pmol/L after one year from RT were found to be the cutoff value for prediction of RIHT. These results can be useful in treatment planning of patients receiving RT to the neck to decrease treatment morbidity where maintaining the functional is the metric of therapeutic success, especially with the rapidly growing numbers of young survivors.

CONSENT

Written informed consent was obtained from the patients prior to enrolment in the study.

ETHICAL APPROVAL

The study protocol was submitted to the IRB board of Mansoura Medicine Faculty in 2/2016 and was granted approval in 3/2016 before initiating the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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